ARIA Insights From Donanemab Trials

Steven M. Greenberg MD PhD¹, Paul Ardayfio PhD², Chakib Battioui PhD², Jennifer A. Zimmer MD², Cynthia D. Evans PhD², Hong Wang PhD², Emel Serap Monkul MD², Ming Lu MD MS MPH², JonDavid Sparks PhD², Scott Andersen MS², Emily C. Collins PhD², Dawn A. Brooks PhD², John R. Sims MD²

¹Massachusetts General Hospital, Boston, MA
²Eli Lilly and Company, Indianapolis, IN

Sponsored by Eli Lilly and Company
Disclosures

- Steven M. Greenberg reports receiving consulting fees from Eli Lilly and Company and participates in safety data monitoring boards or advisory boards for IQVIA/Washington University.

- Amyvid® (Florbetapir F 18) was developed at Avid Radiopharmaceuticals and is marketed by Eli Lilly and Company as a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density; safety and effectiveness of Amyvid® (Florbetapir F 18) has not been established for predicting development of dementia or other neurologic conditions and monitoring responses to therapies.

- Tauvid® (Flortaucipir F 18) is approved for use with PET imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles in adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease.

- All discussions refer to investigational purposes only.
ARIA in donanemab-exposed participants
Larger participant populations with lower amyloid and tau levels will expand current understanding of ARIA in individuals who received donanemab.

Risk factors of ARIA
The genetic APOE ε4 allele increases the risk of ARIA\(^1\). Machine learning approaches can facilitate identification or generate hypotheses for further variables to evaluate, such as baseline characteristics, comorbidities, and concomitant medications that may be associated with ARIA risk\(^2\).

Addendum, additional N=1053
• Open-label donanemab treatment
• Enrolled by amyloid pathology as only neuropathological criterion, including participants with lower amyloid and no/very low tau
• Safety and biomarker assessments

TRAILBLAZER-ALZ 2
A multicenter, randomized, double-blind, placebo-controlled, 18-month Phase 3 trial that enrolled 1736 participants with early symptomatic Alzheimer’s disease (AD) with amyloid and tau pathology confirmation via PET scan.

Abbreviations: APOE= apolipoprotein E; ARIA= amyloid-related imaging abnormalities; PET= Positron Emission Tomography.
## Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Demographics in donanemab-treated (N=131)</th>
<th>TRAILBLAZER-ALZ2 (N=860)</th>
<th>Addendum (N=1053)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%) female</strong></td>
<td>68 (51.9)</td>
<td>493 (57.3)</td>
</tr>
<tr>
<td><strong>Age, mean (SD), in years</strong></td>
<td>75.0 (5.6)</td>
<td>73.0 (6.2)</td>
</tr>
<tr>
<td><strong>Race n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (0.8)</td>
<td>57 (6.6)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>5 (3.8)</td>
<td>19 (2.2)</td>
</tr>
<tr>
<td>White</td>
<td>122 (93.1)</td>
<td>781 (90.9)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>2 (1.5)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Multiple</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Ethnicity</strong>, n (%) Hispanic/Latino</td>
<td>5 (3.8)</td>
<td>35 (5.7)</td>
</tr>
<tr>
<td><strong>APOE ε4 carrier, n (%)</strong></td>
<td>95 (72.5)</td>
<td>598 (69.8)</td>
</tr>
<tr>
<td>ε4 homozygous</td>
<td>25 (19.1)</td>
<td>143 (16.7)</td>
</tr>
<tr>
<td><strong>Screening amyloid Centiloids, mean (SD)</strong></td>
<td>107.6 (36.0)</td>
<td>103.5 (34.5)</td>
</tr>
<tr>
<td><strong>Screening MMSE by clinical category</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild cognitive impairment (≥27)</td>
<td>24 (18.3)</td>
<td>146 (17.0)</td>
</tr>
<tr>
<td>Mild AD (20-26)</td>
<td>88 (67.2)</td>
<td>713 (82.9)</td>
</tr>
<tr>
<td>Moderate AD (&lt;20)</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

Numbers of participants with non-missing data were used as denominators to calculate percentages.

a Phase 2 trial investigating safety and efficacy of donanemab, NCT03367403.

b Ethnicity reporting was limited to participants in the United States/Puerto Rico only.

Abbreviations: AD= Alzheimer’s disease; APOE= apolipoprotein E; MMSE= Mini-Mental State Examination; N= total number of participants; n = number of participants per category; SD= standard deviation.

© 2023 Eli Lilly and Company. All rights reserved.
### ARIA and Macrohemorrhage

<table>
<thead>
<tr>
<th>Event, n (%) in donanemab-treated</th>
<th>TRAILBLAZER-ALZ (N=131)</th>
<th>TRAILBLAZER-ALZ 2 (N=853)</th>
<th>Addendum (N=1047)</th>
<th>Total (N=2031)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ARIA (-E or -H)</td>
<td>51 (38.9)</td>
<td>314 (36.8)</td>
<td>335 (32.0)</td>
<td>700 (34.5)</td>
</tr>
<tr>
<td>ARIA-E</td>
<td>36 (27.5)</td>
<td>205 (24.0)</td>
<td>207 (19.8)</td>
<td>448 (22.1)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>8 (6.1)</td>
<td>52 (6.1)</td>
<td>42 (4.0)</td>
<td>102 (5.0)</td>
</tr>
<tr>
<td>SAE of ARIA-E</td>
<td>2 (1.5)</td>
<td>13 (1.5)</td>
<td>7 (0.7)</td>
<td>22 (1.1)</td>
</tr>
<tr>
<td>ARIA-H</td>
<td>40 (30.5)</td>
<td>268 (31.4)</td>
<td>285 (27.2)</td>
<td>593 (29.2)</td>
</tr>
<tr>
<td>SAE of ARIA-H</td>
<td>0</td>
<td>4 (0.5)</td>
<td>3 (0.3)</td>
<td>7 (0.3)</td>
</tr>
<tr>
<td>Macrohemorrhage</td>
<td>0</td>
<td>3 (0.4)</td>
<td>4 (0.4)</td>
<td>7 (0.3)</td>
</tr>
<tr>
<td>SAE of macrohemorrhage</td>
<td>0</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>3 (0.1)</td>
</tr>
</tbody>
</table>

*ARIA and macrohemorrhage events based on MRI or TEAE cluster.
Abbreviations: ARIA-E= amyloid-related imaging abnormalities-edema/effusions; ARIA-H= amyloid-related imaging abnormalities-hemorrhage/hemosiderin deposition; MRI= Magnetic Resonance Imaging; N, n = number of participants; SAE= serious adverse event; TEAE= Treatment-emergent adverse event.

© 2023 Eli Lilly and Company. All rights reserved
Testing ARIA-E association with 42 baseline variables

Associations with ARIA-E were identified in a post-hoc analysis using machine learning approaches, which incorporated penalized regression and decision tree-based modeling.

- **Demographic**: Age, Sex, Race, Body weight, Yrs diagnosed
- **Genetic**: APOE ε4, BIN1
- **Amyloid/Tau PET**: Tau PET SUVR, Amyloid PET Centiloid
- **Clinical**: MMSE, CDR−SB
- **MRI/vMRI**: # of microhemorrhages, Presence of cortical superficial siderosis, Level of white matter disease, Infarct (stroke, cortical, lacunar, other), Whole cortex volume, Ventricle volume, Hippocampal volume
- **Blood Pressure**: Diastolic blood pressure, Systolic blood pressure, Mean arterial pressure
- **Blood Analytes**: P-tau217, P-tau181, NFL, GFAP, CRP, Platelets, Monocytes, Lymphocytes
- **Concomitant Meds**: Antidepressants, Antihypertensives, Statins, Arthritic/Osteoarthritic, Diabetes, Antithrombotics
- **Comorbidities**: Hypertension, Depression, Myocardial infarction, Diabetes, Stroke, Dyslipidemia

Abbreviations: APOE = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities-edema/effusions; BIN1 = bridging integrator-1; CDR−SB = clinical dementia rating scale− sum of boxes; CRP = c-reactive protein; GFAP = glial fibrillary acidic protein; (v)MRI = (volumetric) magnetic resonance imaging; MMSE = mini-mental state examination; NFL = neurofilament light chain; PET = positron emission tomography; SUVR = standard uptake value ratio; WBC = white blood cells; Yrs = years.
ARIA-E Risk Factors: Factor Evaluation

Univariate Analysis

12 variables identified

Variable ranking

Most important

↑ ARIA association

APOE ε4

# of microhemorrhages

Presence of cortical superficial siderosis

Amyloid PET Centiloid

Diastolic blood pressure

Mean arterial pressure

↓ ARIA association

Antihypertensives

↑ White blood cells

History of myocardial infarction

History of hypertension

↑ Age

Diabetes medications

Logistic regression was applied and variables with FDR adjusted p-value <0.1 are listed.

Machine Learning

6 variables identified

Variable ranking

Most important

↑ ARIA association

APOE ε4

# of microhemorrhages

Presence of cortical superficial siderosis

Amyloid PET Centiloid

Mean arterial pressure

↓ ARIA association

Antihypertensives

History of myocardial infarction

History of hypertension

Diabetes medications

Machine-learning models

- LASSO shrinks less relevant variables to zero using regularization, reducing false-positive discoveries.
- Ensemble tree-based models combine multiple trees to mitigate false positives.
- Both approaches were applied, and 6 variables were selected.

Abbreviations: APOE= apolipoprotein E; ARIA= amyloid-related imaging abnormalities; FDR= false discovery rate; LASSO= least absolute shrinkage and selection operator; PET= positron emission tomography.
Key Baseline Factors Associated With ARIA-E†

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE ε4 genotype</td>
<td>non carrier</td>
<td>2.0 (1.5, 2.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>heterozygous</td>
<td>4.6 (3.3, 6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>homozygous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microhemorrhages</td>
<td>0</td>
<td>1.4 (1.0, 2.1)</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2,3, or 4</td>
<td>2.5 (1.6, 4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Superficial siderosis</td>
<td>No</td>
<td>2.2 (1.2, 4.0)</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>&lt;93</td>
<td>1.4 (1.0, 1.9)</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>≥93 &amp; &lt;97</td>
<td>1.4 (1.1, 1.8)</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>≥97 &amp; &lt;107</td>
<td>1.7 (1.2, 2.5)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>≥107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amyloid PET* Centiloids</td>
<td>tercile 1(&lt;74)</td>
<td>1.0 (0.8, 1.3)</td>
<td>0.971</td>
</tr>
<tr>
<td></td>
<td>tercile 2(≥74&lt;108)</td>
<td>1.3 (1.0, 1.7)</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>tercile 3(≥108)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>No</td>
<td>0.6 (0.5, 0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total sample size N=2021; With ARIA-E n=446. †Analyses completed with multivariate logistic regression using TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2, and Addendum populations. *Cerebellum used as reference region. ‡Pseudo R-square=7.44%.

Abbreviations: APOE= apolipoprotein E; ARIA-E= amyloid-related imaging abnormalities-edema/effusions; CI= confidence interval; CL= Centiloids; mm Hg= millimeter of mercury; MAP= mean arterial pressure; PET= positron emission tomography.
ARIA-E in Participants by Genotype

Multivariate logistic analysis based on 10-fold cross-validation using the combined data.

Abbreviations: APOE = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities—edema and effusions; N = total number of participants; n = number of participants per category; P = p-value.

ARIA-E frequency increases across APOE ε4 genetic type, consistent with other amyloid-targeting agents.

© 2023 Eli Lilly and Company. All rights reserved
ARIA-E in Participants With Baseline Microhemorrhages

Multivariate logistic analysis based on 10-fold cross-validation using the combined data.
Abbreviations: APOE= apolipoprotein E; ARIA-E= amyloid-related imaging abnormalities− edema and effusions; N= total number of participants; n= number of participants per category; P= p-value.

© 2023 Eli Lilly and Company. All rights reserved
ARIA-E in participants with baseline superficial siderosis

ARIA-E Frequency

% of Participants with ARIA-E

Not Present | Present
---|---
Non carrier | ε4 Heterozygous | ε4 Homozygous

12% | 23% | 41% | 29% | 35% | 69%

Presence of Superficial Siderosis

n | 81 | 234 | 110 | 5 | 7 | 9
N | 665 | 1037 | 269 | 17 | 20 | 13

ARIA-E frequency increases within APOE ε genotypes with the presence of baseline superficial siderosis.

Multivariate logistic analysis based on 10-fold cross-validation using the combined data. Abbreviations: APOE= apolipoprotein E; ARIA-E= amyloid-related imaging abnormalities-edema/effusions; N= total number of participants; n= number of participants per category; P= p-value.

© 2023 Eli Lilly and Company. All rights reserved
ARIA-E in Participants With Baseline Antihypertensive Medication use

ARIA-E Frequency decreases with use of antihypertensive medications.

Multivariate logistic analysis based on 10-fold cross-validation using the combined data. Abbreviations: ARIA-E= amyloid-related imaging abnormalities-edema/effusions; N= total number of participants; n= number of participants per category; P= p-value.
The probability of ARIA-E was estimated using univariate logistic regression modeling and included baseline amyloid Centiloid as a covariate.

Abbreviations: ARIA-E= amyloid-related imaging abnormalities-edema/effusions.
Conclusions

- ARIA-E frequency was assessed across 2031 donanemab exposures in populations with concomitant medications and comorbid conditions representative of the US Alzheimer’s disease Medicare population.¹,²

- Machine-learning approaches suggest 6 independent baseline variables associated with ARIA-E frequency: APOE ε4 genotype, number of microhemorrhages, superficial siderosis, mean arterial pressure, amyloid PET Centiloids, and antihypertensive medication use.

- ARIA-E frequency increases within & across APOE ε4 genotype with presence and increase in baseline microhemorrhages and/or presence of superficial siderosis.

- Predominant ARIA risk factors are consistent with pre-existing cerebral amyloid angiopathy.

- These post-hoc exploratory analyses are hypothesis-generating for future work in validation across amyloid-targeting therapies and may yield modifiable factors.

---

¹ Schroeder et al. Characterize demographics, comorbidities and co-medications in newly diagnosed United States (US) Alzheimer’s Disease patients using Medicare claims AAIC. 2023.

² Publication submitted.

Abbreviations: APOE= apolipoprotein E; ARIA-E= amyloid-related imaging abnormalities-edema/effusions

© 2023 Eli Lilly and Company. All rights reserved