INVOKE-2: An Update on the Phase 2 Trial of AL002 in Early AD

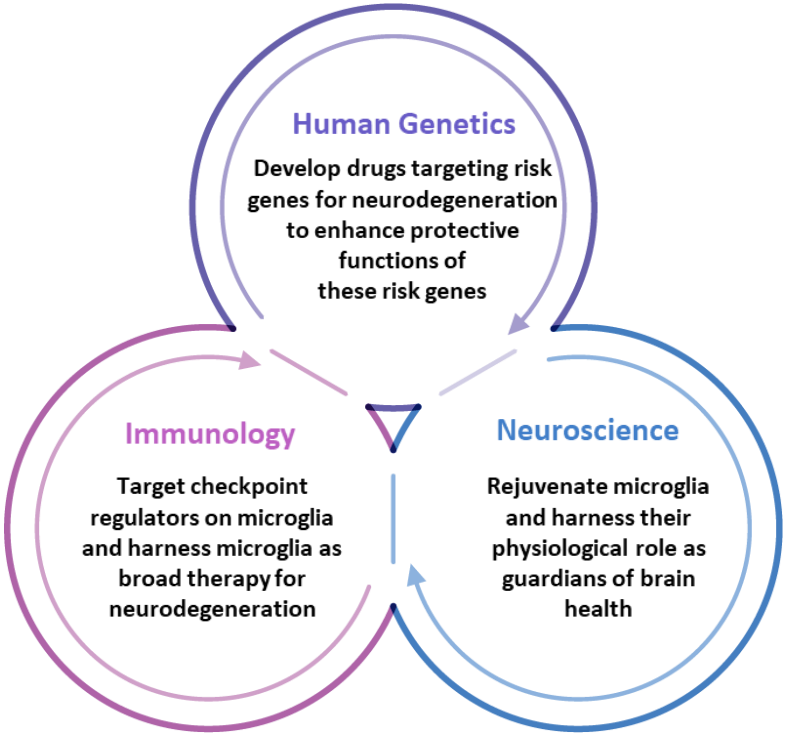
Gary Romano,[1] Arthur Mayorga,[1] Adam Simmons,[1] Brady Burgess,[1] Michael Grundman,[2] Jingjing Gao[1], Arnon Rosenthal[1]

[1]Alector, Inc., San Francisco, CA, USA; [2]Global R&D Partners, LLC, La Jolla, CA, USA

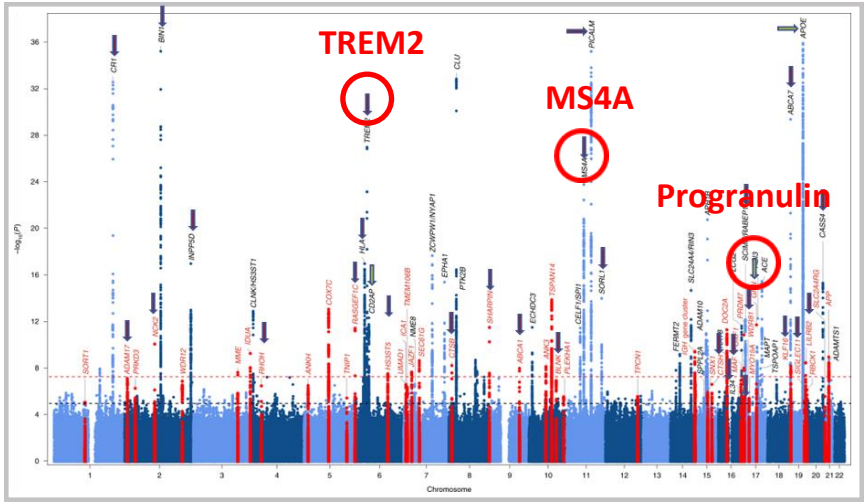
Disclosures

- Gary Romano, Arthur Mayorga, Adam Simmons, Brady Burgess, Jingjing Gao and Arnon Rosenthal are employees of Alector
- Michael Grundman is an employee of Global R&D Partners and a consultant to Alector

Immuno-Neurology: Alector's Therapeutic Strategy for Degenerative Brain Disorders



Many AD risk genes are regulators of microglia[1] (black arrows)
Alector's programs are in circled in ○

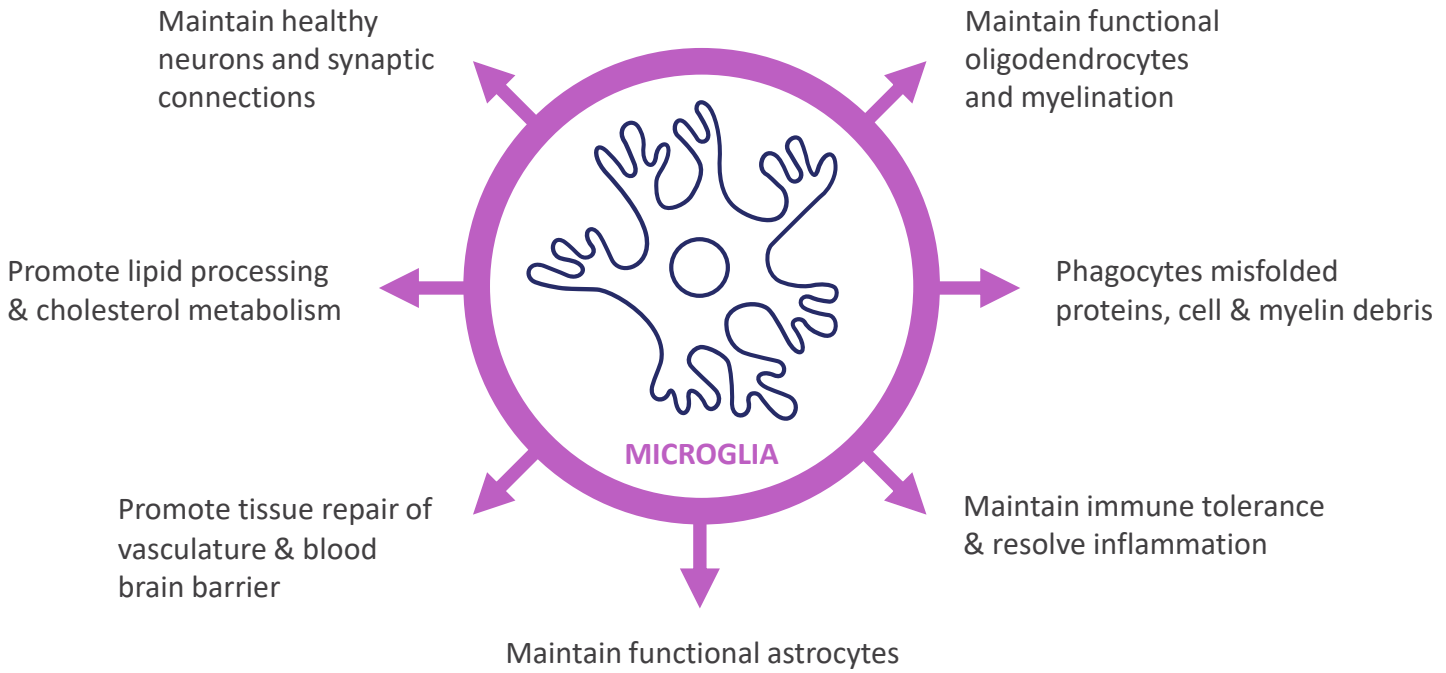


AD, Alzheimer's disease; TREM2, triggering receptor expressed on myeloid cells 2

1. Bellenguez C, et al. Nat Genet. 2022;54:412-436.

Microglia are Essential for Brain Function and Health

Microglia maintain brain health throughout life



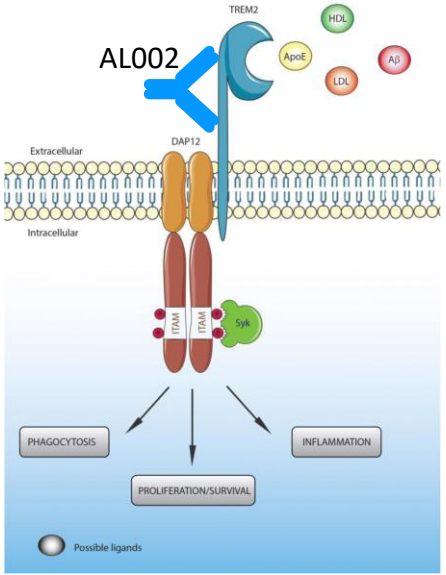
Adapted from Du, et al Molecular Neurobiology 2017;54:7567–7584

TREM2: Microglial Membrane Receptor That Senses Pathological Changes in the Brain

TREM2

- TREM2 binding to its biological substrates initiates signaling pathways that allow the microglia to adopt a defensive response to pathogens and disease[1]
- TREM2 LOF mutations are deleterious:
  - Homozygous mutations cause Nasu-Hakola disease[2]
  - Heterozygous mutation (R47H) increases risk for AD by 3-fold[3]
- AL002 is designed to facilitate clustering of TREM2, activate TREM2 signaling, and enhance microglial function, proliferation, and survival[4]

AL002: Activates TREM2 Signaling



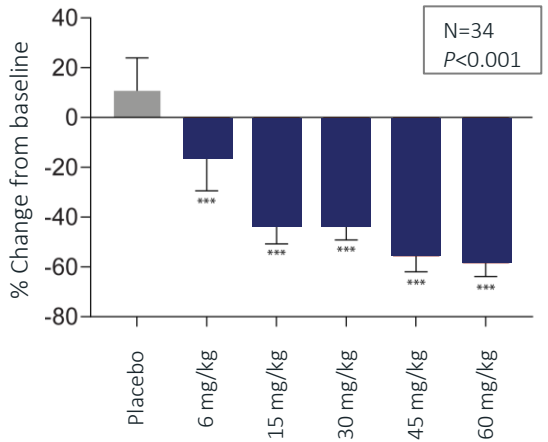
AD, Alzheimer's disease; TREM2, triggering receptor expressed on myeloid cells 2; LOF, loss-of-function

1. Gray SC, et al. *Neural Regen Res.* 2020;15(7):1208-1219. 2. Xing J, et al. *Res Rep Biochem.* 2015;5:89-100. 3. Guerreiro R, et al. *N Engl J Med.* 2013;368:117-127. 4. Wang S, et al. *J Exp Med.* 2020;217(9):e2020078.

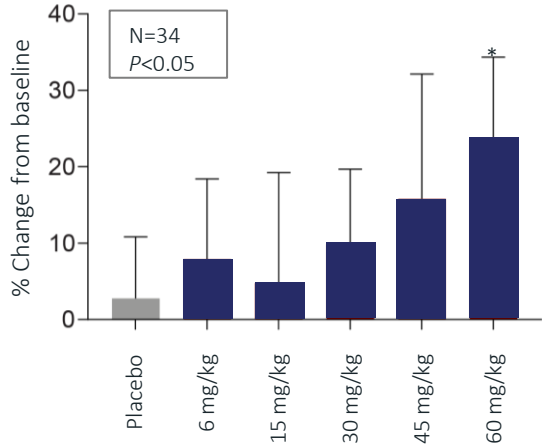
AL002 Ph1 Study: Dose-Related Target Engagement and Microglia Activation

Generally well-tolerated in healthy volunteers[1]

Dose-Dependent Reduction in Soluble TREM2[2]



Dose-Dependent Elevation in CSF sCSF-1R[2]



CSF, cerebrospinal fluid; TREM2, triggering receptor expressed on myeloid cells 2

Data are presented as mean ± SD; cohort n=6 (placebo, 6 mg/kg, 15 mg/kg, 30 mg/kg) and 5 (45 mg/kg, 60 mg/kg).

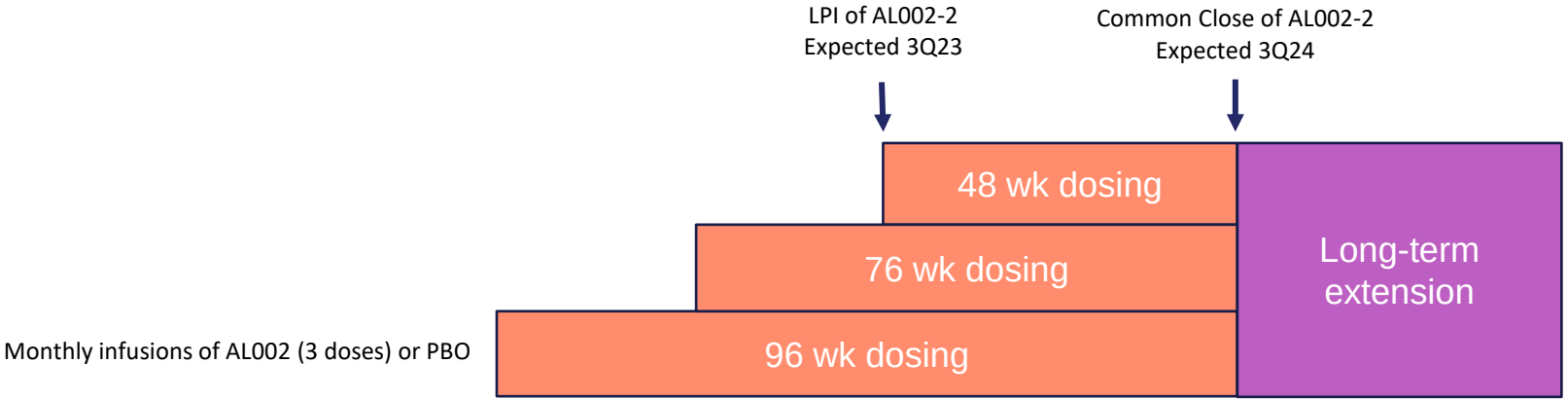
*P=0.026 at 60 mg/kg vs pooled placebo. ***P=0.0001 for 6 mg/kg and P<0.0001 for all other doses vs pooled placebo control.

1. Phase 1 data presented at AAIC 2021; NCT03635047. 2. Wang S, et al. *J Exp Med*. 2020;217(9):e20200785.

alector

INVOKE-2 Phase 2 AL002 Study in Individuals With Early Alzheimer's Disease

Randomized, double-blind, placebo-controlled 4-arm common close study (48-96 weeks); randomizing 328 participants with early Alzheimer's disease



PRIMARY ENDPOINT
CDR-SB

SECONDARY CLINICAL OUTCOME ASSESSMENTS
RBANS, ADAS-Cog13, ADCS-ADL-MCI, MMSE

EXPLORATORY ENDPOINTS
vMRI, amyloid PET, tau PET, CSF and plasma biomarkers

This study remains blinded to treatment assignment

Treatment-Emergent MRI Features Resembling Amyloid-Related Imaging Abnormalities[1] (ARIA)

- Early in the trial, 3 participants presented with treatment-emergent clinically serious neurological adverse events occurring within the first 3 months of treatment
- Clinical presentations included transient focal signs, seizures, and mental status changes requiring hospitalization; each participant eventually recovered following suspension of study drug and treatment with corticosteroids
- MRIs revealed vasogenic edema, sulcal effusions, and hemosiderin deposits, as may be seen with ARIA-E and ARIA-H
- Each of these 3 SAEs occurred in participants who are ApoE ε4/ε4 homozygotes

1. Salloway S, et al. Alzheimers Res Ther. 2018;10(1):96.

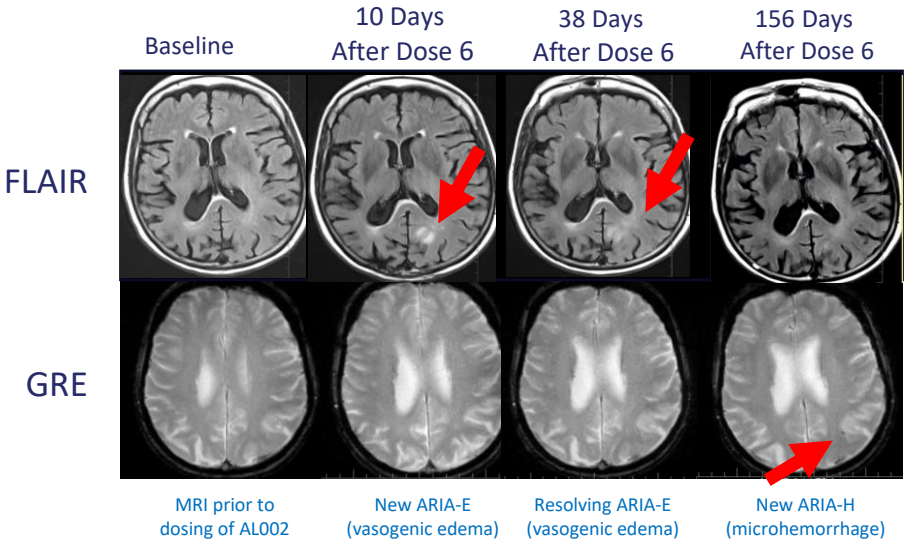
INVOKE-2 Protocol Modifications

- Dose titration
- MRI surveillance at baseline, before each dose titration, and every 3 months thereafter
- Dosing guidelines for ARIA management
- ApoE ε4/ε4 homozygotes excluded from study participation

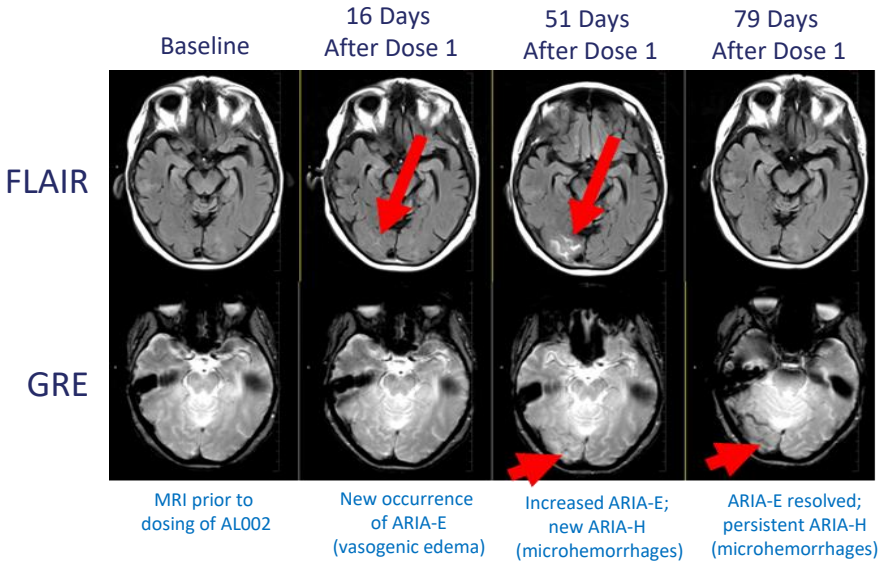
➢ An Independent Data Monitoring Committee reviews data regularly and has recommended to continue the trial

Examples of Radiographic Features in Participants With ARIA-E and ARIA-H

77 y/o (ApoE ε3/ε4) female participant with ARIA-E and ARIA-H



81 y/o (ApoE ε3/ε3) female participant with ARIA-E and ARIA- H



Most ARIA-E occurred within the first 3 months of treatment and resolved within 4 months after detection

Time to First ARIA-E Occurrence (Days)	
n	49
Mean (SD)	72.0 (46.25)
Median	54.0

Time to ARIA-E Resolution (Days)	
n	42
Mean (SD)	105.0 (79.52)
Median	85.5

ARIA incidence and radiographic severity were reduced after exclusion of ApoE ε4/ε4

ARIA-E	ApoE ε4/ε4†	Current Study Population (Non–ApoE ε4/ε4)
ARIA-E incidence, n/N (%)	8/15 (71)*	41/206 (27)*
Radiographic severity (scale of 1-5), mean (SD)	2.5 (1.6)	2.3 (1.4)

ARIA-H	ApoE ε4/ε4†	Current Study Population (Non–ApoE ε4/ε4)
ARIA-H incidence, n/N (%)	8/15 (71)*	46/206 (29)*
ARIA-H radiographic severity (%)		
Mild	1/8 (12.5)	18/46 (39)
Moderate	2/8 (25)	15/46 (33)
Severe	5/8 (62.5)	13/46 (28)

This study remains blinded to treatment assignment.

*Placebo controlled; assumes all ARIA occurs in active treatment arms.

†ApoE ε4 homozygote carriers no longer enrolling.

ARIA incidence is higher in ApoE ε4 carriers

ARIA-E	n/N (%)
ApoE ε4 noncarriers	12/85 (19)*
ApoE ε4 heterozygote carriers	29/121 (32)*
ApoE ε4 homozygote carriers†	8/15 (71)*

ARIA-H	n/N (%)
ApoE ε4 noncarriers	14/85 (22)*
ApoE ε4 heterozygote carriers	32/121 (35)*
ApoE ε4 homozygote carriers†	8/15 (71)*

This study remains blinded to treatment assignment.

*Placebo controlled; assumes all ARIA occurs in active treatment arms.

† ApoE ε4 homozygote carriers no longer enrolling.

Most participants with radiographic ARIA in the current trial population (excludes APOE ε4/ε4) have been asymptomatic

Symptomatic ARIA in Current Trial Population†	
Total participants dosed (excluding ApoE ε4/ε4)†	206
Participants with ARIA-E (%)	41 (27)*
Asymptomatic (%)	36/41 (88)
Symptomatic (%)	5/41 (12)
Clinically serious ARIA (%)	2/206 (1)

This study remains blinded to treatment assignment.

*Placebo controlled; assumes all ARIA occurs in active treatment arms.

†ApoE ε4 homozygote carriers no longer enrolling.

All participants with isolated ARIA-H were asymptomatic

INVOKE-2 Update: Summary

- Treatment-emergent MRI findings resembling ARIA have occurred in a subset of participants in the INVOKE-2 trial of AL002, a monoclonal antibody that activates TREM2 signaling
- These findings resemble the ARIA reported following treatment with anti-amyloid antibodies regarding:
  - MRI features, incidence, timing of onset, relatedness to number of ApoE ε4 alleles
  - Frequency and spectrum of associated clinical manifestations
- Exclusion of ApoE ε4/ε4 homozygotes reduced the incidence and severity of ARIA
- We do not yet know whether these events are related to amyloid clearance or other treatment-related changes in microglial function
- We are collecting clinical and functional outcome measures, brain MRI, amyloid PET, tau PET, and CSF and plasma fluid biomarkers in this study and expect to report those data late next year