

Baseline Characteristics for INVOKE-2: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study Evaluating AL002 in Early Alzheimer's Disease

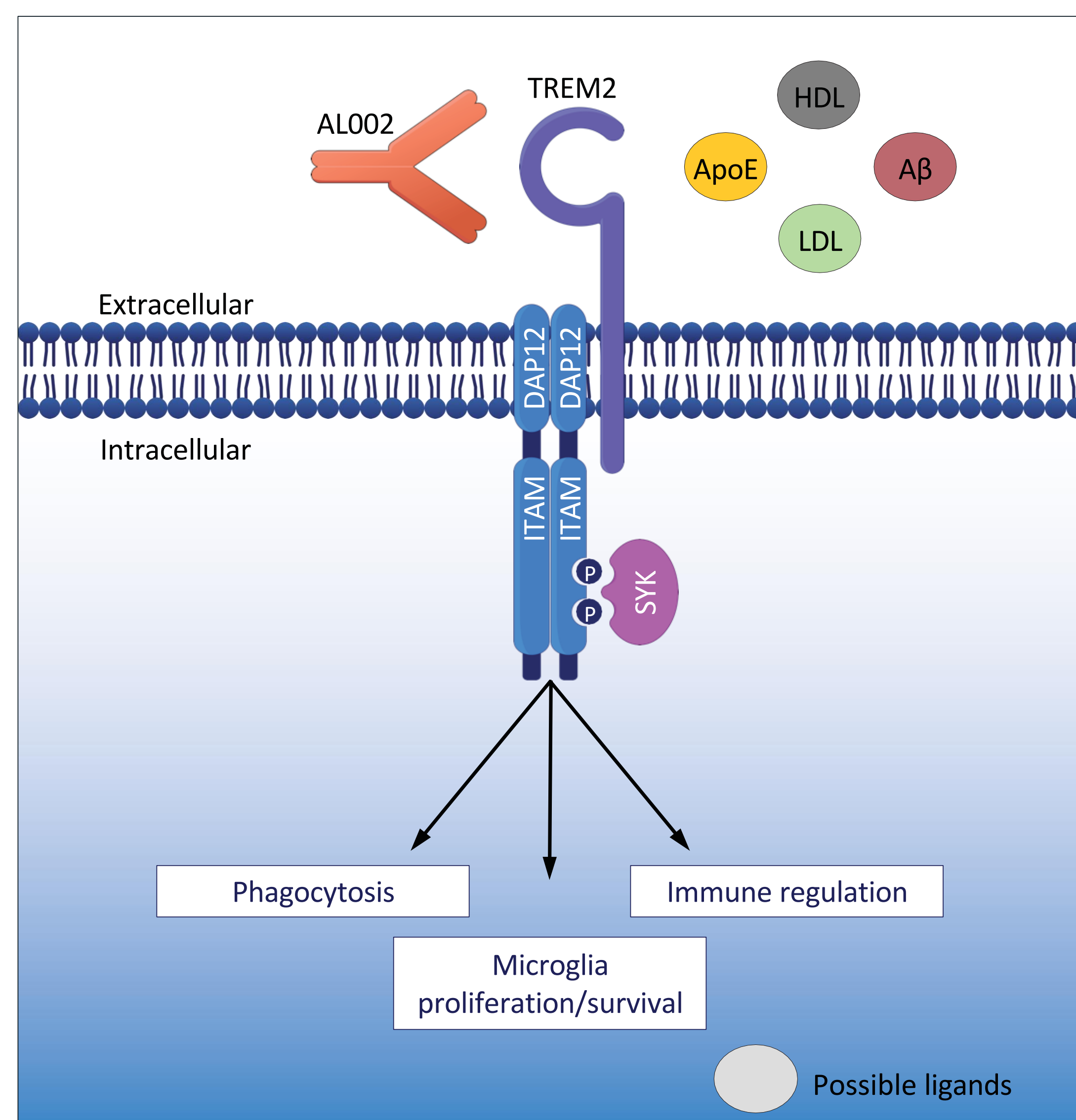
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Introduction

- Variants of the gene coding for TREM2, an innate immune receptor expressed in microglia, increase the risk of developing late-onset AD^{1,2}
- Evidence from animal models suggests that TREM2 agonism may beneficially alter the progression of AD³⁻⁵
- AL002 is an investigational, humanized, TREM2-selective, agonistic IgG1 monoclonal antibody (Figure 1)
- A preclinical variant of AL002 induced microglial proliferation and reduced toxic filamentous plaques and neurite dystrophy in a 5x FAD mouse model expressing human TREM2⁶
- A phase 1 study of a single infusion of AL002 in healthy volunteers demonstrated target engagement based on dose-dependent reductions of sTREM2 in CSF along with parallel increases in biomarkers of TREM2 signaling^{6,7}
- AL002 was generally safe and well tolerated among healthy volunteers at all doses tested (0.003-60 mg/kg)^{6,7}
- Here, we present the baseline characteristics for INVOKE-2 (NCT04592874), a phase 2 study designed to evaluate the efficacy and safety of monthly infusions of AL002 in participants with early AD

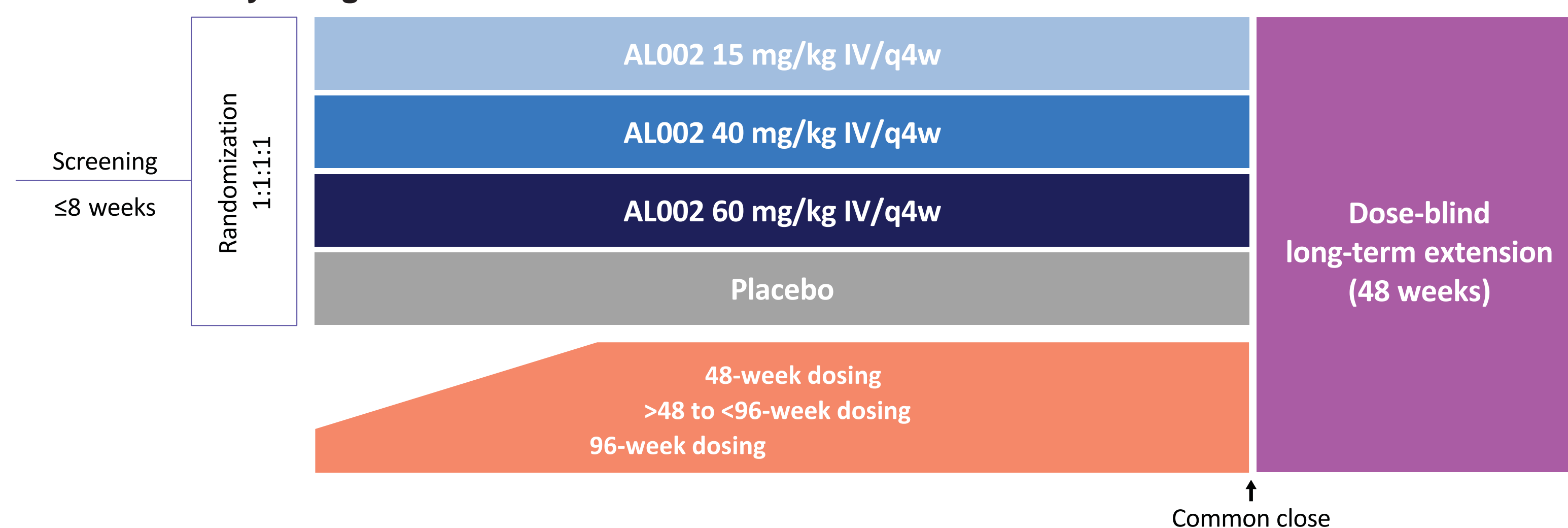
Figure 1. Proposed Mechanism of Action of AL002



Methods

- INVOKE-2 is a randomized, double-blind, parallel-group, dose-ranging, placebo-controlled study followed by a 48-week, dose-blind, LTE in participants with early AD; it is being conducted in North America, Australia, Europe, and South America
- The primary objective is to evaluate the efficacy of AL002 in delaying disease progression in participants with early AD
- Participants were randomized (1:1:1:1) across 4 treatment groups (15-, 40-, 60-mg/kg AL002 or placebo) to receive IV infusions every 4 weeks for at least 48 weeks and up to 96 weeks (Figure 2)
- Treatment group assignment was stratified based on APOE ε4 status

Figure 2. INVOKE-2 Study Design



Key eligibility criteria

- Participants (aged 50-85 years) must (1) be in the Alzheimer's continuum as defined by the 2018 NIA-AA Research Framework,⁸ which requires evidence of cerebral amyloidosis (A+), and (2) must demonstrate clinical severity consistent with Stages 2, 3, or early Stage 4 as defined in the 2018 Research Framework, further constrained by entrance criteria for the CDR-GS (0.5 or 1), MMSE (≥20 points), and the RBANS-Update DMI (≤95)
- Participants receiving symptomatic AD medications must have a stable dosing regimen for 60 days prior to screening that is not expected to change during study participation
- Due to treatment-emergent brain MRI changes resembling ARIA that were of greater incidence and severity in participants with the APOE ε4/ε4 genotype, participants with this genotype were discontinued from the study and excluded from future enrollment

Study endpoints

- The primary efficacy endpoint is disease progression as measured by the change from baseline in CDR-SB
- Secondary endpoints include change from baseline in the MMSE, RBANS-Update, ADAS-Cog13, ADCS-ADL-MCI, and ADCOMS
- Safety endpoints include: the incidence of adverse events; changes from baseline in laboratory and vital sign values; incidence of findings from physical, neurological, ECG, MRI, and ophthalmological exams; reports of suicidal ideation/behavior (C-SSRS)
- Exploratory endpoints include biomarker assessments of target engagement (sTREM2), microglial signaling (CSF1R, osteopontin, IL-1RA), AD pathophysiology (pTau217, MTBR-Tau243, pTau181, Aβ 42/40, amyloid PET, tau PET), astrogliosis (GFAP, YKL-40), and neuronal/synaptic injury (NFL, neurogranin, volumetric MRI)

Dose-blind LTE study

- Participants who complete the planned 48- to 96-week treatment period will have the opportunity after their final visit to enroll in the 48-week, dose-blind LTE study (NCT05744401) to evaluate the long-term safety, tolerability, and efficacy of AL002
- Participants who were randomized to AL002 treatment in the parent study will remain at their previously assigned dose, while those randomized to placebo will receive dose titration of AL002
- Participants, study partners, those conducting COAs, investigators, site staff, and site monitors will remain blinded to the original treatment assignments; the CRO and the sponsor will also remain blinded to the treatment assignments, except in circumstances described in the protocol

Results

- A total of 381 participants were randomized in INVOKE-2 (Table 1)
- The median age was 71 years, with 78% of participants ≥65 years of age

Table 1. Demographic and Baseline Characteristics^a

	N=381
Age, median (min, max), years	71.0 (51, 85)
Age group, n (%)	
<65 years	84 (22.0)
65 to <75 years	176 (46.2)
≥75 years	121 (31.8)
Age ≥65 years, n (%)	297 (78.0)
Female, n (%)	191 (50.1)
Race, n (%)	
White	357 (93.7)
Asian	4 (1.0)
Black/African American	3 (0.8)
Multiple	1 (0.3)
Not reported/Missing/Unknown	16 (4.2)
Ethnicity	
Hispanic/Latino	17 (4.5)
Not Hispanic/Latino	348 (91.3)
Not reported/Missing/Unknown	16 (4.2)
Region, n (%)	
United States	80 (21.0)
Rest of world	301 (79.0)

^aAs of June 2024.

- Baseline COA data were consistent with an early AD population (Table 2)
- Amyloid positivity was confirmed in all participants prior to enrollment by analysis of CSF or amyloid PET
- Of the 381 participants, 59% were heterozygous APOE ε4 carriers

Table 2. Baseline Clinical Characteristics

	N=381
Clinical diagnosis, n (%)	
Mild cognitive impairment due to AD	256 (67.2)
Mild dementia due to AD	125 (32.8)
APOE genotype, n (%)	
ε2/ε3	5 (1.3)
ε2/ε4	6 (1.6)
ε3/ε3	137 (36.0)
ε3/ε4	218 (57.2)
ε4/ε4 ^a	15 (3.9)
Amyloid PET Centiloids, mean (SD), (n=244)	100.1 (38.9)
CDR-GS, n (%)	
0.5	297 (78.0)
1	84 (22.0)
CDR-SB, mean (SD)	3.4 (1.4)
MMSE, mean (SD)	24.5 (2.4)
RBANS, mean (SD)	66.4 (12.1)
ADAS-Cog13, mean (SD)	29.2 (8.6)
ADCS-ADL-MCI, mean (SD)	40.3 (7.2)
ADCOMS, mean (SD)	0.43 (0.16)

^aAPOE4 homozygotes were discontinued from the study.

Conclusions

- INVOKE-2 is the first phase 2 trial to evaluate the efficacy and safety of a TREM2 agonistic antibody in participants with AD
- The baseline characteristics of INVOKE-2 participants are representative of an early AD population, enabling clinical evaluation of a TREM2 agonist in participants with AD
- INVOKE-2 was initiated in January 2021 and enrollment was completed in September 2023

References

1. Guerreiro R, et al. *N Engl J Med.* 2013;368(2):117-127.
2. Jonsson T, et al. *N Engl J Med.* 2013;368(2):107-116.
3. Wang Y, et al. *J Exp Med.* 2016;213(5):667-675.
4. Price BR, et al. *J Neuroinflammation.* 2020;17(1):238.
5. Schlepckow K, et al. *EMBO Mol Med.* 2020;12(4):e111227.

6. Wang S, et al. *J Exp Med.* 2020;217(9):e20200785.

7. Ward, M, et al. A phase 1 study of AL002 in healthy volunteers. Poster presentation at Alzheimer's Association International Conference (AAIC), July 26-30, 2021, Denver, CO.

8. Jack CR, et al. *Alzheimers Dement.* 2018;14(4):535-562.

Abbreviations

AD, Alzheimer's disease; 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; Aβ, amyloid-β; APOE, apolipoprotein E; ARIA, amyloid-related imaging abnormalities; CDR-GS, Clinical Dementia Rating-Global Score; CDR-SB, Clinical Dementia Rating-Sum of Boxes; COA, clinical outcome assessment; CRO, clinical research organization; CSF, cerebrospinal fluid; CSF1R, colony stimulating factor 1 receptor; C-SSRS, Columbia-Suicide Severity Rating Scale; DMI, Delayed Memory Index; ECG, electrocardiogram; FDA, Food and Drug Administration; GFAP, glial fibrillary acidic protein; HDL, high-density lipoprotein; IgG1, immunoglobulin G1; IL-1RA, interleukin-1 receptor antagonist; IV, intravenous; LDL, low-density lipoprotein; LTE, long-term extension; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; MTBR-Tau243, microtubule-binding region of tau containing the residue 243; NIA-AA, National Institute on Aging and Alzheimer's Association; NFL, neurofilament light; PET, positron emission tomography; pTau181, phosphorylated tau at threonine 181; q4w, every 4 weeks; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; sTREM2, soluble TREM2; TREM2, triggering receptor expressed on myeloid cells-2; YKL-40, chitinase 3 like 1 (CHI3L1).

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