Insights from TRAILBLAZER-ALZ 2 (Donanemab): Potential Clinical Translation

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Disclosures

- Jennifer Zimmer, Alessandro Biffi, Emily C Collins, Alette Wessels, Melissa Veenhuizen, Cynthia Evans, Ming Lu, JonDavid Sparks, Chakib Battioui, Sergey Shcherbinin, Paul A Ardayfio, Dawn Brooks, John Sims, and Mark Mintun are employees of Eli Lilly and Company and minor shareholders of Eli Lilly and Company.
- Robert Alexander reports consulting income from Alkermes, Boehringer- Ingelheim, Biohaven, and Cardiff University Medicines Discovery Unit, Immunobrain, Lundbeck, Novartis, Novo Nordisk, Reunion Neuro, T3D Therapeutics, and Vigil Neuro. Banner is a collaborator with Eli Lilly on the TRAILBLAZER-ALZ 3 trial.

Today's session

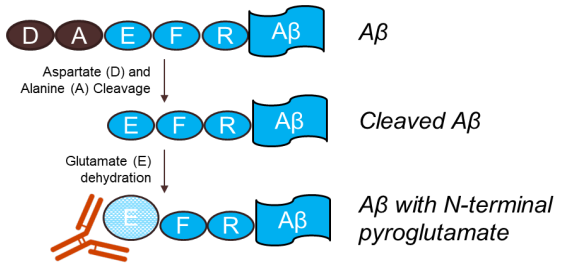
Topic	Presenter
TRAILBLAZER-ALZ 2: Clinical Efficacy	Jennifer Zimmer
Managing ARIA Risk	Alessandro Biffi
Limited Duration Dosing	Emily Collins
Next Steps	Robert Alexander
Question/Answer Session	Robert Alexander, Mark Mintun (moderators)

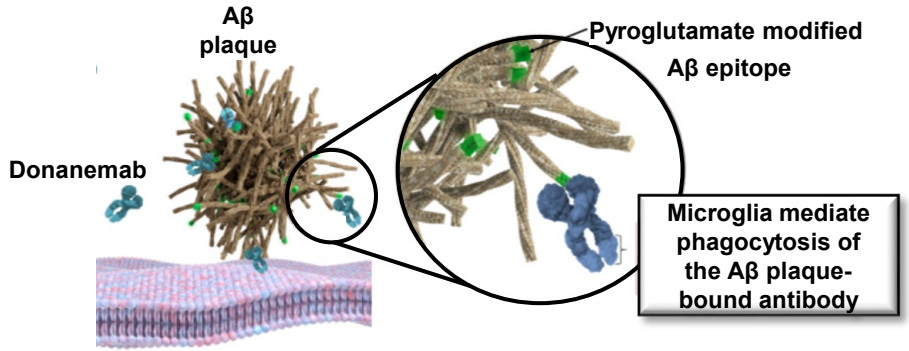
Insights from TRAILBLAZER-ALZ 2 (Donanemab): Clinical Efficacy

Jennifer Zimmer, MD
Associate Vice President, Neuroscience Clinical Development
Eli Lilly and Company

Donanemab mechanism of action

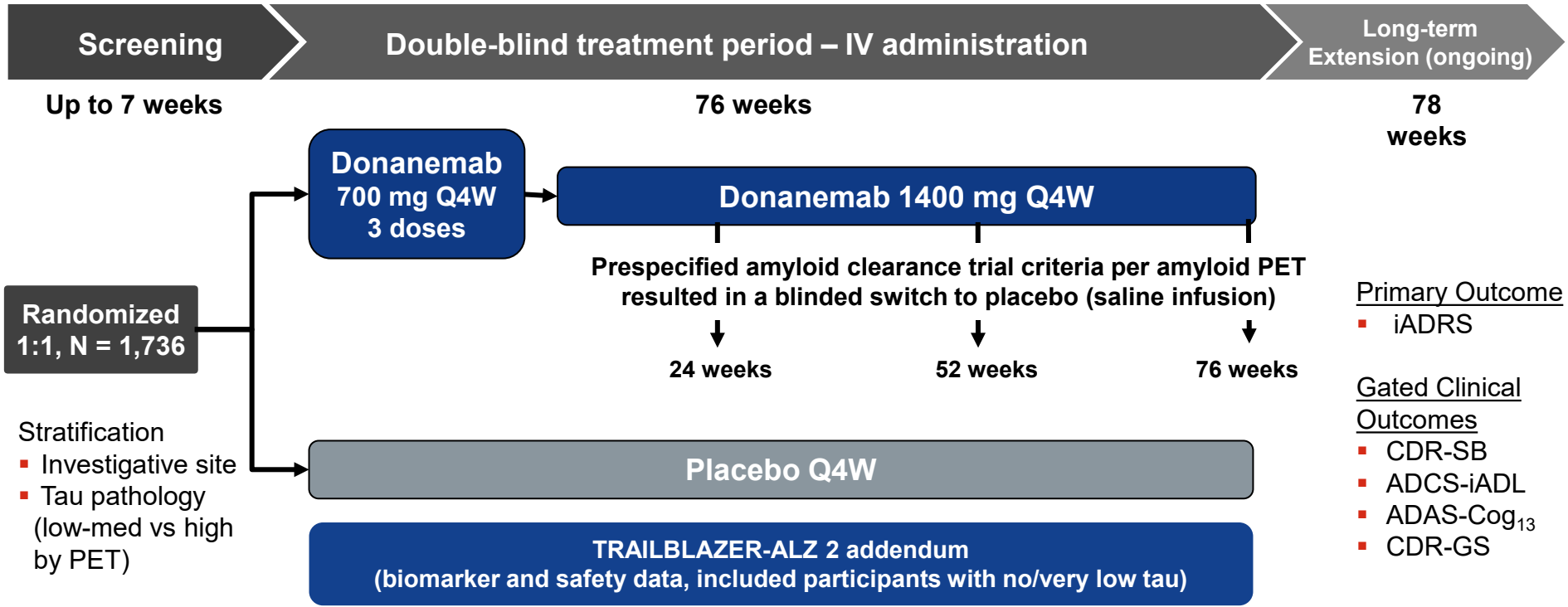
Donanemab is an IgG1 monoclonal antibody directed against an insoluble, modified, N-terminal truncated form of amyloid-β (N3pG) present only in brain amyloid plaques





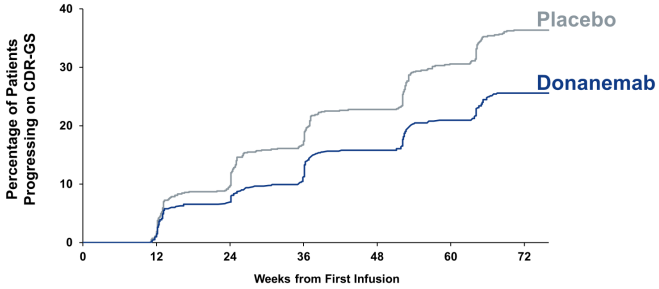
Abbreviations: Aβ=amyloid beta

TRAILBLAZER-ALZ 2 study design

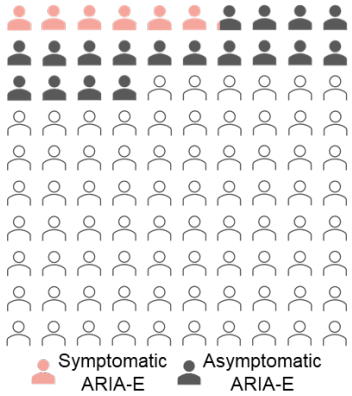


Abbreviations: ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale–13-item Cognitive subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living Inventory; CDR-GS = Clinical Dementia Rating Global Score; CDR-SB = Clinical Dementia Rating–Sum of Boxes; iADRS = Integrated Alzheimer's Disease Rating Scale; PET = positron emission tomography; Q4W = every 4 weeks

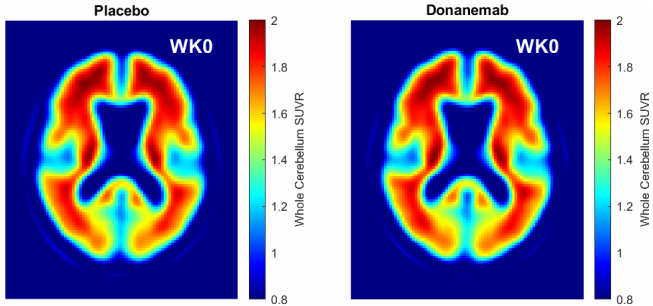
Summary of TRAILBLAZER-ALZ 2 highlights



- Donanemab treatment reduced risk of progression to the next stage of Alzheimer's disease by **37%** by CDR-GS at 76 weeks in the overall population



- ARIA-E was a common side-effect (**24%** of donanemab-treated participants)
- **Three** out of 853 participants randomized to the donanemab arm died from ARIA-related complications

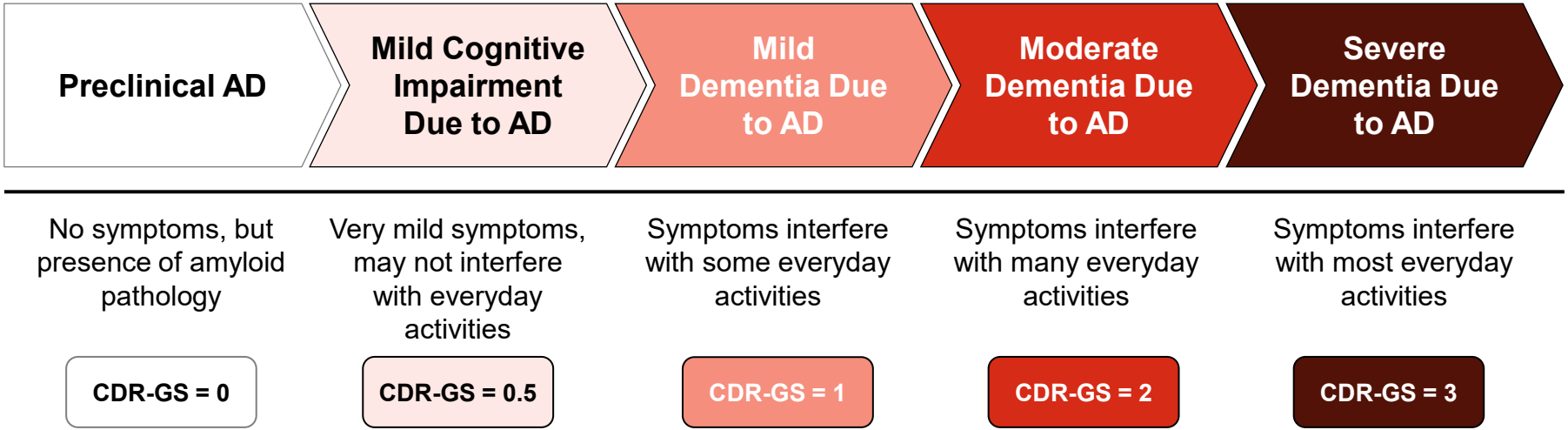


- Donanemab treatment reduced amyloid plaque by **87 Centiloids** in 76 weeks
- **69%** of participants switched from donanemab to placebo by 76 weeks based on trial amyloid reduction criteria

Sims JR et al. JAMA. 2023 doi: 10.1001/jama.2023.13239.
Abbreviations: ARIA-E = amyloid-related imaging abnormalities of edema/effusion; CDR-GS = Clinical Dementia Rating Global Score

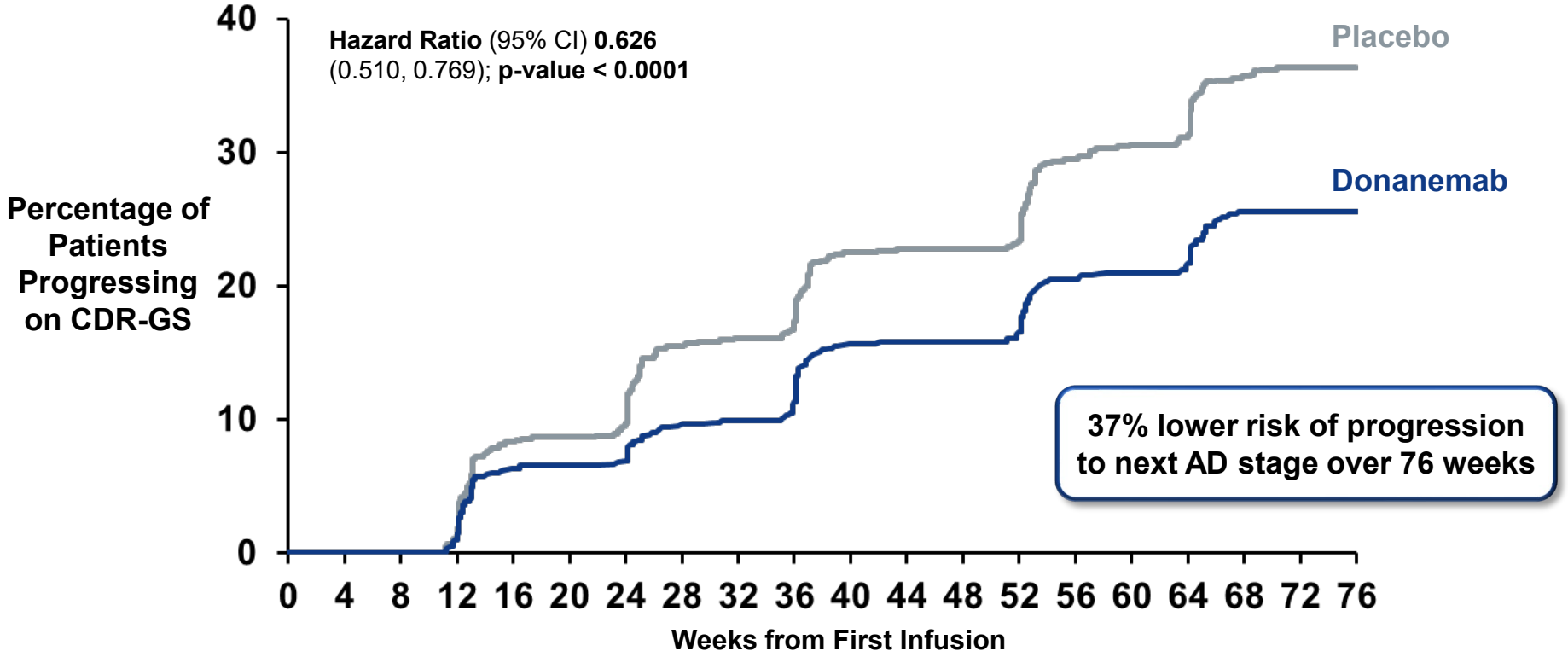
Slowing progression to the next clinical stage

Patients assessed by CDR-Global Score every 3 months for progression to next stage of AD



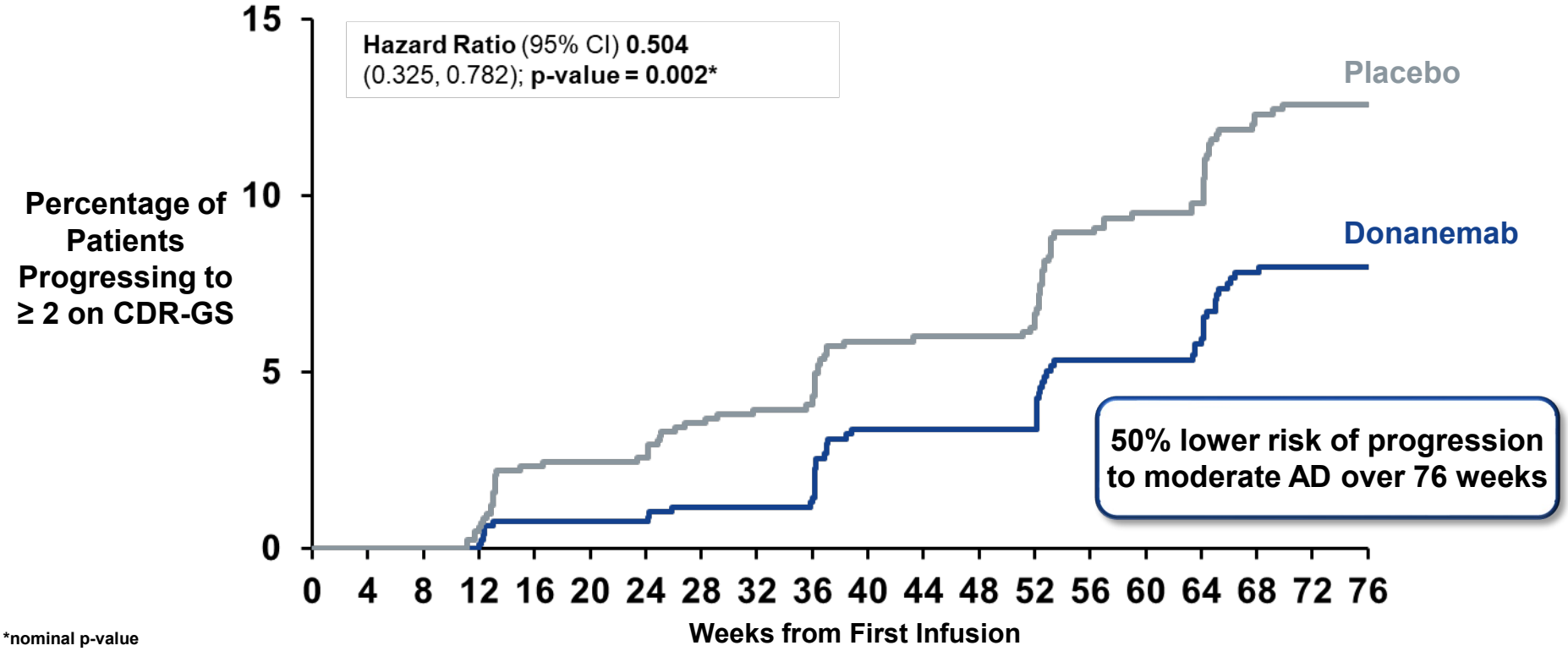
Alzheimer's Association 2022
Abbreviations: AD = Alzheimer's disease; CDR-GS = Clinical Dementia Rating Global Score

Donanemab treatment lowered risk of AD progression: CDR-Global Score (overall population)



Abbreviations: AD = Alzheimer's disease; CDR-GS = Clinical Dementia Rating Global Score

Donanemab treatment lowered risk of progression to moderate AD: CDR-Global Score (overall population)



*nominal p-value

Abbreviations: AD = Alzheimer's disease; CDR-GS = Clinical Dementia Rating Global Score

Fewer donanemab patients progressed to next clinical stage compared to placebo (first CDR-GS worsening)

	Donanemab	Placebo	
CDR-GS shift from baseline*	**Participants progressing to next clinical stage, n/N (%)**	**Participants progressing to next clinical stage, n/N (%)**	**P-value†**
From 0 to 0.5	1/2 **(50)**	3/4 **(75)**	1.0
From 0.5 to 1	134/502 **(27)**	202/521 **(39)**	<0.0001
From 1 to 2	51/292 **(18)**	82/302 **(27)**	0.0057
From 2 to 3	0/23	1/24 **(4)**	1.0

***Shift represents change in CDR-GS from baseline at 2 consecutive visits. Drop-outs not accounted for in this analysis. † nominal p-value**

Abbreviations: CDR-GS = Clinical Dementia Rating Global Score

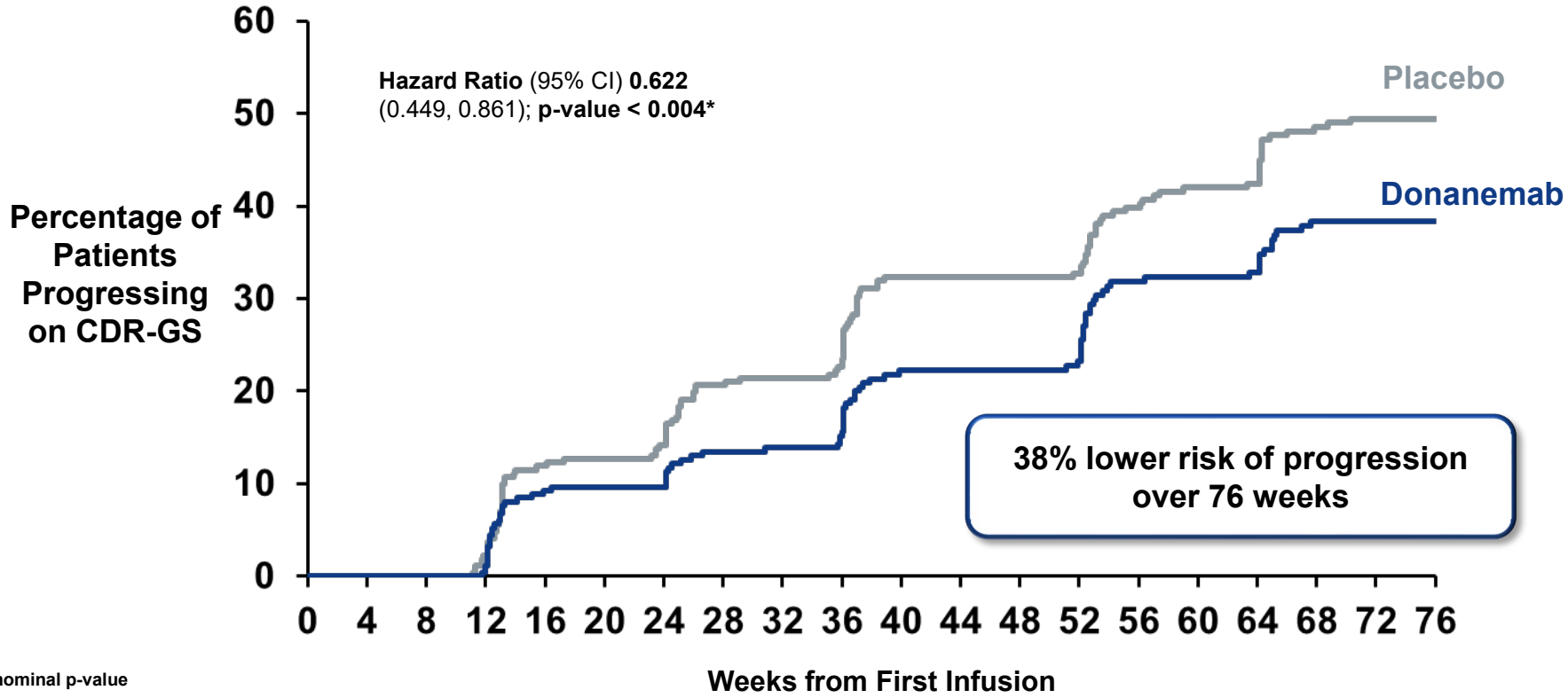
Efficacy across tau populations

	Overall*		Low-Medium Tau		High Tau†	
	Donanemab N = 860	Placebo N = 876	Donanemab N = 588	Placebo N = 594	Donanemab N = 271	Placebo N = 281
CDR-SB (MMRM)						
Change from baseline	1.72	2.42	1.20	1.88	2.64	3.34
Difference from placebo **% slowing** **p-value**	**-0.70** 29% p < 0.001		**-0.67** 36% p < 0.001		**-0.69** 21% p < 0.01	
CDR-GS Risk of Progressing‡						
Reduced risk of advancing to the next stage of disease at 18 months (% risk reduction)	**37%** p < 0.0001		**39%** p < 0.001		**38%** p < 0.01§	

***TRAILBLAZER-ALZ 2 Overall Population; †High tau was a subpopulation that was not statistically powered in TRAILBLAZER-ALZ 2; ‡Time-to-event analysis; § nominal p-value**

Abbreviations: CDR-GS = Clinical Dementia Rating Global Score; CDR-SB = Clinical Dementia Rating–Sum of Boxes; MMRM = Mixed Model for Repeated Measures; N, n = number of participants

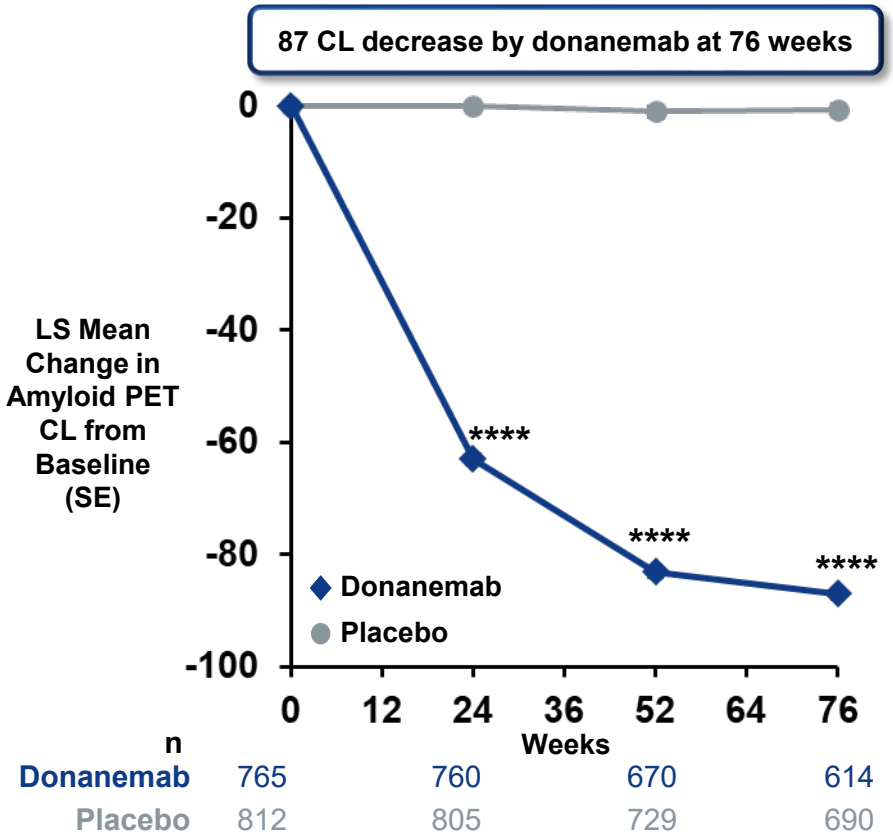
Donanemab treatment lowered risk of progression in high tau group



*nominal p-value

Abbreviations: CDR-GS = Clinical Dementia Rating Global Score

Amyloid reduction and effect in disease-relevant biomarkers supported donanemab use in all baseline tau participant groups



****p < 0.0001; Overall Population

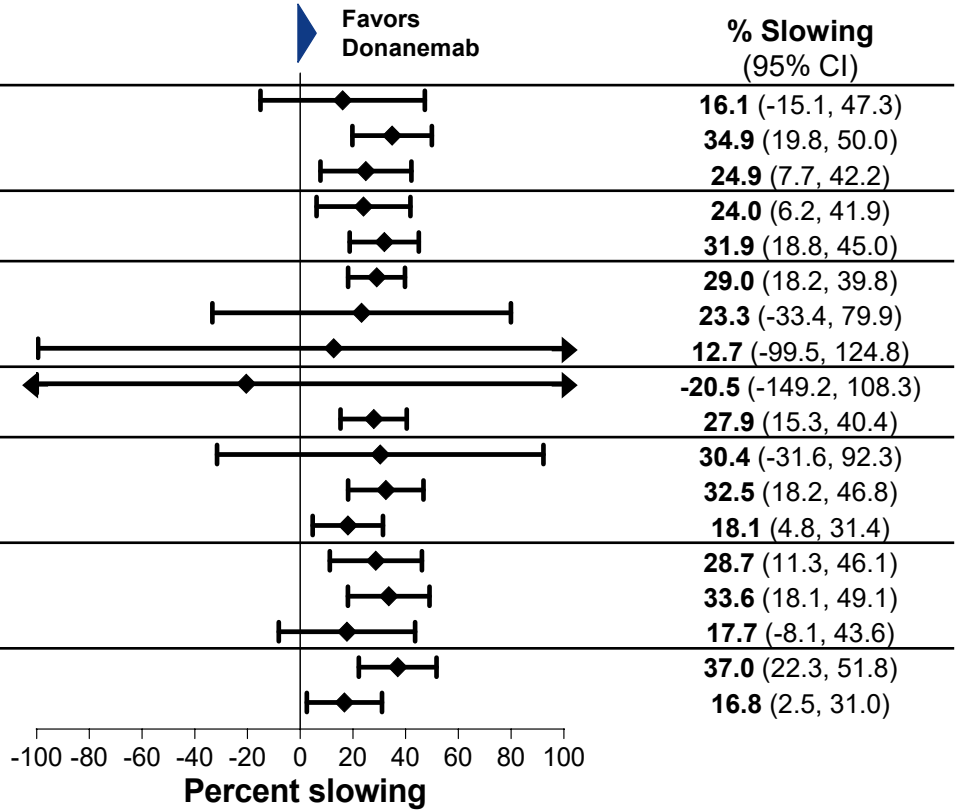
Percent* change from baseline at 76 weeks	No / Very-Low Tau† N (195-203)	Low – Medium Tau N (395-433)	High Tau N (173-181)
Amyloid reduction	86%	85%	80%
P-tau217 reduction	56%	39%	33%
GFAP reduction	22%	21%	18%

*Percentages are based on estimated mean changes from MMRM analyses
† Data from TRAILBLAZER-ALZ 2 addendum, which collected biomarker and safety data in amyloid positive participants and included participants with no/very low tau.

Abbreviations: CL = Centiloids; GFAP = glial fibrillary acidic protein; LS = least square; MMRM = mixed model repeated measures; N, n = number of participants; PET = positron emission tomography; P-tau217 = phosphorylated tau217; SE = standard error

CDR-SB: Consistent Efficacy Observed Across Subgroups (Overall Population)

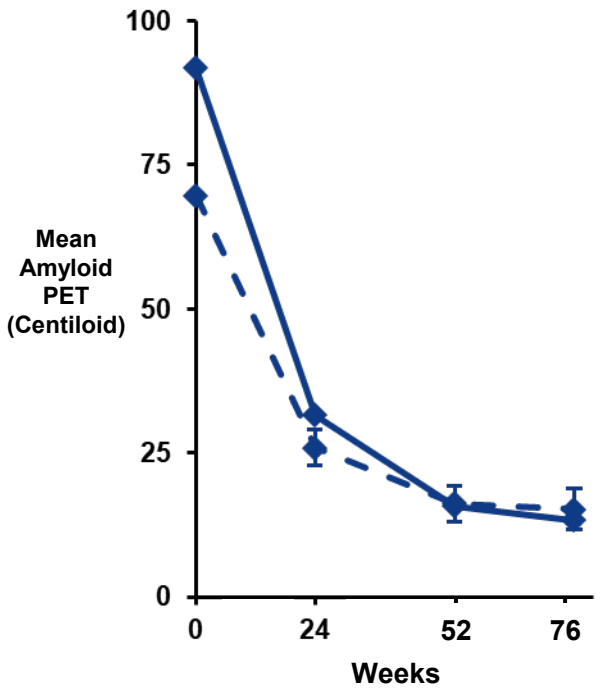
		Placebo	Donanemab	% Slowing (95% CI)
Age	< 65	73	64	**16.1** (-15.1, 47.3)
	65-74	328	296	**34.9** (19.8, 50.0)
	≥ 75	271	238	**24.9** (7.7, 42.2)
Sex	Male	294	262	**24.0** (6.2, 41.9)
	Female	378	336	**31.9** (18.8, 45.0)
Race	White	615	539	**29.0** (18.2, 39.8)
	Asian	39	42	**23.3** (-33.4, 79.9)
	Black/African American	17	15	**12.7** (-99.5, 124.8)
Ethnicity	Hispanic/Latino	22	23	**-20.5** (-149.2, 108.3)
	Non-Hispanic/Latino	465	403	**27.9** (15.3, 40.4)
Clinical Stage	MCI (≥27)	105	108	**30.4** (-31.6, 92.3)
	Mild AD (20-26)	421	370	**32.5** (18.2, 46.8)
	Moderate AD (<20)	145	115	**18.1** (4.8, 31.4)
APOE ε4 Genotype	Noncarrier	184	181	**28.7** (11.3, 46.1)
	Heterozygote	365	320	**33.6** (18.1, 49.1)
	Homozygote	123	97	**17.7** (-8.1, 43.6)
Tau PET Category	Low/medium	459	424	**37.0** (22.3, 51.8)
	High	212	174	**16.8** (2.5, 31.0)



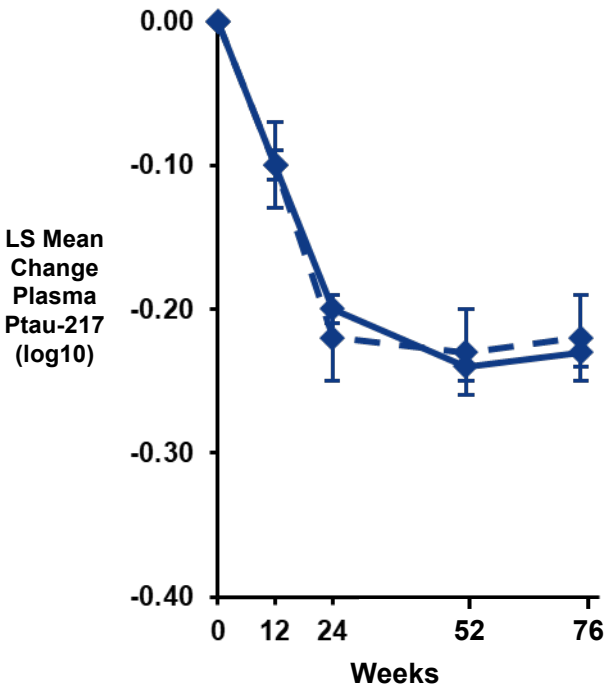
Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E; CDR-SB = Clinical Dementia Rating – Sum of Boxes; MCI = mild cognitive impairment; PET = positron emission tomography

Amyloid PET, plasma P-tau217, and plasma GFAP post-treatment change similar in Hispanic/Latino patients*

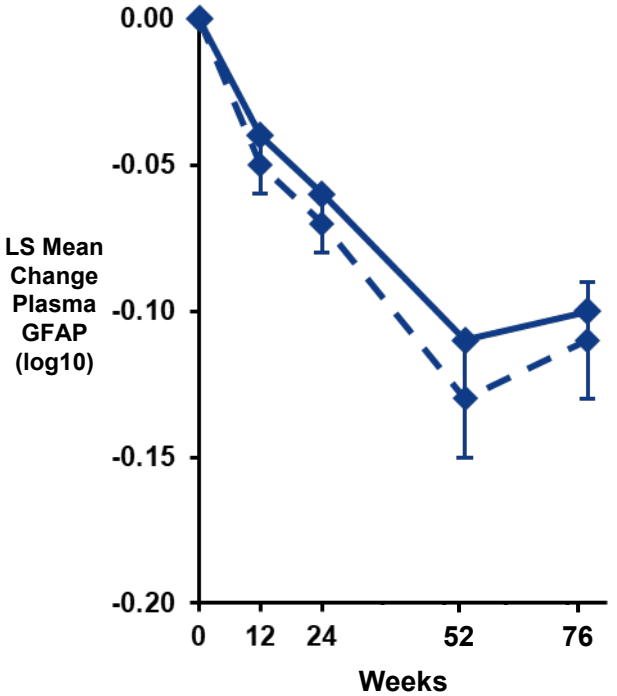
Amyloid PET



Plasma P-tau217



Plasma GFAP



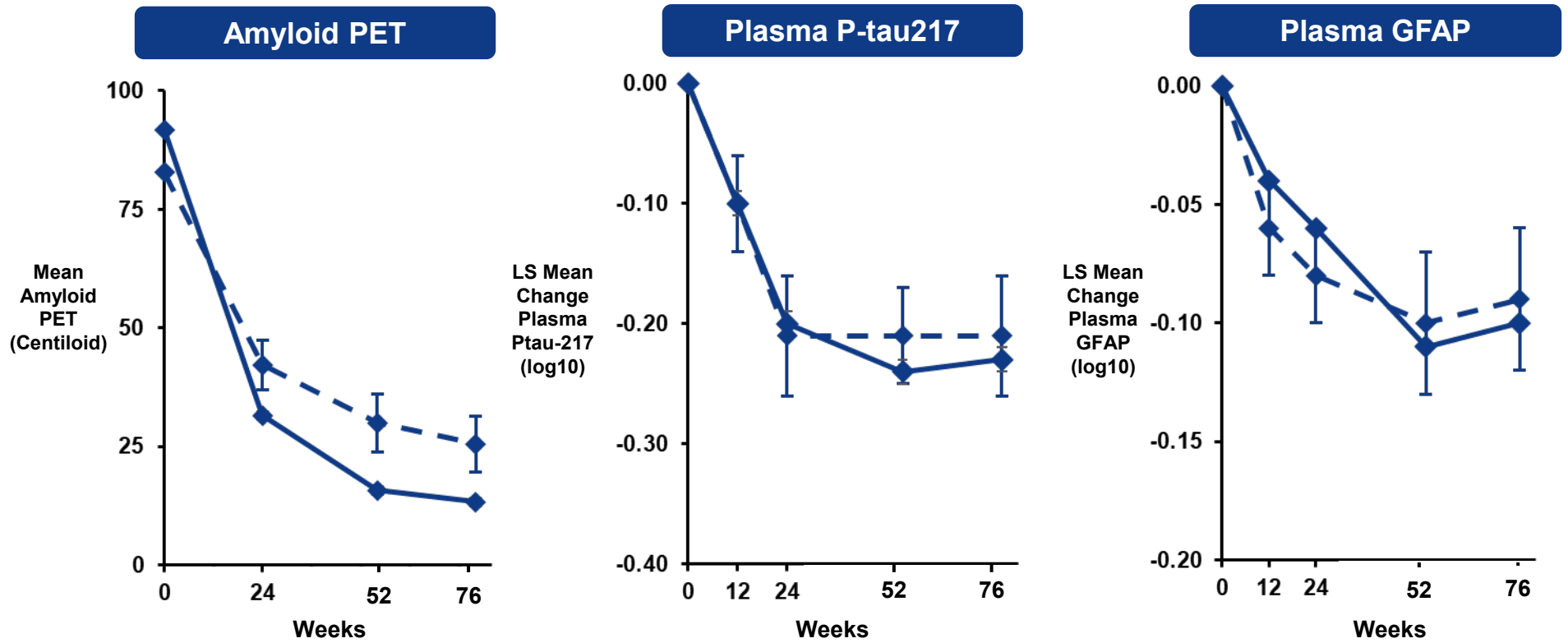
*analyses based on pooled data from TRAILBLZER-ALZ 2 and TRAILBLAZER-ALZ 2 safety addendum

Donanemab – Hispanic/Latino

Donanemab

Abbreviations: GFAP = Glial fibrillary acidic protein; LS = least square; PET = positron emission tomography

Amyloid PET, plasma P-tau217, and plasma GFAP post-treatment change similar in Black/African American patients*



*analyses based on pooled data from TRAILBLZER-ALZ 2 and TRAILBLAZER-ALZ 2 safety addendum

Abbreviations: GFAP = Glial fibrillary acidic protein; LS = least square; PET = positron emission tomography

Donanemab treatment lowered the risk of Alzheimer's disease progression in TRAILBLAZER-ALZ 2

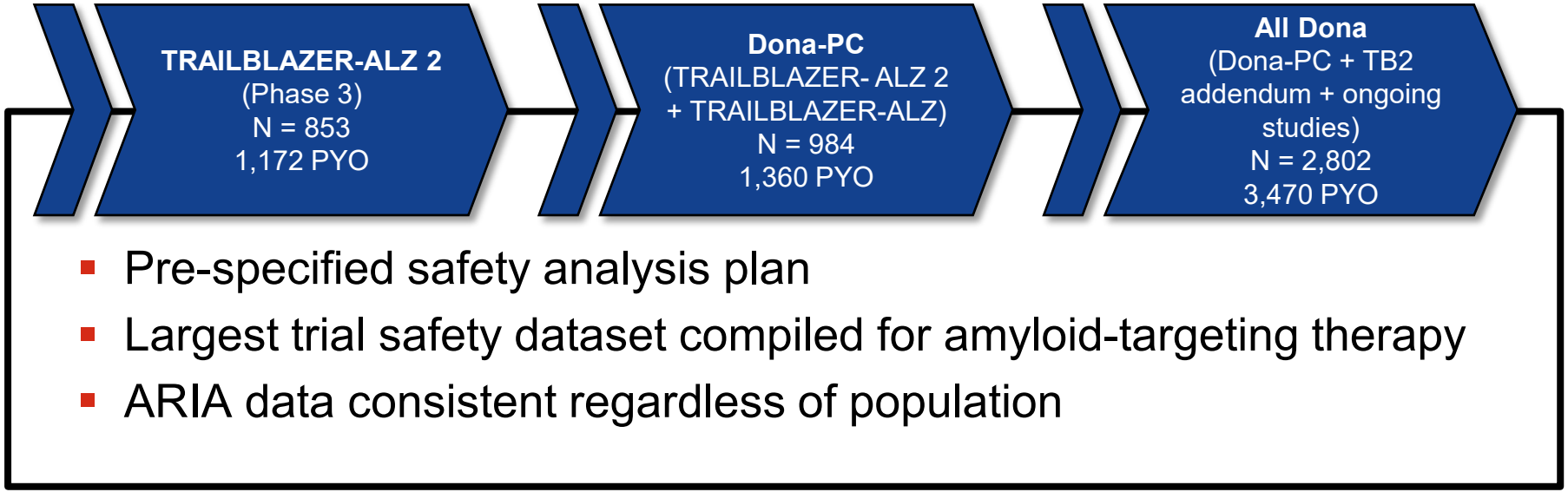
- Lower risk of disease progression across all tau populations on the CDR-GS, a measure of cognition and function
- Outcome measures of clinical efficacy were consistent across subgroups
- Biomarker data is consistent across no/very low, low-medium, and high tau
- Biomarker measures were consistent among underrepresented populations and the overall, pooled donanemab dataset

Abbreviations: CDR-GS = Clinical Dementia Rating Global Score.

Insights from TRAILBLAZER-ALZ 2 (Donanemab): Managing ARIA Risk

Alessandro Biffi, MD
Associate Vice President, Neuroscience Medical Affairs
Eli Lilly and Company

ARIA evaluated in three large populations



Abbreviations: ARIA = amyloid-related imaging abnormalities; PC = placebo controlled; PYO = patient years of observation; TB2 = TRAILBLAZER-ALZ 2

ARIA is a class-related safety risk associated with amyloid removal

ARIA class-related symptoms

Frequent symptoms

Headache | Confusion | Nausea / Dizziness

Less frequent symptoms

Gait Disturbance | Neuropsychiatric Symptoms | Visual Symptoms

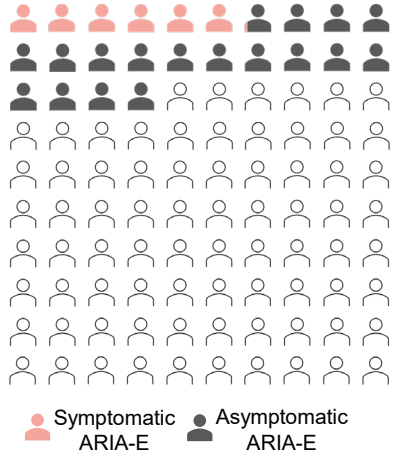
Least frequent symptoms:

Seizure • Focal deficits • Encephalopathy

ARIA-related focal neurologic deficits can mimic an ischemic stroke

Donanemab

ARIA-E in 24% of donanemab-treated participants (TRAILBLAZER-ALZ 2)



Adapted from: Sims JR, et al. *JAMA*. 2023;330(6):512-527.

- ARIA-E events were largely mild to moderate radiographically (93%)
  - 18% asymptomatic ARIA-E
  - 6% symptomatic ARIA-E
- 1.5% of donanemab-treated participants had serious ARIA-E events
- 3 participants (0.4%) had serious ARIA events resulting in death

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

ARIA frequency in donanemab clinical trials

Event*, n (%)	Placebo (N=874)	Donanemab (N=853)
Any ARIA (-E or -H)	130 (14.9)	314 (36.8)
Any SAE of ARIA	0 (0)	14 (1.6)
ARIA-E	18 (2.1)	205 (24.0)
Asymptomatic	17 (1.9)	153 (17.9)
Symptomatic	1 (0.1)†	52 (6.1)
SAE of ARIA-E	0 (0)	13 (1.5)
ARIA-H	119 (13.6)	268 (31.4)
SAE of ARIA-H	0 (0)	4 (0.5)
Isolated ARIA-H	108 (12.4)	108 (12.7)
Macrohemorrhage	2 (0.2)	3 (0.4)
SAE of Macrohemorrhage	1 (0.1)	1 (0.1)

ARIA by APOE Status %	Placebo	Donanemab
ARIA-E		
Non-carrier	0.8%	15.7%
APOE ε3/ε4 carrier	1.9%	22.8%
APOE ε4/ε4 carrier	3.4%	40.6%
ARIA-H		
Non-carrier	11.2%	18.8%
APOE ε3/ε4 carrier	12.0%	32.3%
APOE ε4/ε4 carrier	20.5%	50.3%

- **ARIA is common, with highest frequency among APOE ε4 homozygotes**
- **Macrohemorrhage is uncommon**

***ARIA and macrohemorrhage events based on MRI or treatment-emergent AE cluster**
†One placebo-treated participant had ARIA-E during the placebo-controlled period; however, the participant developed symptoms during the long-term extension period

Abbreviations: APOE = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities-edema/effusions; ARIA-H = amyloid-related imaging abnormalities-hemorrhage/hemosiderin deposition; N, n = number of participants; SAE = serious adverse event

Majority of rechallenges were not associated with recurrent ARIA

In participants receiving donanemab*

- The majority of those with ARIA-E had only one episode of ARIA-E (n = 182, 18.5% of all donanemab-treated participants)
- 68% were re-dosed following any ARIA-E event
  - 70% of those did not have ARIA-E re-occur
- 98% of initially asymptomatic ARIA-E were asymptomatic on recurrence
- ~80% of initially symptomatic ARIA-E were asymptomatic on recurrence
- Majority of recurrent ARIA-E were mild to moderate in severity

***includes donanemab-treated patients from TB-ALZ and TB2, as well as additional donanemab-treated patients from other ongoing studies and the TB2 addendum**

Abbreviations: ARIA-E = amyloid-related imaging abnormalities-edema/effusions; TB-ALZ = TRAILBLAZER-ALZ; TB2 = TRAILBLAZER-ALZ 2

Machine learning testing ARIA association with 42 baseline variables

Associations with ARIA-E and ARIA-H were identified in a post-hoc analysis using machine learning approaches

Demographic

Age
Sex
Race
Body weight
Yrs diagnosis

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
WBC
Platelets
Monocytes
Lymphocytes

Concomitant Meds

Antidepressants
Antihypertensives
Statins
Arthritic/Osteoarthritic
Diabetes
Antithrombotics

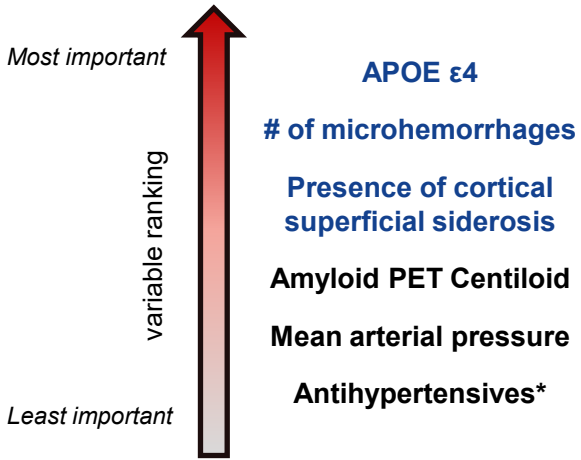
Comorbidities

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; MMSE = mini-mental state examination; NFL = neurofilament light chain; PET = positron emission tomography; SUVR = standard uptake value ratio; WBC = white blood cells. C_2N plasma P-tau217 and Quanterix Simoa® GFAP, NFL and P-tau181 assays.

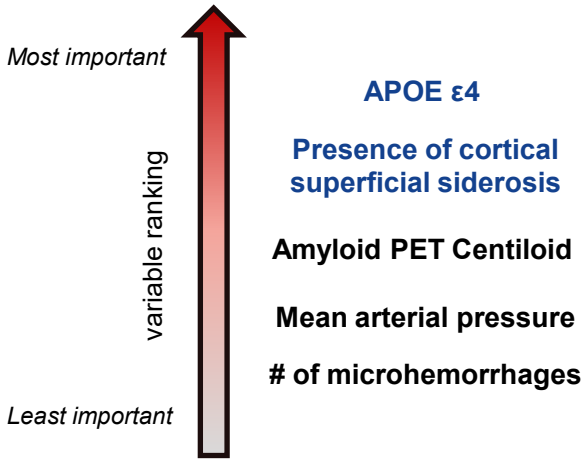
Machine learning models for evaluating ARIA risk factors

ARIA-E predictive risk factors
treatment arm analysis
42 variables analyzed and 6 identified



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.

ARIA-H predictive risk factors
2-arm analysis
42 variables analyzed and 5 identified

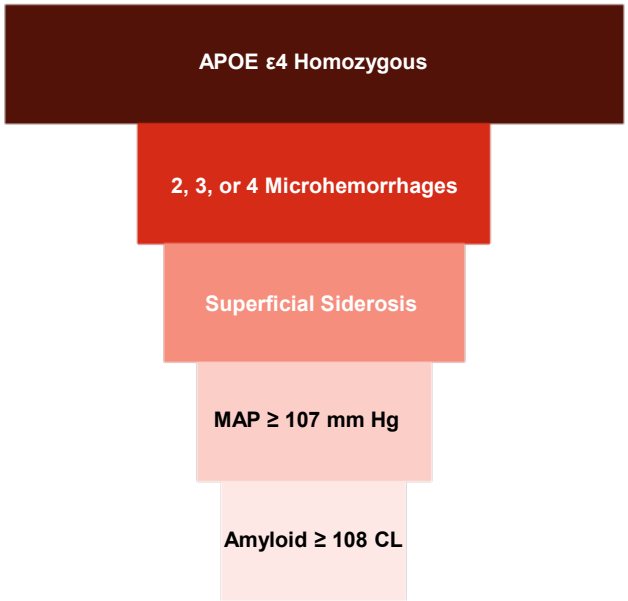


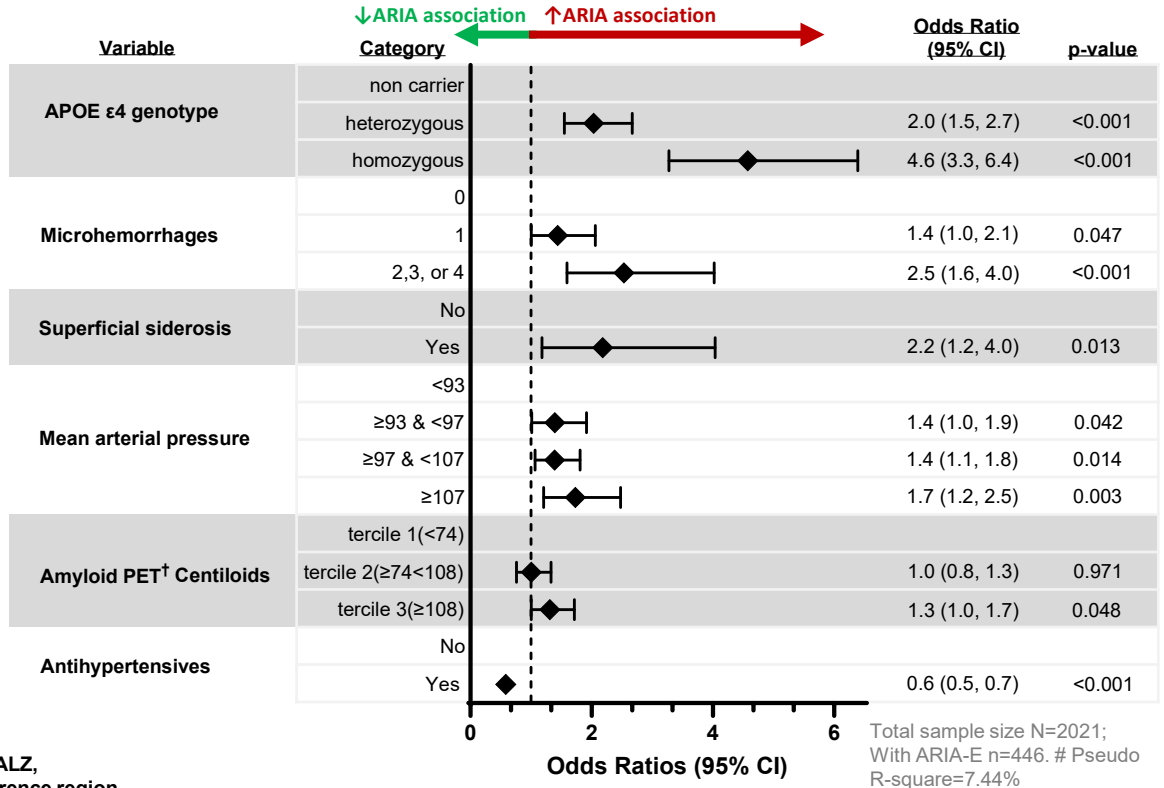
Machine-learning models
- Causal forest estimates the heterogeneous treatment effects (HTEs).
- Treatment-Specified Detection Tool (TSDT) builds multiple decision trees and aggregate their results using resampling techniques to mitigate false positives.

***antihypertensives were identified as a protective factor**

Abbreviations: APOE = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities- edema/effusions; ARIA-H = amyloid-related imaging abnormalities-hemorrhage/hemosiderin deposition; FDR = false discovery rate; LASSO = least absolute shrinkage and selection operator; PET = positron emission tomography.

APOE ε4 genotype and baseline MRI are the greatest contributing factors to ARIA-E*



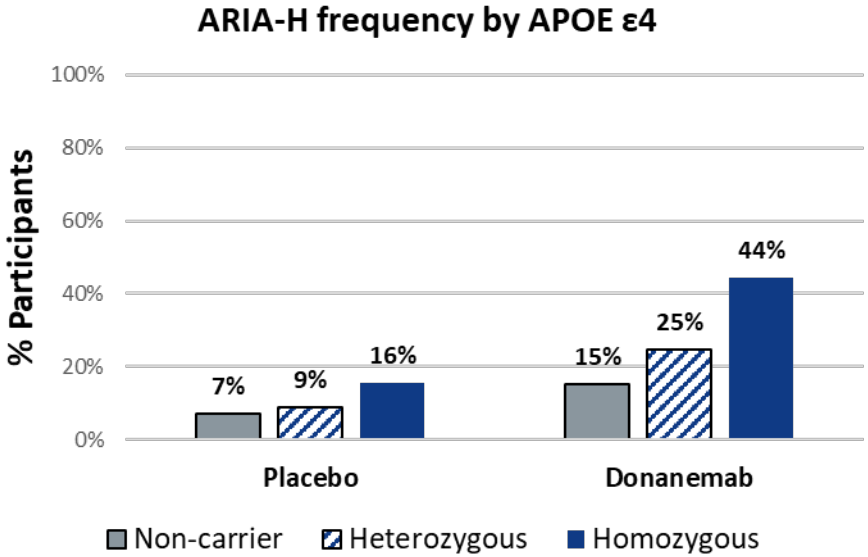


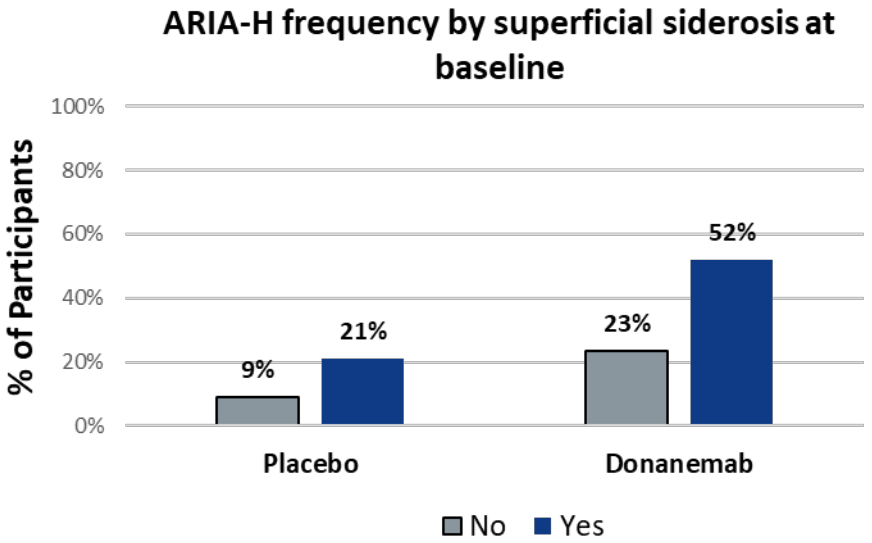
Total sample size N=2021; With ARIA-E n=446. # Pseudo R-square=7.44%

***Analyses completed with multiple logistic regression using TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2, and Addendum populations. †Cerebellum used as reference region**

Abbreviations: *APOE* = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities- edema/effusions; CI = confidence interval; MAP = Mean arterial pressure; PET= positron emission tomography.

APOE ε4 genotype and superficial siderosis are greatest risk factors for ARIA-H





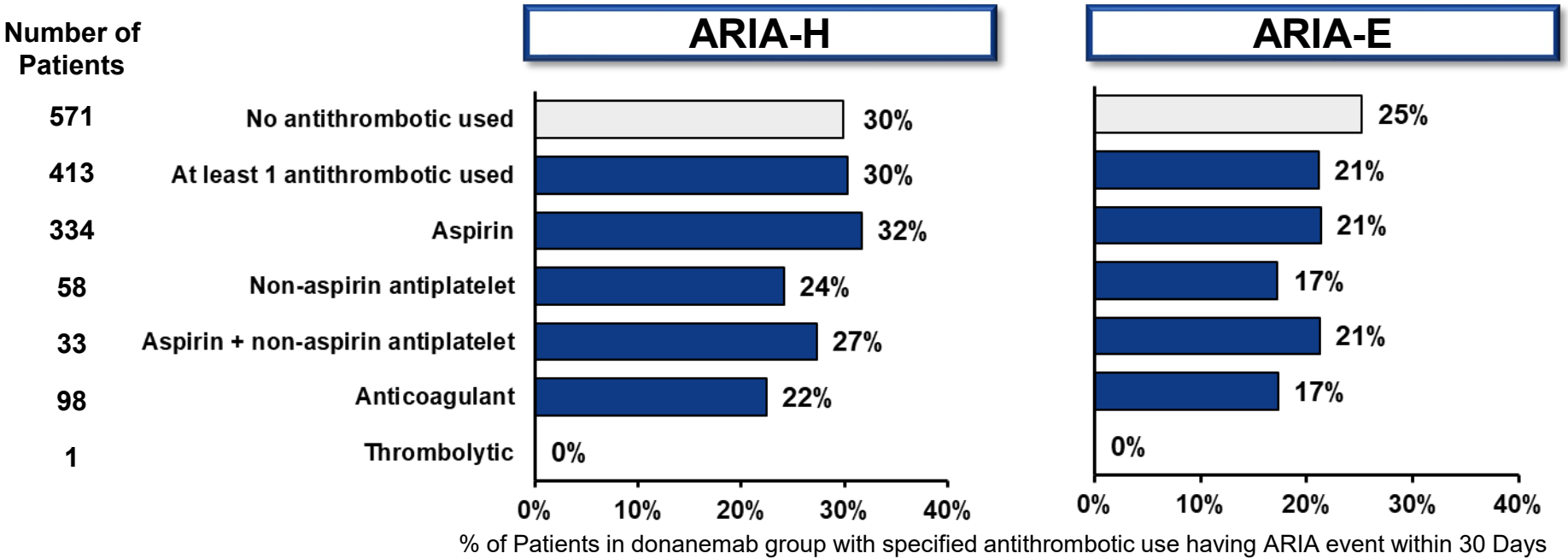
APOE ε4	Placebo N (%)	Donanemab N (%)
Non-carrier	282 (7%)	682 (15%)
Heterozygous	538 (9%)	1057 (25%)
Homozygous	174 (16%)	282 (44%)

Presence of Superficial Siderosis	Placebo N (%)	Donanemab N (%)
No	960 (9%)	1981 (23%)
Yes	38 (21%)	50 (52%)

Abbreviations: APOE = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities- edema/effusions; ARIA-H = amyloid-related imaging abnormalities-hemorrhage/hemosiderin deposition; N, n = number of participants

Antithrombotics did not increase risk for ARIA

In Dona-PC patients, 10% used anti-coagulants and 40% used anti-platelets



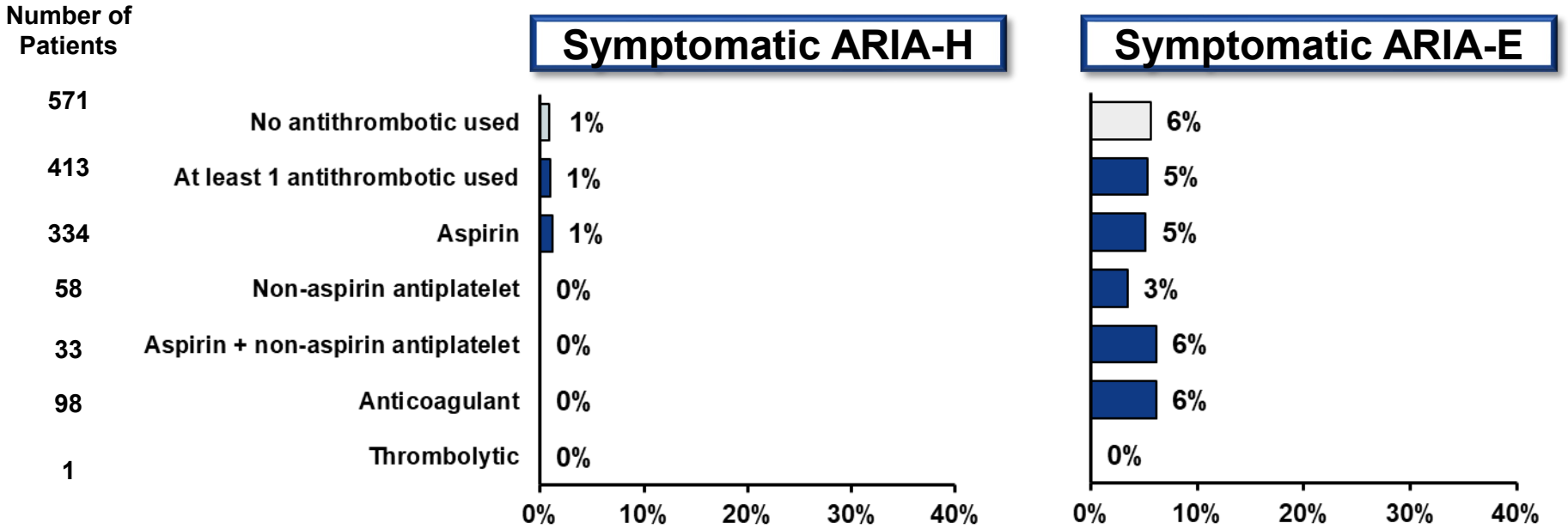
% of Patients in donanemab group with specified antithrombotic use having ARIA event within 30 Days

No evidence of interaction between antithrombotic medications and APOE ε4 genotype

Abbreviations: APOE = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities- edema/effusions; ARIA-H = amyloid-related imaging abnormalities- hemorrhage/hemosiderin deposition; Dona-PC = TRAILBLAZER- ALZ 2 + TRAILBLAZER-ALZ

Antithrombotics did not increase symptomatic ARIA

In Dona-PC patients, 10% used anti-coagulants and 40% used anti-platelets



% of Patients in donanemab group with specified antithrombotic use having ARIA event w/in 30 days of use

Abbreviations: APOE = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities-edema/effusions; ARIA-H = amyloid-related imaging abnormalities- hemorrhage/hemosiderin deposition; Dona-PC = TRAILBLAZER- ALZ 2 + TRAILBLAZER-ALZ

ARIA risk factors* and multifaceted risk management approach

Risk consistently driven by:

ARIA-E

- APOE ε4 genotype
- Number of baseline microhemorrhages
- Presence of superficial siderosis at baseline

ARIA-H

- APOE ε4 genotype
- Presence of superficial siderosis at baseline

- **Limited Impact on ARIA**
  - Baseline Amyloid
  - Mean arterial pressure
- **No Consistent Impact on ARIA**
  - Demographics
  - Body weight
  - Time since onset of AD symptoms
  - Baseline MMSE
  - Baseline tau PET
  - Baseline white matter disease
  - Medication use (acetylcholinesterase, antithrombotics)

* As assessed by machine learning

ARIA risk management

- Identifying higher risk patients prior to treatment
- Adhering to MRI monitoring schedule
- Dose titration, interruption, or discontinuation
- Use of corticosteroids for serious or symptomatic ARIA

Abbreviations: AD = Alzheimer's disease; APOE= apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities- edema/effusions; ARIA-H = amyloid-related imaging abnormalities- hemorrhage/ hemosiderin deposition; MMSE= mini-mental state examination; PET = positron emission tomography.

ARIA risk can be managed during treatment with donanemab

- Most ARIA cases in clinical trials of donanemab were asymptomatic
- Recurrent ARIA-E was uncommon, and the majority of rechallenges were not associated with recurrent ARIA
- ARIA occurred more frequently among carriers of APOE ε4
- APOE genotype and pre-treatment MRI provide the greatest insights into underlying ARIA risk
- Use of anti-thrombotic medications was not associated with higher frequency of ARIA (including symptomatic ARIA)
- ARIA is appropriately addressed by:
  - identification of high-risk patients
  - adherence to monitoring schedule
  - dosing titration, interruption, or discontinuation

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

Other safety considerations: infusion related reactions

- Infusion related reactions (IRRs) reported by 9% of donanemab-treated patients
  - 94% mild to moderate
  - Majority occurred during infusion or within 30 minutes of end of infusion
- Most common signs and symptoms of IRRs: erythema, nausea / vomiting, chills, and sweating
  - Majority were transient and resolved on same day
- Anaphylactic reactions in 0.3% (n = 3)
- Of those rechallenged, 60% did not have another IRR

Insights from TRAILBLAZER-ALZ 2 (Donanemab): Limited Duration Dosing

Emily C. Collins, PhD
Global Imaging Platform Leader
Eli Lilly and Company

Clinical trial data may be translated to support limited duration dosing

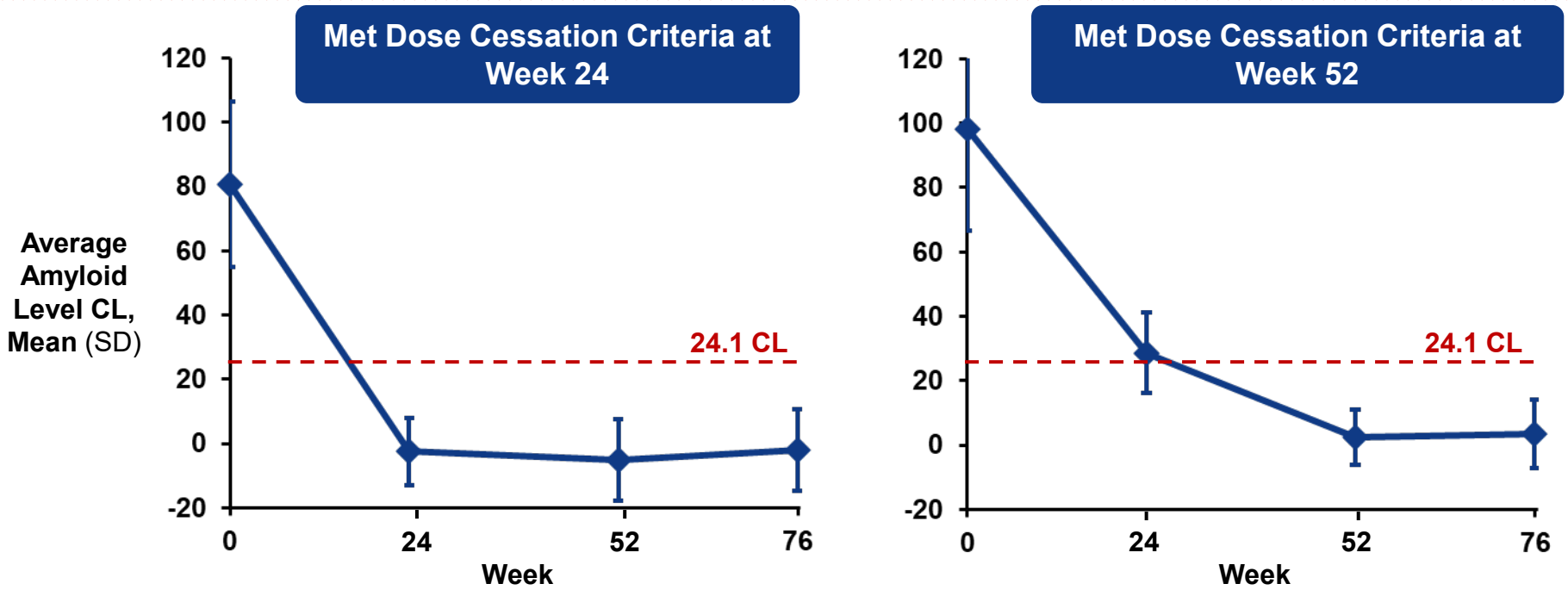
What is the evidence supporting persistent amyloid reduction following donanemab treatment?

What is reasonable timing for an amyloid PET?
Does baseline amyloid PET contribute?

Can clinicians use other biomarkers beyond amyloid PET to monitor amyloid reduction?

Abbreviations: PET = positron emission tomography.

Amyloid levels remained low after TRAILBLAZER-ALZ 2 dose cessation criteria were met

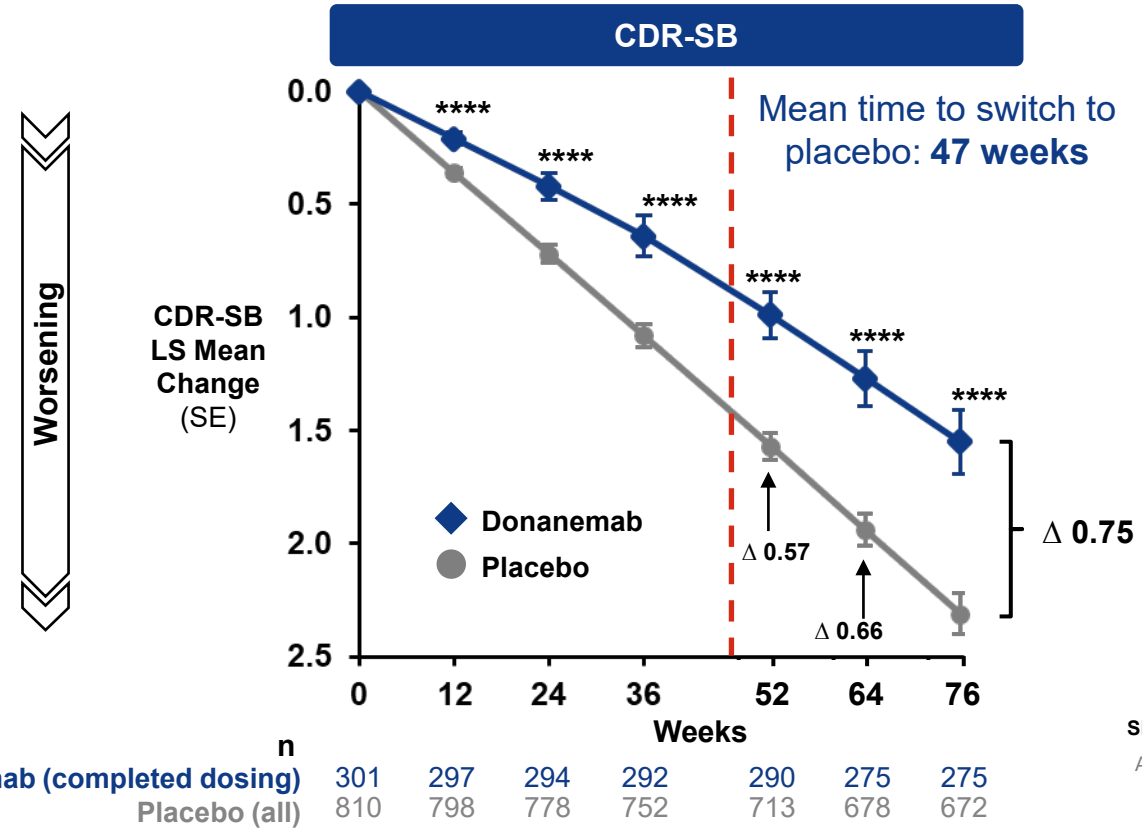


Re-accumulation rate of 2.8 CL / year - similar to natural accumulation rate[1]

Dose cessation criteria were <11 CL at a single scan or 11-25 CL for 2 consecutive amyloid measures (Sims et al JAMA 2023);
Abbreviations: CL = Centiloids; n = number of participants

[1]Jagust and Landau, Neurol 2021

Widening between group difference after treatment completion shows persistent benefit and supports limited duration dosing



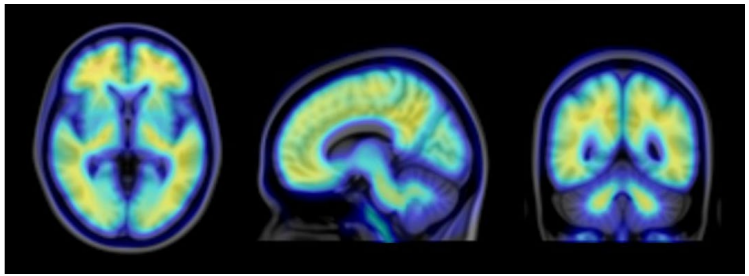
n							
Donanemab (completed dosing)	301	297	294	292	290	275	275
Placebo (all)	810	798	778	752	713	678	672

****nominal p < 0.0001; Overall Population
Similar finding with propensity matched analysis

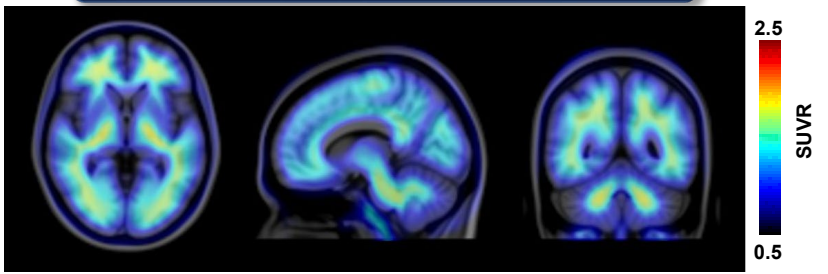
Abbreviations: CDR-SB = Clinical Dementia Rating–Sum of Boxes; LS = least square; n = number of participants; SE = standard error

Trial patients reaching amyloid negativity are visually similar to Aβ- in ADNI

Pre-treatment

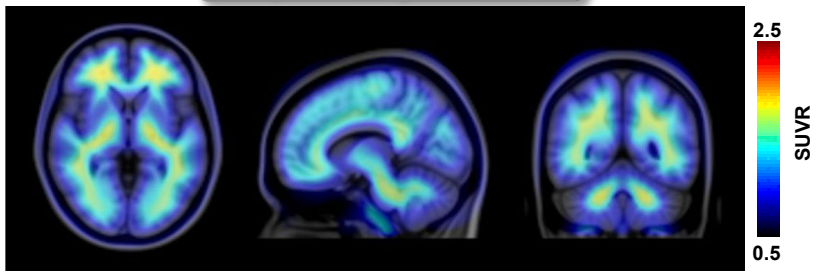


Donanemab 6 months post- treatment



- **TRAILBLAZER studies used image quantitation**
- **Prespecified analysis at < 24.1 CL was chosen to be consistent with a visually negative scan**
- **Visual reads are currently performed in clinical practice**

Amyloid negative ADNI

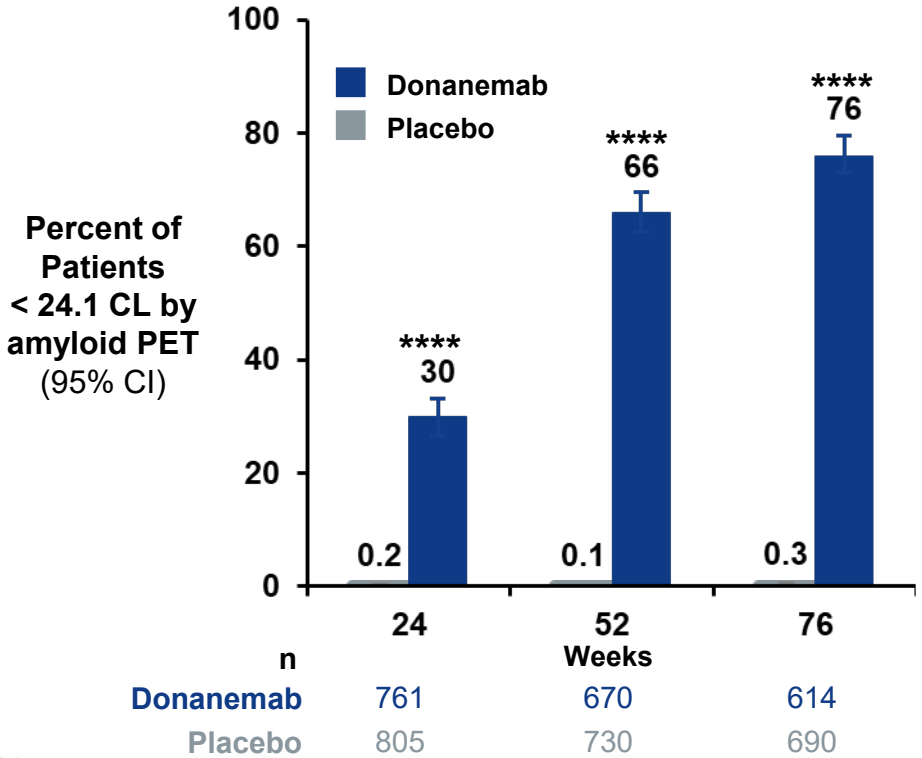


Note: Averaged florbetapir images used in this slide were obtained from TRAILBLAZER-ALZ and the ADNI database (adni.loni.usc.edu).

The investigators within ADNI contributed to the design and implementation of ADNI and/or provided data

Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; CL = Centiloids; SUVR = standardized uptake value ratio with a whole cerebellum as a reference region; Aβ = amyloid beta

Approximately 2/3 of patients reached < 24.1 Centiloids by 12 months of donanemab treatment

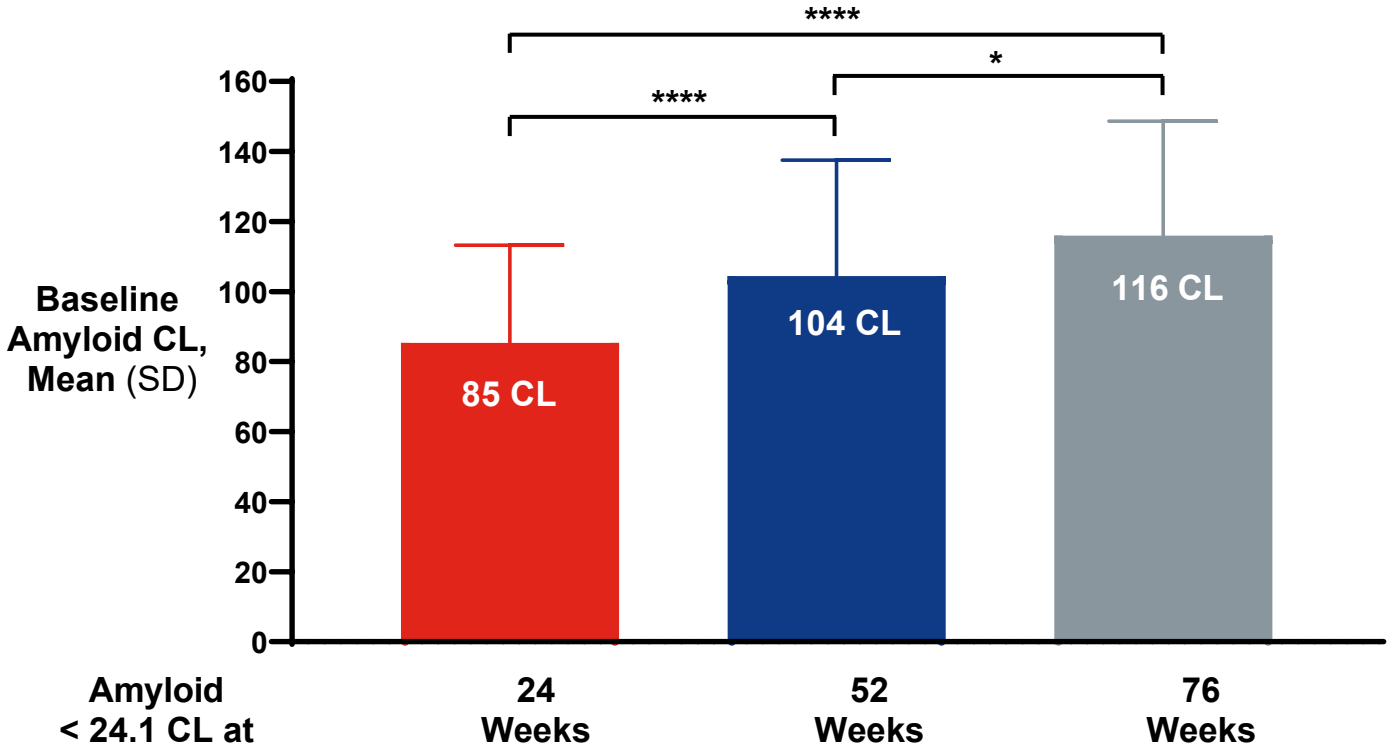


- **Prespecified analysis at < 24.1 CL**
- **66% reached < 24.1 CL by 12 months**

****p < 0.0001; Overall Population**

Abbreviations: CL = Centiloids; PET = positron emission tomography.

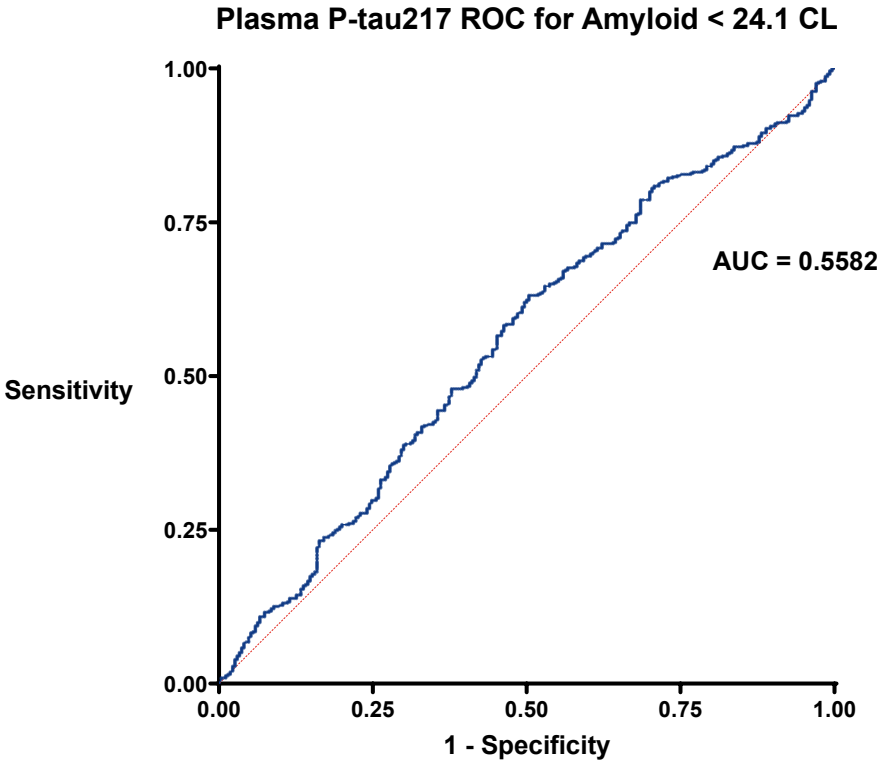
Baseline amyloid corresponds with time to achieve a threshold of < 24.1 CL



****p < 0.0001; *p <0.05

Abbreviations: CL = Centiloids; SD = standard deviation

Plasma P-tau217* not currently established for monitoring amyloid removal



- Plasma P-tau217 correlates with both amyloid and tau
- After amyloid removal, P-tau217 still reflects tau pathology
- Current evidence does not support utilizing plasma P-tau217 for determining donanemab amyloid removal

*C_2N Plasma P-tau217 assay

Abbreviations: AUC = area under the curve; CL= Centiloids; ROC = receiver operating characteristic

Translating limited duration dosing into clinical practice

A visually negative scan may be used to determine the timing of treatment cessation

Approximately 2/3 had amyloid PET < 24.1 CL at 1 year

Lower baseline amyloid predicts earlier reduction

Current plasma P-tau217 data does not support use for determining treatment cessation

Abbreviations: CL = Centiloids; PET = positron emission tomography

Next Steps

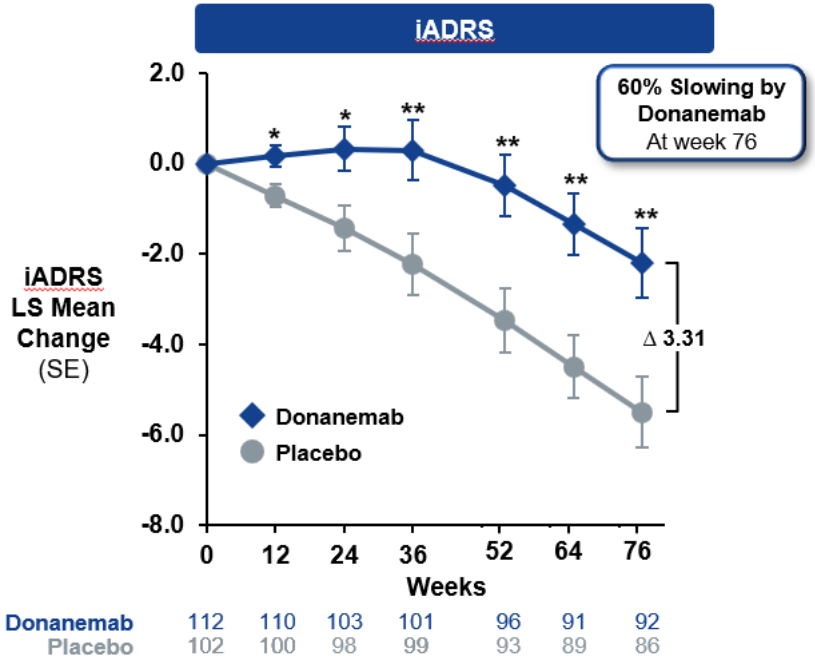
Robert Alexander, M.D.
Banner Alzheimer's Institute

Ultimate goal: Alzheimer's disease symptom prevention

Preclinical AD
TRAILBLAZER-ALZ 3 (NCT05026866)

- Evidence from TRAILBLAZER-ALZ 2 showed that earlier treatment gave even better benefit, so the TRAILBLAZER-ALZ 3 opportunity in the preclinical population is exciting
- Event-based outcome study will measure delay in progression to symptomatic AD stages with donanemab treatment
- Enrollment complete to support primary endpoint

TRAILBLAZER-ALZ 2
MCI with low-medium tau



Abbreviations: iADRS = Integrated Alzheimer's Disease Rating Scale; LS = least square; MCI = mild cognitive impairment; SE = standard error

nominal p-values: * p < 0.05, ** p < 0.01

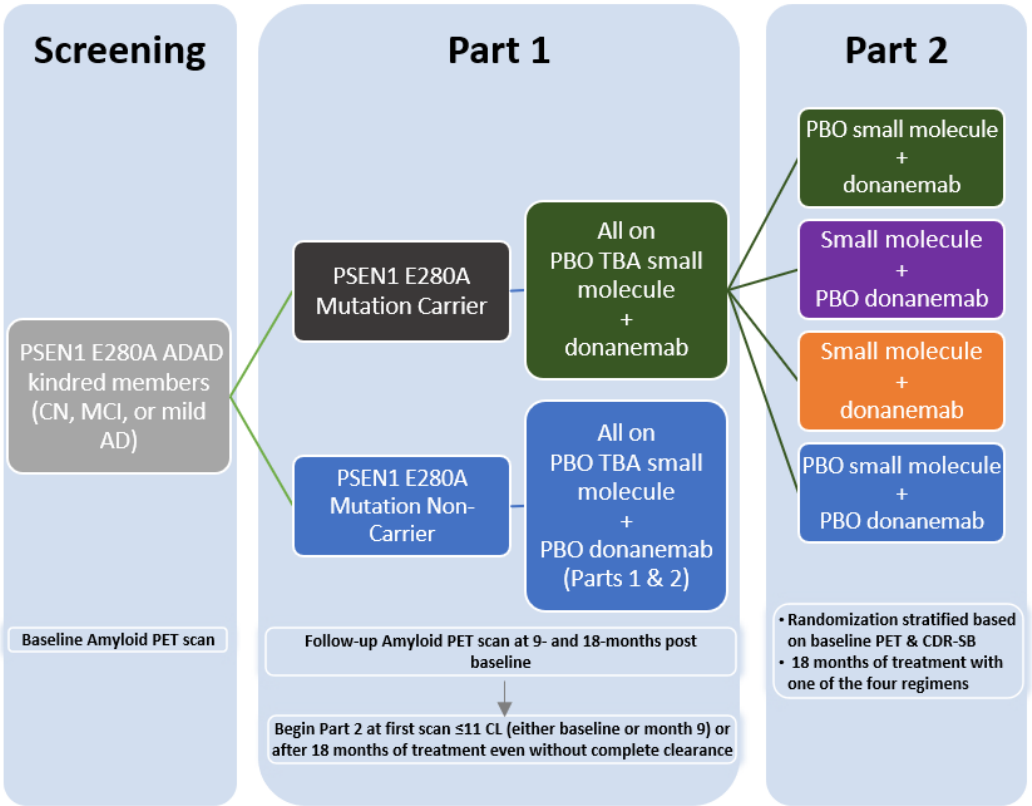
TRAILBLAZER-ALZ 3: exploring secondary prevention

Trial Summary	
Target population	▪ Cognitively unimpaired with evidence of Alzheimer's disease pathology (plasma P-tau217)
Treatments	▪ 1:1 ratio to receive double blind donanemab or placebo up to 9 doses Q4 weeks
Pop. size	▪ ~2600 participants (US and Japan)
Primary Endpoint	▪ Time to event of clinical progression as measured by CDR-GS ▪ Primary event is two consecutive CDR-GSs > baseline in CDR-GS = 0 population ▪ 350 events (all cause; adjudicated AD events for secondary analysis)
Secondary Endpoints	▪ Multiple cognitive and functional scales
Optional Addenda	▪ PET (florbetapir and flortaucipir) ▪ APOE disclosure

Abbreviations: APOE= apolipoprotein E; CDR-GS = Clinical Dementia Rating Global Score; Q4 = every 4; PET = positron emission tomography

Amyloid-targeting therapies in Autosomal-Dominant Alzheimer's disease (ADAD)

- World's largest known kindred of ADAD is near Medellin.
- Banner Alzheimer Prevention Initiative has engaged this group in the past for a previous ADAD trial.
- Awaiting Notice of Award from NIH. MPIs: Alexander, Langbaum, Lopera, Reiman



ALZHEIMER'S PREVENTION INITIATIVE

Abbreviations: AD = Alzheimer's disease; CDR-SB = Clinical Dementia Rating–Sum of Boxes; CL = Centiloids; CN = cognitively normal; E280A =glutamic acid to alanine mutation at codon 280; MCI = mild cognitive impairment; MPI = multiple primary investigator; PBO = placebo; PSEN1 =presenilin 1; TBA = to be announced

Alzheimer's disease in people with Down syndrome

- AD dementia:
  - leading cause of death in adults with DS over age 35 years
  - Individuals with DS have a 95% lifetime risk for developing AD dementia
- Disease-modifying therapeutics urgently needed due to genetically-determined AD
- Longitudinal AD biomarker data demonstrates accelerated disease progression
- The revised diagnosis and AD staging criteria (Jack et al, 2024) now includes DS as Stage 0 in the AD continuum
- **ALADDIN** – Amyloid Lowering for Alzheimer's in Down's with Donanemab INvestigation
  - A Randomized, Double-Blind, Placebo-Controlled, Phase 4 Dose-Escalation Study Evaluating the Safety, Tolerability, and Efficacy of Donanemab in Adults with Down Syndrome
  - Led by Michael Rafii, MD, PhD, Alzheimer's Therapeutic Research Institute, Keck School of Medicine USC

Abbreviations: AD = Alzheimer's disease; DS = Down syndrome

ACTC-DS
Alzheimer's Clinical Trials Consortium
Down Syndrome

Question/Answer Session

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AAIC slides