# Use of a Blood-Based Amyloid Test for Screening in INVOKE-2: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study Evaluating AL002 in Early Alzheimer's Disease

Brady Burgess, MSc; Tuan Nguyen, PhD; Adam Simmons, MD; Ruchi Gupta, PhD; Tiffany Chow, MD; Gary Romano, MD, PhD

*Alector, Inc., South San Francisco, CA, USA*

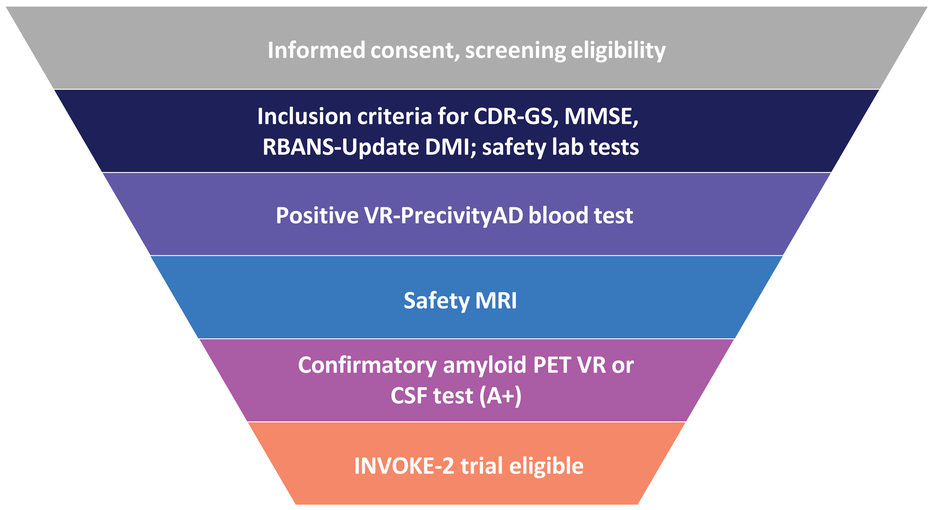
## Introduction

- The PrecivityAD® test is a validated, CLIA-approved laboratory developed test[1] that has shown robust performance in identifying brain amyloidosis among individuals with mild cognitive impairment and AD[2-4]
- INVOKE-2 (NCT04592874) is a randomized, double-blind, placebo-controlled phase 2 trial evaluating AL002, a novel humanized monoclonal TREM2-activating antibody, in participants with early AD who are amyloid positive[5,6]
- To improve screening efficiency in INVOKE-2 and reduce unnecessary PET scans and lumbar punctures, participants were prescreened for amyloid using the PrecivityAD amyloid blood test. A positive PrecivityAD test result was required for eligibility prior to a confirmatory amyloid test by amyloid PET visual read (VR) or CSF biomarker
- INVOKE-2 used a prototype PrecivityAD algorithm validated against amyloid PET VR status in contrast to the standard algorithm validated to predict a quantitative amyloid PET scan of ≥25 CL
- We hypothesized that a test validated against amyloid PET VR status would show high concordance with trial eligibility criteria that included amyloid confirmation by VR

## Methods

- The PrecivityAD blood test ($C_2$N Diagnostics) incorporates plasma Aβ42/40 ratio, apoE proteotype, and age to generate an amyloid probability score (APS), which corresponds to the likelihood of a positive amyloid PET scan
- A prototype visual read (VR)-validated PrecivityAD (VR-PrecivityAD) was validated to identify participants with a positive amyloid PET VR
  - Customized thresholds for APS were defined as low (VR-APS=0-31), intermediate (32-57), or high (58-100) likelihood of amyloid positivity
- The standard CL-validated PrecivityAD (CL-PrecivityAD) test was validated to detect individuals with amyloid PET scan ≥25 CL
  - Thresholds were defined as low (CL-APS=0-35), intermediate (36-57), or high (58-100) likelihood of amyloid positivity[2,3]
- INVOKE-2 is a randomized, double-blind, placebo-controlled study to evaluate the efficacy of AL002 in delaying disease progression in participants with early AD
- Early AD was defined as **(1)** being in the Alzheimer's continuum as defined by the 2018 NIA-AA Research Framework[5], which requires evidence of cerebral amyloidosis (A+), and **(2)** demonstrating clinical severity consistent with Stages 2, 3, or early Stage 4, as defined in the 2018 Research Framework, further constrained by entrance criteria defined for the CDR-GS (0.5 or 1), MMSE (≥20), and the RBANS-Update DMI (≤95)
- During screening, participants who met cognitive inclusion/exclusion criteria were required to have a positive VR-PrecivityAD blood test (intermediate or high VR-APS result) prior to a confirmatory amyloid PET VR or CSF test (**Figure 1**)
- To evaluate performance of the prototype assay, VR-PrecivityAD test results were rescored using the standard test (CL-PrecivityAD) to facilitate comparison
- Positive predictive value (PPV) was defined as the number of individuals with confirmed positive blood tests as a percentage of all positive blood tests
- Prevalence of amyloid was calculated using the formula: Prevalence = PPV × (1−Specificity) / [(PPV × (1−Specificity) + (1−PPV) (Sensitivity))]

**Figure 1. INVOKE-2 Screening Funnel**




## Results

- Positive VR-PrecivityAD results were reported for 51% of eligible individuals (362/710) with a PPV of 87% overall (95% CI: 84-91), 91% for high, and 82% for intermediate results (**Table 1**)
- PPV was higher for *APOE* ε4 carriers (91%) vs non-carriers (81%) (**Table 2**)
- PPV trended better for younger participants (≤70 years; 91%) compared with those >70 years of age (85%) (**Table 2**)
- PPV was equivalent for males and females (**Table 2**)
- A hypothetical comparison of the VR-PrecivityAD test used in INVOKE-2 against the standard CL-PrecivityAD algorithm suggested the prototype VR-validated algorithm resulted in a higher rate of eligible participants than the standard test; 58% of individuals would have scored negative on CL-PrecivityAD compared with only 49% on VR-PrecivityAD despite similar PPVs of 89% vs 87%, respectively (**Table 1**)
- Comparison of VR-APS against CL-APS results indicated the INVOKE-2 positivity threshold (VR-APS ≥32) was equivalent to an effective CL-APS threshold of ~25, which is lower than the established CL-PrecivityAD threshold (CL-APS ≥36)
- The theoretical incidence of amyloid positivity in the eligible screening population was estimated to be 77% based on the observed PPV of 89%, reported sensitivity of 93.7%, and specificity of 61.4% established for the VR-PrecivityAD test at the selected threshold
- Importantly, 80% (52/65) of discordant individuals with positive VR-PrecivityAD and negative CL-PrecivityAD results had a subsequent positive confirmatory test (**Table 3**)

**Table 1. VR-PrecivityAD Results and Hypothetical Results for CL-PrecivityAD Test**

| APS Category | n | PPV (95% CI) | Amyloid Load by APS Category | | | |
|---|---|---|---|---|---|---|
| | | | Positive Confirmatory Test | | Negative Confirmatory Test | |
| | | | Mean CL (SD) | n | Mean CL (SD) | n |
| **VR-PrecivityAD: Positive Tests=51% (362/710)** | | | | | | |
| **Negative (Low)** | 348 | – | – | – | – | – |
| **Positive (High+ Int.)** | 362 | 87% (84-91) | 100 (39) | 223 | 12 (22) | 35 |
| *High* | 214 | 91% (87-95) | 100 (39) | 136 | 27 (24) | 13 |
| *Intermediate* | 148 | 82% (76-88) | 100 (40) | 87 | 3 (15) | 22 |
| **CL-PrecivityAD: Positive Tests=42% (297/710)** | | | | | | |
| **Negative (Low)** | 413 | – | – | – | – | – |
| **Positive (High+ Int.)** | 297 | 89% (85-92) | 99 (41) | 190 | 18 (23) | 25 |
| *High* | 219 | 91% (88-95) | 99 (40) | 140 | 26 (24) | 13 |
| *Intermediate* | 78 | 82% (74-91) | 98 (45) | 50 | 9 (20) | 12 |

**Table 2. Effect of Covariates on VR-PrecivityAD Performance**

| Population by Covariates | | n | PPV (95% CI) |
|---|---|---|---|
| **Total eligible screening population** | | 710 | 87% (84-91) |
| **APOE ε4 status** | Carrier | 299 | 91% (88-95) |
| | Noncarriers | 411 | 81% (74-87) |
| **Age** | Younger (≤70 years[a]) | 382 | 91% (87-96) |
| | Older (>70 years[a]) | 328 | 85% (80-89) |
| **Sex** | Male | 353 | 87% (82-92) |
| | Female | 357 | 88% (83-93) |

[a]Median age was 70 years.

**Table 3. Discordant Results**

| APS Category | n | PPV (95% CI) | Amyloid Load by APS Category | | | |
|---|---|---|---|---|---|---|
| | | | Positive Confirmatory Test | | Negative Confirmatory Test | |
| | | | Mean CL (SD) | n | Mean CL (SD) | n |
| **VR-PrecivityAD Positive & CL-PrecivityAD Negative** | 65 | 80% (70-90) | 106 (29) | 33 | −3 (7) | 10 |

## Conclusions

- To facilitate enrollment in INVOKE-2 and reduce unnecessary PET scans and lumbar punctures, a noninvasive blood-based diagnostic test for cerebral amyloid was used as a prescreen for determining treatment eligibility
- Among INVOKE-2 screening participants, the prototype VR-PrecivityAD blood test was highly predictive (PPV=87%) of amyloid positivity, confirmed by VR-PET or CSF
- Performance of the VR-PrecivityAD test was better for *APOE* ε4 carriers (vs noncarriers), trended better for younger participants (≤70 years of age), and was not affected by sex
- In the INVOKE-2 screening population, use of a more lenient VR-APS threshold correctly identified more amyloid positive participants (without a meaningful increase in false positives) than would have been observed with the standard CL-APS threshold
- INVOKE-2, the first phase 2 trial to evaluate the efficacy and safety of a TREM2 agonistic antibody in participants with AD, is ongoing

### References

1. Kirmess KM, et al. *Clin Chim Acta*. 2021;519:267-275.
2. Hu Y, et al. *JAMA Netw Open*. 2022;5(4):e228392.
3. Fogelman I, et al. *Ann Clin Transl Neurol*. 2023;10(5):765-778.
4. West T, et al. *Mol Neurodegener*. 2021;16(1):30.
5. Jack CR Jr, et al. *Alzheimers Dement*. 2018;14(4):535-562.

### Abbreviations

Aβ, amyloid-β; AD, Alzheimer's disease; apoE, apolipoprotein E; APS, amyloid probability score; CDR-GS, Clinical Dementia Rating Global Score; CLIA, Clinical Laboratory Improvement Amendments; CI, confidence interval; CL, Centiloid; CSF, cerebrospinal fluid; DMI, Delayed Memory Index; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NIA-AA, NIA-AA, National Institute on Aging and Alzheimer's Association; RBANS-Update, Repeatable Battery for the Assessment of Neuropsychological Status- Update; PET, positron emission tomography; PPV, positive predictive value; SD, standard deviation; TREM2, triggering receptor expressed on myeloid cells-2; VR, visual read.

### Disclosures and Acknowledgments

All authors are employees of Alector, LLC and may have an equity interest in Alector, Inc.
We thank the study participants and their family members, and the investigators and their site personnel. Medical writing support was provided by Scient Healthcare Communications and funded by Alector, Inc. This study was funded by Alector, Inc.

**Presented at the Alzheimer's Association International Conference | July 28-August 1, 2024 | Philadelphia, PA**