A Phase 1 Study of AL002 in Healthy Volunteers

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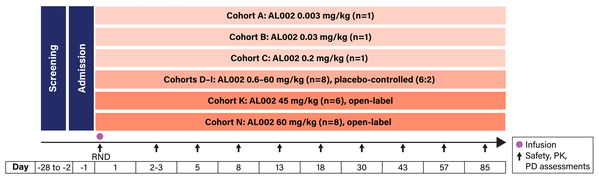
Background

- 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[6]
- Fluid biomarkers of TREM2 signaling have been previously identified:
  - AL002-mediated TREM2 activation promotes its internalization thus resulting in reduced soluble TREM2 (sTREM2) production at the cell surface
  - Soluble colony stimulating factor 1 receptor (sCSF1R), secreted phosphoprotein 1 (SPP1), and interleukin-1 receptor antagonist (IL1RN) are downstream biomarkers of TREM2 signaling[5,6]
  - SPP1 and IL1RN regulate neuroinflammation, and SPP1 is known to increase microglia survival[7-9]

Methods

- INVOKE-1 (NCT03635047) was a first-in-human phase 1, multicenter, randomized, placebo-controlled, double-blind study designed to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AL002 in healthy volunteer (HV) participants in North America, Australia, and Europe
- A total of 64 HVs participated in the single ascending dose (SAD) portion of the trial (53 received single-dose AL002 administered intravenously [IV], and 11 received placebo)
- Among 11 dose cohorts (**Figure 1**):
  - Cohorts A–C: 3 HVs were enrolled into 3 single-participant cohorts sequentially and treated with AL002 0.003 mg/kg, 0.03 mg/kg, or 0.2 mg/kg
  - Cohorts D–I : cohorts of 8 HVs (6 active: 2 placebo) were sequentially enrolled and treated with single doses of AL002 or placebo, at dose levels ranging from 0.6 to 60 mg/kg
  - In addition, 2 open-label cohorts were enrolled:
    - Cohort K enrolled 6 participants treated with AL002 at 45 mg/kg
    - Cohort N enrolled 8 participants treated with AL002 at 60 mg/kg
- For Cohorts F–K, lumbar puncture was performed at pre-dose baseline, Day 3, and Day 13 to obtain cerebrospinal fluid (CSF) samples to measure PK and exploratory biomarker levels
- Cohort N had lumbar puncture performed at pre-dose baseline, Day 13, 30, 43, or 57
- All participants were followed for safety for 12 weeks after single-dose AL002 or placebo

Figure 1. AL002-1 Study Design



Key inclusion criteria

- Adults aged 18 to 85 years with body weight between 50 and 120 kg and in good physical health based on no clinically significant findings from medical history, physical examination, 12-lead electrocardiogram (ECG), clinical laboratory evaluations, and vital signs, as judged by the investigator
- Females must be nonpregnant and nonlactating, and either surgically sterile, using a highly effective contraceptive method from screening through the follow-up period, abstinent from heterosexual intercourse, or postmenopausal for ≥12 months
- Negative test for selected drugs of abuse at screening (does not include alcohol) and at admission (includes alcohol breath test)

Key exclusion criteria

- Pregnant or lactating, or intending to become pregnant within 16 weeks after last dose of study drug
- Participants who have received an experimental vaccine against a central nervous system (CNS) target, such as beta-amyloid or tau, are not eligible
- Any nonexperimental vaccine within 2 weeks of randomization, until 2 weeks after the last dose of the study drug
- Surgery or hospitalization during the 4 weeks prior to screening
- Planned procedure or surgery during the study
- Clinically significant systemic immunocompromised condition because of continuing effects of immune-suppressing medication
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins
- History of seizures, with the exception of childhood febrile seizures
- The use of all prescribed medication is not allowed ≤30 days prior to admission to the clinical research center until follow-up; the use of all over-the-counter medication is not allowed ≤14 days prior to admission to the clinical research center until follow-up; the use of paracetamol/acetaminophen (≤2000 mg/day) is allowed for the treatment of headache or any other pain

Safety endpoints

- Incidence, nature, severity, and seriousness of all adverse events (AEs) and all treatment emergent adverse events (TEAEs)
- Incidence of dose-limiting adverse events (DLAEs), treatment discontinuations due to adverse events (AEs), and dose reductions due to AEs
- Mean changes in clinical laboratory tests and vital signs from baseline over time
- Incidence of treatment-emergent abnormal laboratory values and abnormal vital sign measurements
- Incidence of suicidal ideation/behavior

PK and PD endpoints

- Serum and CSF concentration profiles of AL002 and relevant PK parameters
- Incidence of treatment-emergent anti-drug antibodies (ADAs)
- CSF concentrations of sTREM2, sCSF1R, SPP1, IL1RN

Results

- Among 64 enrolled HVs, 53 participants received AL002 and 11 participants received placebo (**Table 1**)
- All participants completed the study with the exception of 1 participant in the 60 mg/kg cohort who withdrew consent

Table 1. Baseline Demographics

	Total AL002 (n=53)	Pooled Placebo (n=11)
Female sex, n (%)	31 (58.5%)	8 (72.7%)
Age, years, mean (SD)	32.1 (11.25)	39.7 (15.86)
Race, n (%)		
White	37 (69.8%)	11 (100.0%)
Asian	6 (11.3%)	0
Black/African American	3 (5.7%)	0
Other	7 (13.2%)	0
Hispanic/Latino ethnicity, n (%)	8 (15.1%)	2 (18.2%)
BMI at screening, kg/m², mean (SD)	25.01 (3.486)	24.45 (3.839)
Day 1 pre-dose body weight, kg, mean (SD)	72.53 (13.856)	70.21 (13.417)

BMI, body mass index. SD, standard deviation.

Safety

- Overall, 69.8% of participants in the total AL002 group experienced treatment-emergent adverse events (TEAEs) compared with 81.8% of participants in the pooled placebo group (**Table 2**)
  - No drug-induced or drug-related SAEs or DLAEs occurred during the study
  - 1 participant in the pooled placebo group experienced an SAE that was not considered related to study drug
  - 2 participants experienced AEs considered probably related to AL002 that led to withdrawal of study drug; one participant (AL002 45 mg/kg) experienced nausea (mild), and one participant (AL002 60 mg/kg) experienced parasthesias (moderate), nausea (mild), and retching (mild)

Table 2. Safety[a]

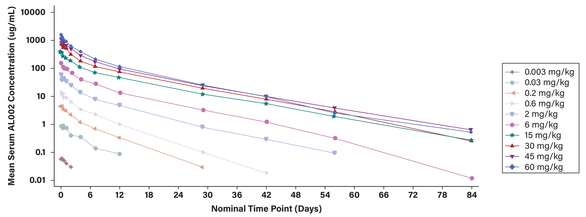
System Organ Class Preferred Term	AL002 0.003-0.2 mg/kg (n=3) n (%)	AL002 0.6 mg/kg (n=6) n (%)	AL002 2 mg/kg (n=6) n (%)	AL002 6 mg/kg (n=6) n (%)	AL002 15 mg/kg (n=6) n (%)	AL002 30 mg/kg (n=6) n (%)	AL002 45 mg/kg (n=6) n (%)	AL002 60 mg/kg (n=14) n (%)	Pooled Placebo (n=11) n (%)
Participants with ≥1 TEAE	2 (66.7%)	3 (50.0%)	2 (33.3%)	5 (83.3%)	5 (83.3%)	4 (66.7%)	6 (100.0%)	10 (71.4%)	9 (81.8%)
Participants with ≥1 treatment-related TEAE[b]	2 (66.7%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	4 (66.7%)	5 (83.3%)	7 (50.0%)	6 (54.5%)
Treatment-related TEAEs in ≥5% of participants in the total AL002 group									
Headache	1 (33.3%)	1 (16.7%)	2 (33.3%)	2 (33.3%)	1 (16.7%)	4 (66.7%)	2 (33.3%)	2 (14.3%)	4 (36.4%)
Dizziness postural	1 (33.3%)	0	1 (16.7%)	0	0	1 (16.7%)	0	0	1 (9.1%)
Nausea	0	0	1 (16.7%)	1 (16.7%)	0	0	1 (16.7%)	6 (42.9%)	2 (18.2%)
Vomiting	0	0	0	0	0	0	0	3 (21.4%)	2 (18.2%)
Any TEAE leading to study drug withdrawal	0	0	0	0	0	0	1 (16.7%)	1 (7.1%)	0

[a]A TEAE is defined as an AE that commenced on or after the time of first study drug administration. If a participant has multiple occurrences of a TEAE, the subject is counted only once in the subject count (n) column for a given System Organ Class and Preferred Term. Any AEs with a missing or unknown severity are counted as severe. Adverse events were coded to system organ class and preferred term using MedDRA Version 21.1.
[b]A treatment-related TEAE is defined as a TEAE with a relationship to study drug of possible, probable, missing, or unknown.
AE, adverse event; TEAE, treatment emergent adverse event.

PK

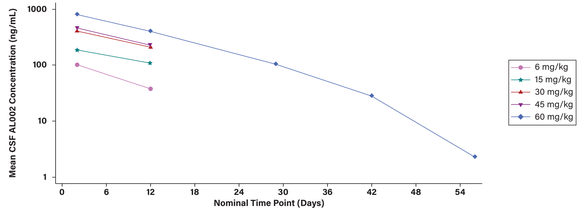
- Mean serum concentrations of AL002 increased in a dose-dependent manner (**Figure 2**)
- AL002 has an approximately dose-proportional C_{max} and $AUC_{0-\infty}$
- Mean CSF concentration-time profiles for AL002 were similar for each cohort, with mean peak exposures on Day 2 followed by a decline in exposure as AL002 was eliminated (**Figure 3**)
  - The mean CSF concentrations of AL002 were generally elevated across the entire profile with each increasing dose
- The geometric mean (coefficient of variation [CV] %) partition coefficients (CSF over serum) at Day 13 ranged from 0.17% (171.0) to 0.28% (73.0) for the AL002 6 mg/kg, 15 mg/kg, 30 mg/kg, 45 mg/kg, and 60 mg/kg cohorts
  - For the AL002 60 mg/kg cohort, the geometric mean (CV%) CSF over serum partition coefficients were 0.47% (46.8) for Day 30 and 0.30% (55.3) for Day 43

Figure 2. Mean Serum AL002 Concentration Profiles Over Time by Treatment Group (semi-log)



Note: Lower limit of quantification is 0.0200 ug/mL.

Figure 3. Mean CSF AL002 Concentration Profiles Over Time by Treatment Group (semi-log)



Note: Lower limit of quantification is 5.00 ng/mL.

CSF biomarkers

- AL002 treatment dose-dependently decreased sTREM2 in CSF, indicating engagement of AL002 to the TREM2 target (**Figure 4A, 4B**)
- In Cohort N, CSF sTREM2 was still reduced from baseline at Day 30
- AL002 treatment caused an increase in CSF levels of sCSF1R, SPP1, and IL1RN (**Figures 5-7**)

Figure 4. Mean (SD) Percent Change From Baseline of CSF sTREM2

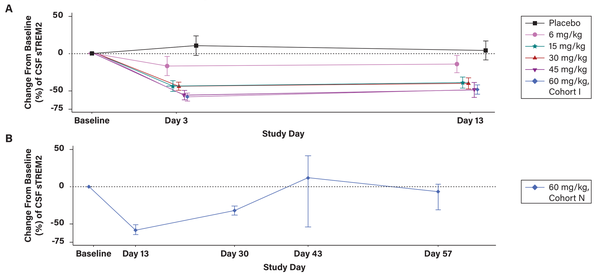


Figure 5. Mean (SD) Percent Change From Baseline of CSF sCSF1R

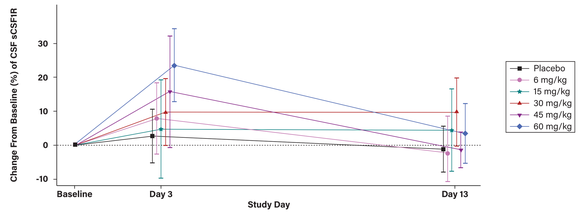


Figure 6. Mean (SD) Percent Change From Baseline of CSF SPP1

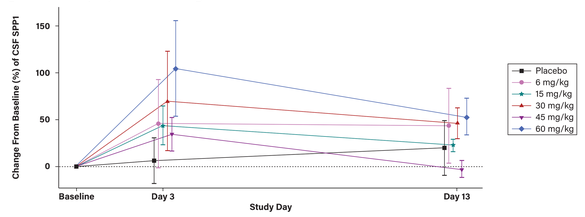
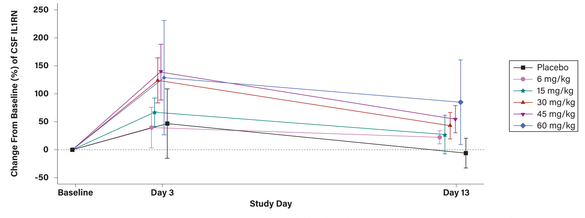


Figure 7. Mean (SD) Percent Change From Baseline of CSF IL1RN



Note: Outlier values (1280.3% above baseline at Day 3; 949.3% above baseline at Day 13) from 1 participant in the 30 mg/kg dose group were omitted from the graph.

Conclusions

- In this first-in-human phase 1 study, AL002 was found to be generally safe and well-tolerated
- Following a single IV infusion of AL002 at 0.003 to 60 mg/kg, mean serum concentrations of AL002 were consistently elevated across the entire profile with each increasing dose
- Serum C_{max} and $AUC_{0-\infty}$ increased in a dose-proportional manner. AL002 was distributed into the CNS as evidenced by CSF concentrations
- AL002 showed robust target engagement in the brain based on changes in CSF sTREM2 and CSF biomarkers (sCSF1R, SPP1, IL1RN) that reflect TREM2 signaling
- The favorable safety profile and evidence of TREM2 target engagement support further clinical development of the anti-TREM2 antibody AL002 for treating AD
- Population PK and PD modeling of serum and CSF AL002 and CSF sTREM2 supports a 4-week (q4w) dosing schedule at 3 IV dose levels (15, 40, 60 mg/kg) in the AL002 phase 2 trial
- The phase 2 trial (INVOKE-2) to investigate the efficacy and safety of AL002 (q4w for 48–96 weeks) in approximately 265 participants with early AD is ongoing

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Disclosures

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