Donanemab for Treatment of Patients with Early Symptomatic Alzheimer's Disease

Eli Lilly and Company

Peripheral and Central Nervous System Drugs Advisory Committee

June 10, 2024

Introduction

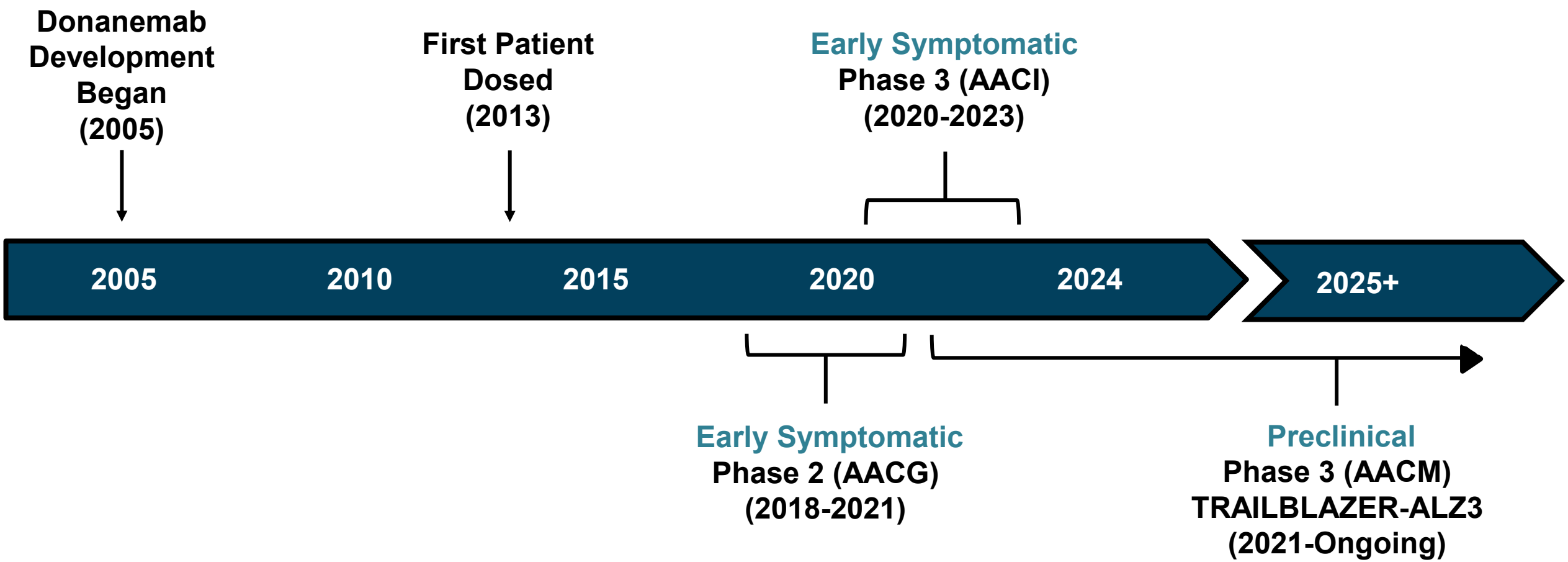
David Hyman, MD

Chief Medical Officer

Eli Lilly and Company

Overview of Donanemab Development Program

Ultimate Goal: Alzheimer's Disease Prevention



Agenda

Donanemab Clinical Program	**Mark Mintun, MD** Group Vice President - Neuroscience Eli Lilly and Company
Efficacy Results	**John Sims, MD** Head of Medical - Donanemab Eli Lilly and Company
Safety Results	**Melissa Veenhuizen, DVM, MS** Vice President-Global Patient Safety Eli Lilly and Company
Clinical Perspective	**Reisa Sperling, MD** Brigham and Women's Hospital Massachusetts General Hospital Harvard Medical School

Donanemab Clinical Program

Mark Mintun, MD

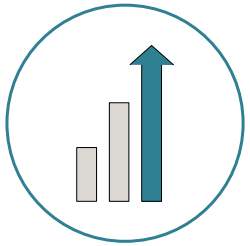
Group Vice President – Neuroscience R&D

Eli Lilly and Company

Urgent Problem of Alzheimer's Disease and Other Dementia

EVERY 65 SECONDS

NEW CASES: Someone develops Alzheimer's disease every 65 seconds. Alzheimer's disease (AD) is #6 cause of death in the US.



MANY AMERICANS

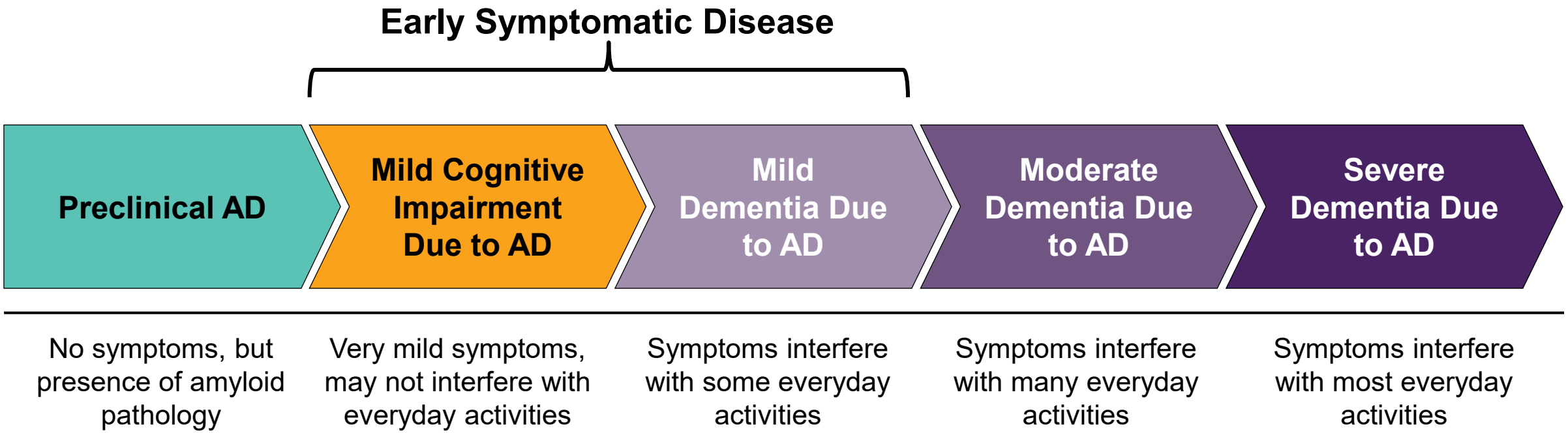
HEALTH: One-third of Americans have a relative with AD.[1]

CARE PARTNERS

BURDEN: Extensive financial, psychological, and physical stress for care partners and families.[2,3] In 2023, caregivers of people with AD provided an estimated 18.4 billion hours of unpaid assistance.

1. Ipsos, 2020; 2. Alzheimer's Association, 2024; 3. Suehs, 2014

Irreversible AD Progression Highlights Need for Disease-Modifying Treatments



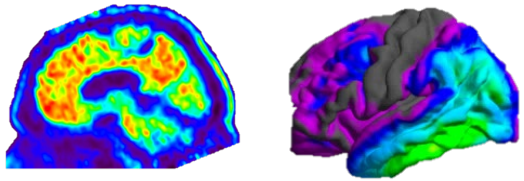
Highlights of Evolution of Alzheimer's Disease Diagnosis and Monitoring

Clinical Trials

Standardized Cognitive and Functional Measures

- MMSE
- CDR
- ADAS-Cog
- ADCS-iADL

PET Biomarkers Imaging



Amyloid PET Tau PET

- Amyloid PET
- Tau PET

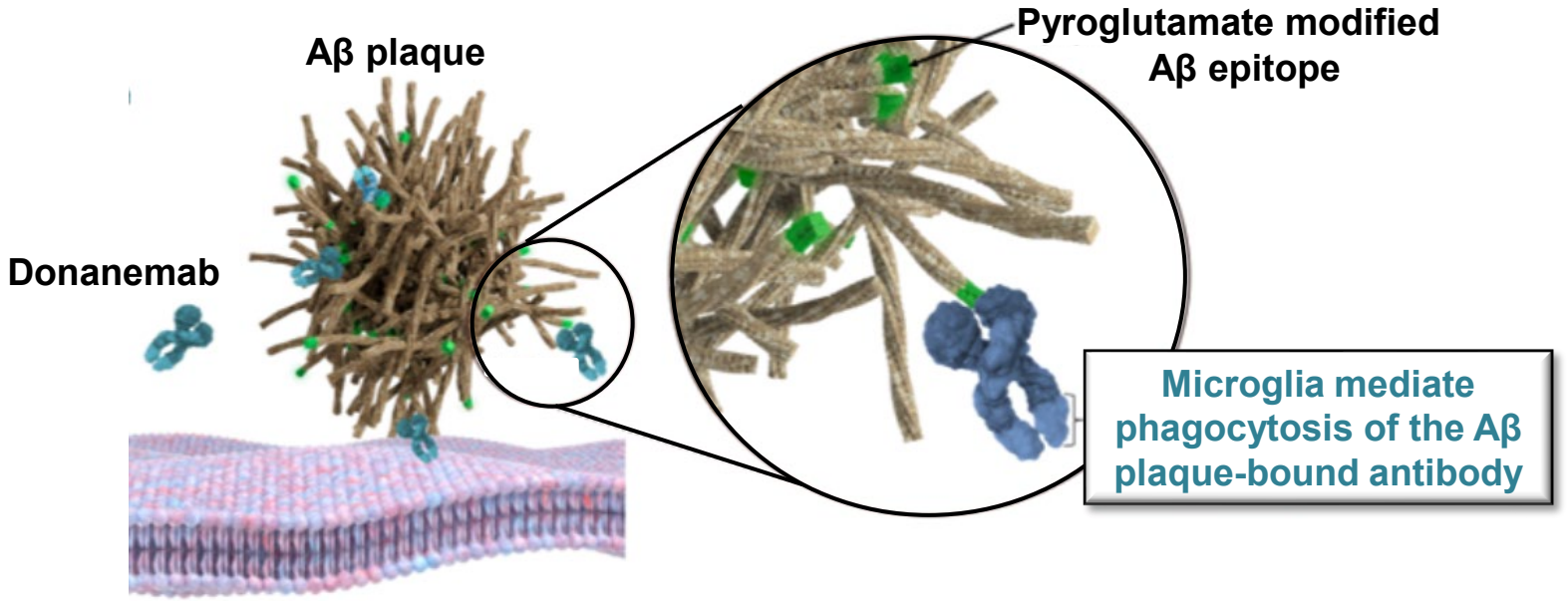
Clinical Practice

Amyloid Pathology Confirmation

- Amyloid PET
- CSF Biomarkers (Aβ42 / Aβ40 ratio)
- Emerging: Plasma Biomarkers

Donanemab Efficiently Clears Amyloid Plaques

- Donanemab is an IgG1 monoclonal antibody directed at pyroglutamate modified Aβ epitope found within β-amyloid plaques[1]
- Facilitates removal of amyloid plaques through microglial phagocytosis[2-4]
- May aid in reduction of other AD-related pathologies through clearance of plaques (e.g., reduction in neuronal damage and synaptic loss)[1,2,5,6]



1. Mintun, 2021; 2. DeMattos, 2012; 3. Drolle, 2014; 4. Kent, 2020; 5. Jawhar, 2011; 6. Sims, 2021

Proposed Indication

Indicated for the treatment of Alzheimer's disease. Treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials.

Label to include confirmation of amyloid pathology

Proposed Dosing

- 700 mg IV Q4W first 3 doses
- 1400 mg IV Q4W

Consider stopping dosing when amyloid plaque is cleared

Donanemab Meets the Need for Disease-Modifying Therapy in Patients with AD

Unmet Need

- Irreversible, cognitive and functional decline
- Ultimately fatal disease
- Patient treatment options to individualize benefit, risk, and burden

Efficacy

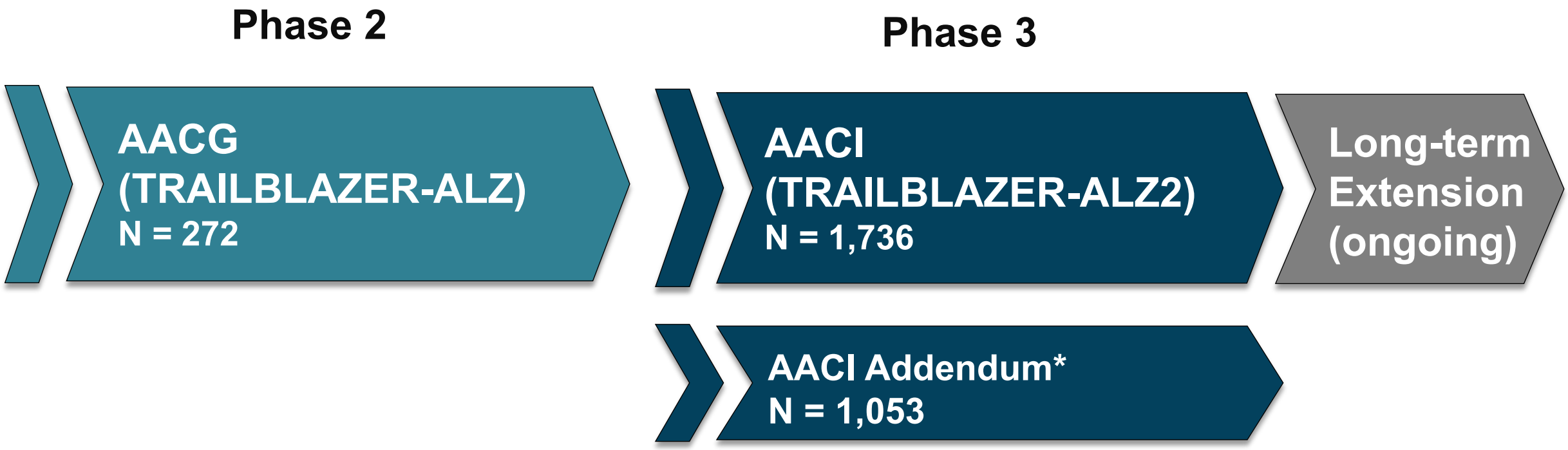
- Clinically meaningful and statistically significant slowing of clinical progression
- Met Primary and Secondary endpoints across studies, supported by biomarker activity
- Dosing regimen reduces burden to patients and health care system

Safety

- Well-characterized safety profile
- Data consistent with known class risks
- Extensive ARIA management plan for prescribers, patients, and caregivers

Donanemab Clinical Trial Design

Development Program in Patients with Early Symptomatic Alzheimer's Disease



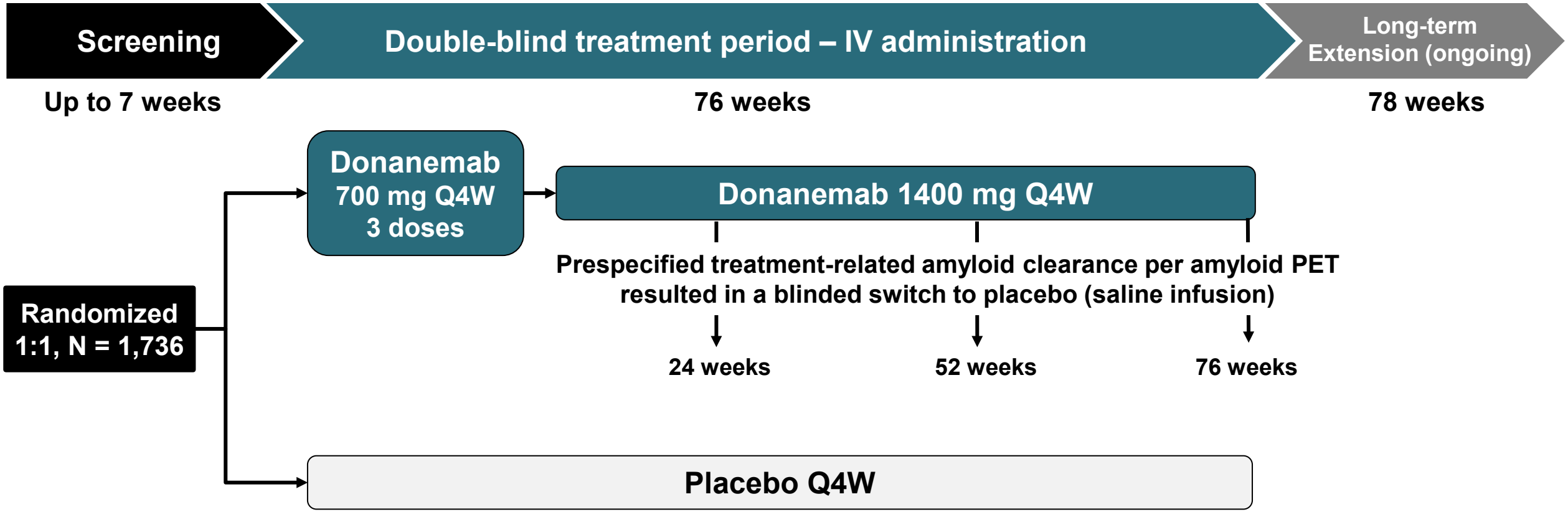
*Assessed amyloid clearance, safety, and additional biomarkers with open label donanemab treatment irrespective of tau pathology

Prospective Tau Characterization in Donanemab Development Program

- Tau levels are prognostic of rate of clinical decline and prospectively characterized to
  - Ensure treatment groups were well-balanced
  - Enroll patients likely to have measurable clinical deterioration in 18-month study period
- Patients enrolled according to tau level across donanemab program

Tau Level	AACG (Phase 2)	AACI (Phase 3)	AACI Addendum
No / Very-Low			✓
Low-Medium	✓	✓	✓
High		✓	✓

Phase 3 Study AACI Design



Stratification

- Investigative site
- Tau pathology (low-med vs high by PET)

Key Enrollment Criteria

- Patients 60 – 85 years of age
- Early symptomatic AD as evidenced by
  - ≥ 6 months of memory impairment
  - MMSE of 20 – 28
- Brain amyloid plaque and tau pathology
- Allowed comorbidities like stroke and vascular abnormalities

FDA Guidance, Early Alzheimer's Disease: Developing Drugs for Treatment 2024; MMSE = Mini-Mental State Exam

Clinical Development Program Enrolled High Risk Population

- Compared to contemporary AD trials, patients
  - Older adults
  - Higher baseline amyloid plaque
  - More progressed by clinical scales and stage
  - Allowed baseline superficial siderosis
  - Larger portion using symptomatic AD medications

Validated Clinical Endpoints Measure Change in Cognition and Function

Endpoint	Assessment Overall and low-medium tau populations
iADRS ADAS-Cog$_{13}$ and ADCS-iADL	**Cognition and Function**
Key Clinical Gated Secondaries	
CDR-SB	**Cognition and Function**
ADAS-Cog$_{13}$	**Cognition**
ADCS-iADL	**Function**
CDR-G	**Clinical Staging of Disease**

iADRS = integrated Alzheimer's Disease Rating Scale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living subscale; CDR-G = Global Scale

Efficacy Results

John Sims, MD

Head of Medical - Donanemab

Eli Lilly and Company

AACI: Baseline Demographics (Overall Population)

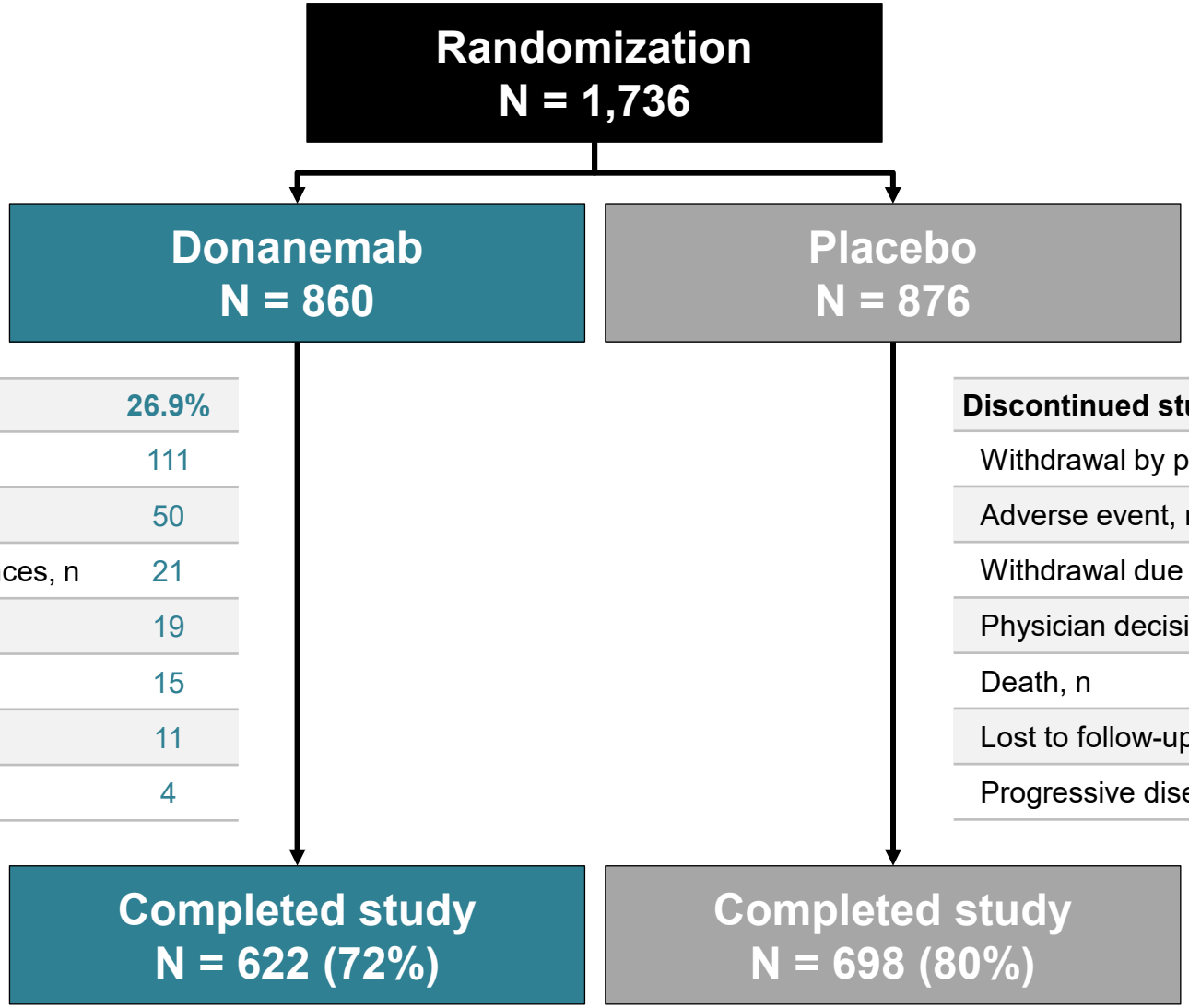
Demographic, n (%)	Donanemab N = 860	Placebo N = 876
Sex, female	493 **(57%)**	503 **(57%)**
Age, mean **(SD) years**	73.0 **(6.2)**	73.0 **(6.2)**
Race		
White	781 **(91%)**	807 **(92%)**
Asian	57 **(7%)**	47 **(5%)**
Black or African American	19 **(2%)**	21 **(2%)**
American Indian or Alaskan Native	2 **(0.2%)**	**0**
Ethnicity, Hispanic/Latino	35 **(6%)**	36 **(6%)**
APOE ε4 carrier	598 **(70%)**	621 **(71%)**
AChEI and/or memantine use	521 **(61%)**	538 **(61%)**

AACI: Baseline Clinical and Biomarker Measures (Overall Population)

Scale/biomarker, mean (SD)	**Donanemab N = 860**	**Placebo N = 876**
iADRS	**104.1** (14.3)	**103.6** (14.0)
ADAS-Cog$_{13}$	**28.7** (8.8)	**29.3** (8.9)
ADCS-iADL	**47.8** (7.9)	**47.8** (7.8)
ADCS-ADL	**66.3** (8.6)	**66.4** (8.3)
MMSE	**22.4** (3.8)	**22.2** (3.9)
CDR-SB	**4.0** (2.1)	**3.9** (2.1)
CDR-G, n (%)		
0.5	**514** (61%)	**532** (61%)
1	**304** (36%)	**308** (35%)
Amyloid PET, Centiloids	**103.5** (34.5)	**101.6** (34.5)
Tau PET AD signature weighted SUVr	**1.3** (0.3)	**1.4** (0.3)
Plasma P-tau217, pg/mL	**7.5** (18.5)	**6.8** (15.4)

SUVr = Standardized Uptake Value Ratio

AACI: Patient Disposition

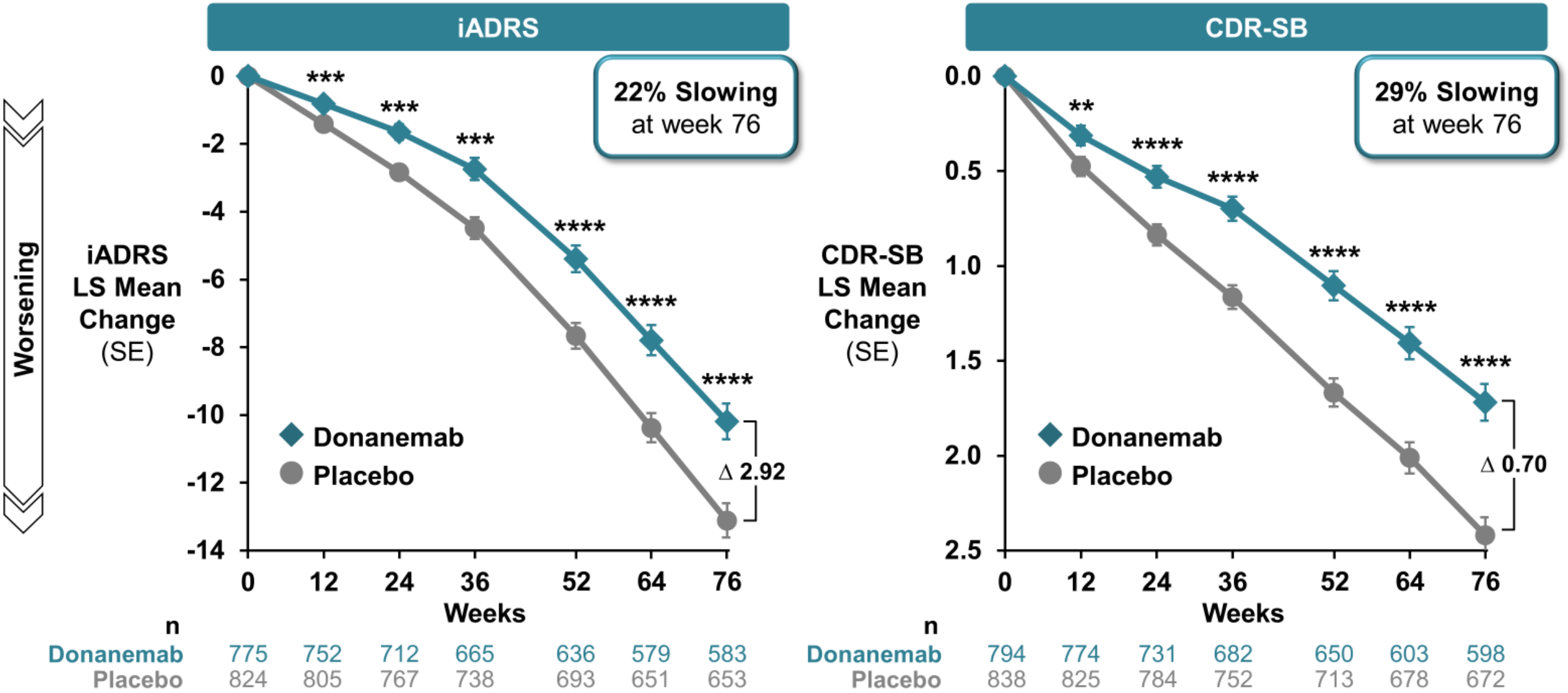


Discontinued study (%)	26.9%
Withdrawal by participant, n	111
Adverse event, n	50
Withdrawal due to caregiver circumstances, n	21
Physician decision, n	19
Death, n	15
Lost to follow-up, n	11
Progressive disease, n	4

Discontinued study (%)	19.7%
Withdrawal by participant, n	94
Adverse event, n	21
Withdrawal due to caregiver circumstances, n	20
Physician decision, n	10
Death, n	10
Lost to follow-up, n	11
Progressive disease, n	7

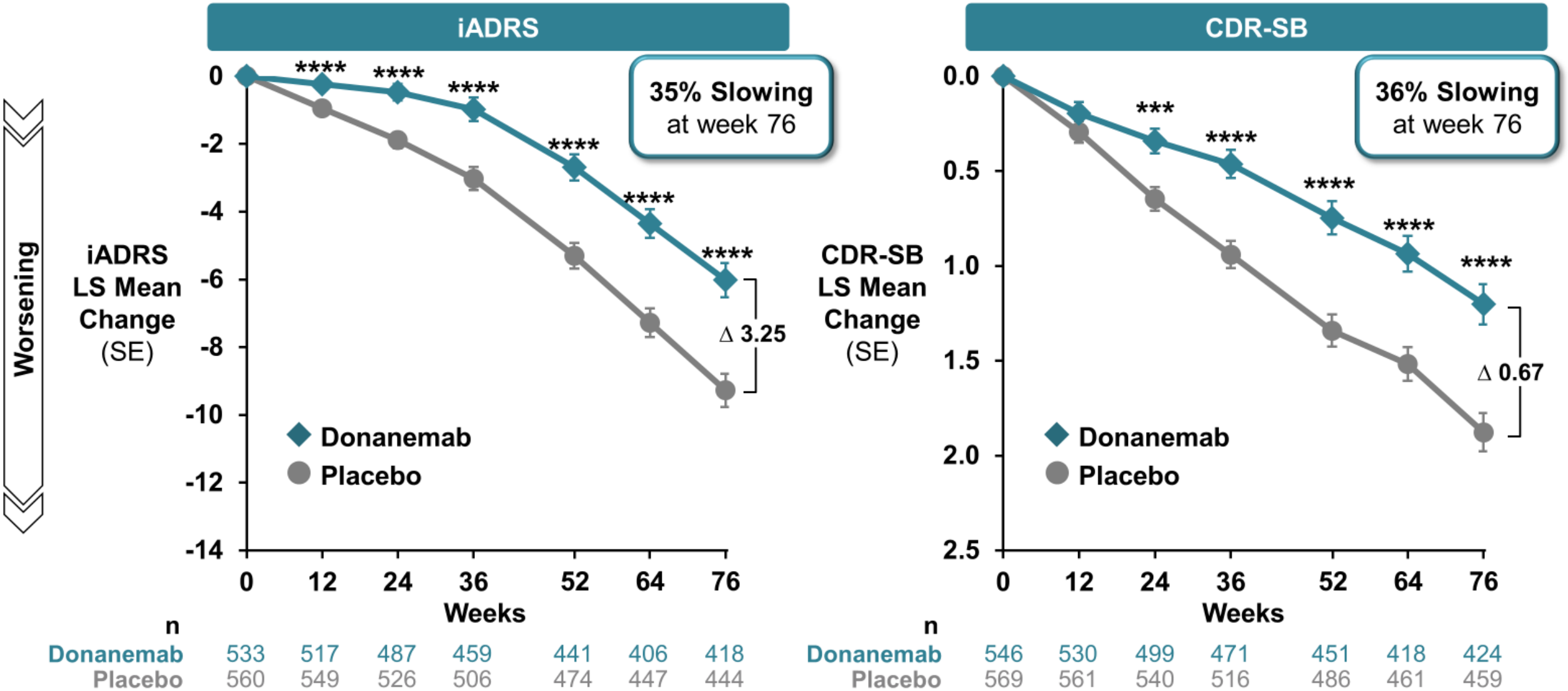
Primary Database Lock

Significant Slowing of Clinical Progression for Primary and Key Secondary Endpoint (Overall Population)



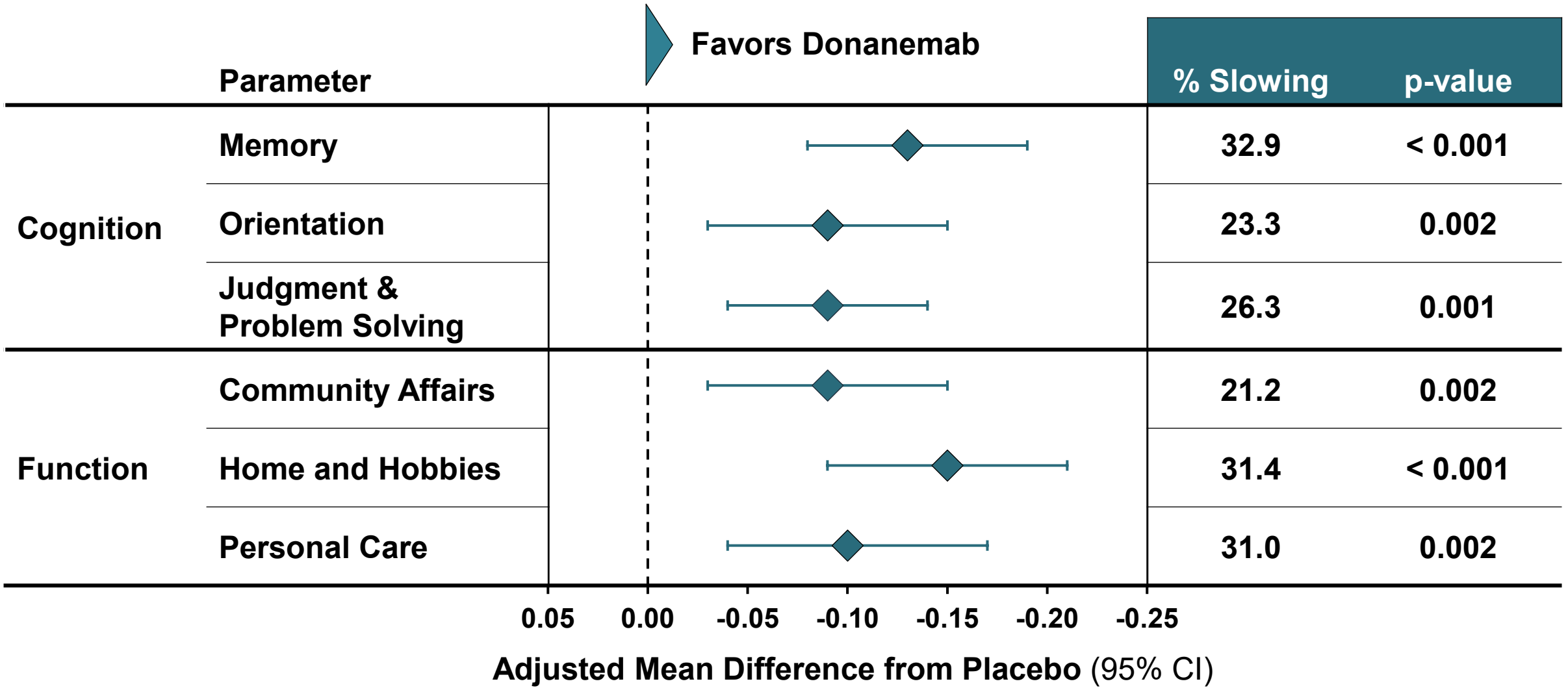
**p < 0.01; ***p < 0.001; ****p < 0.0001

Low-Medium Tau Results Consistent with Overall Population



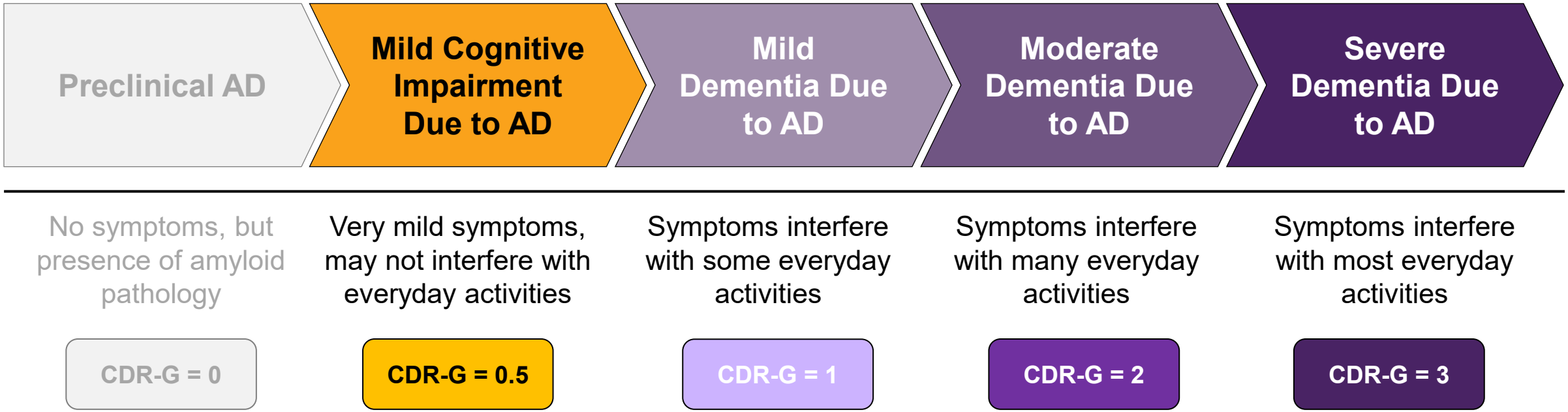
***p < 0.001; ****p < 0.0001

Clinically Relevant Treatment Effect Across CDR-SB Domains at 76 Weeks (Overall Population)

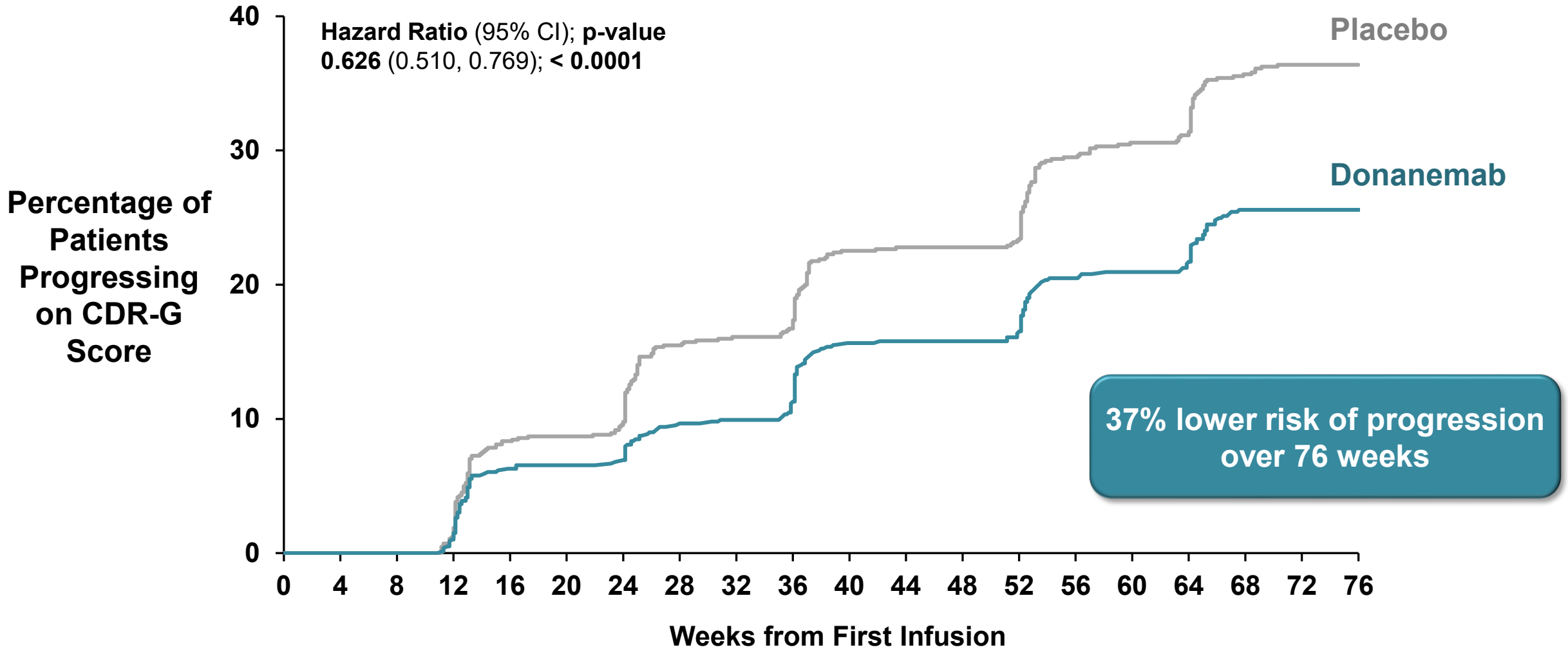


Meaningful Benefit: Slowing Progression to Next Clinical Stage

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

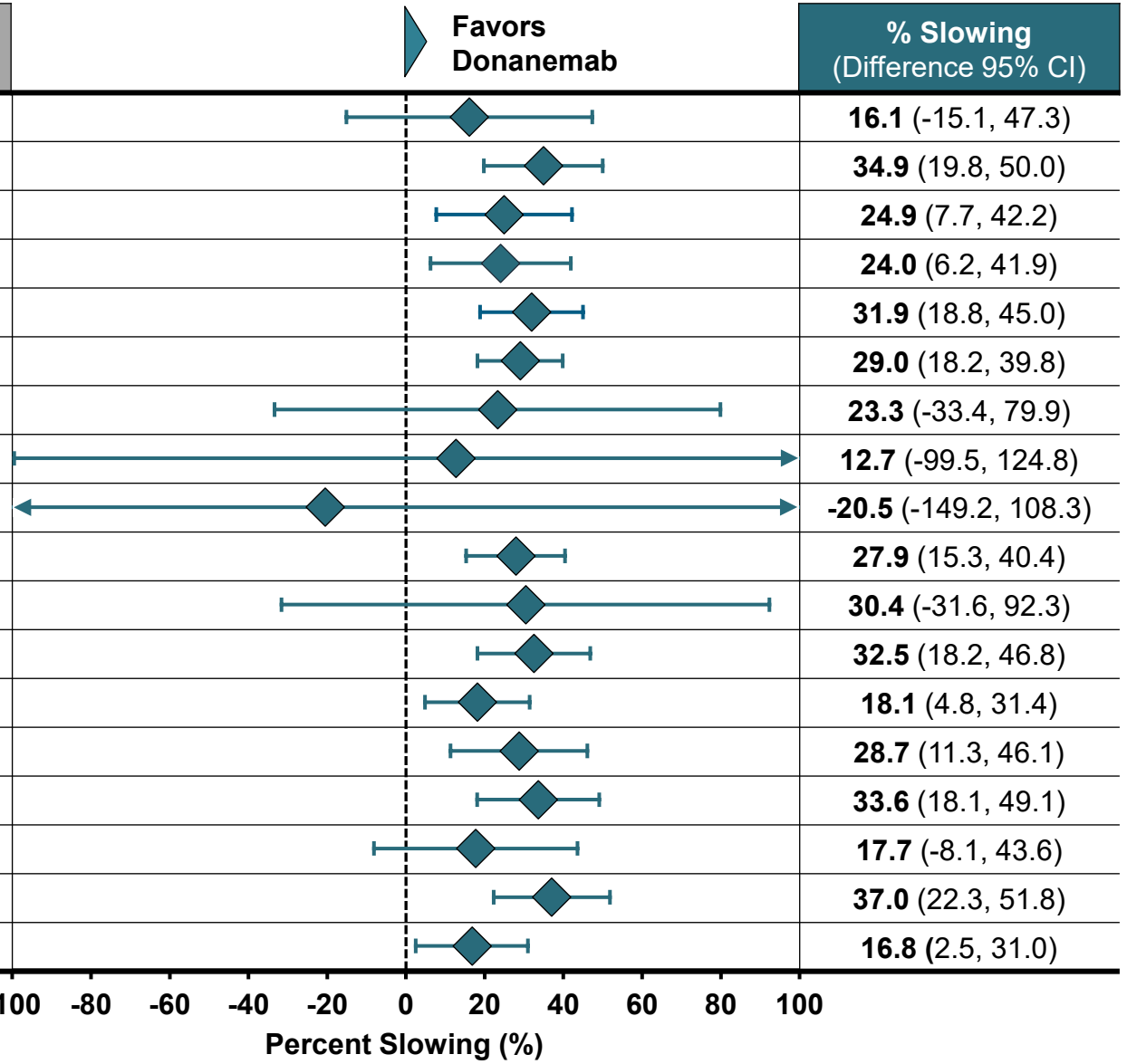


Donanemab Treatment Lowers Risk of Progression: CDR-Global Score (Overall Population)

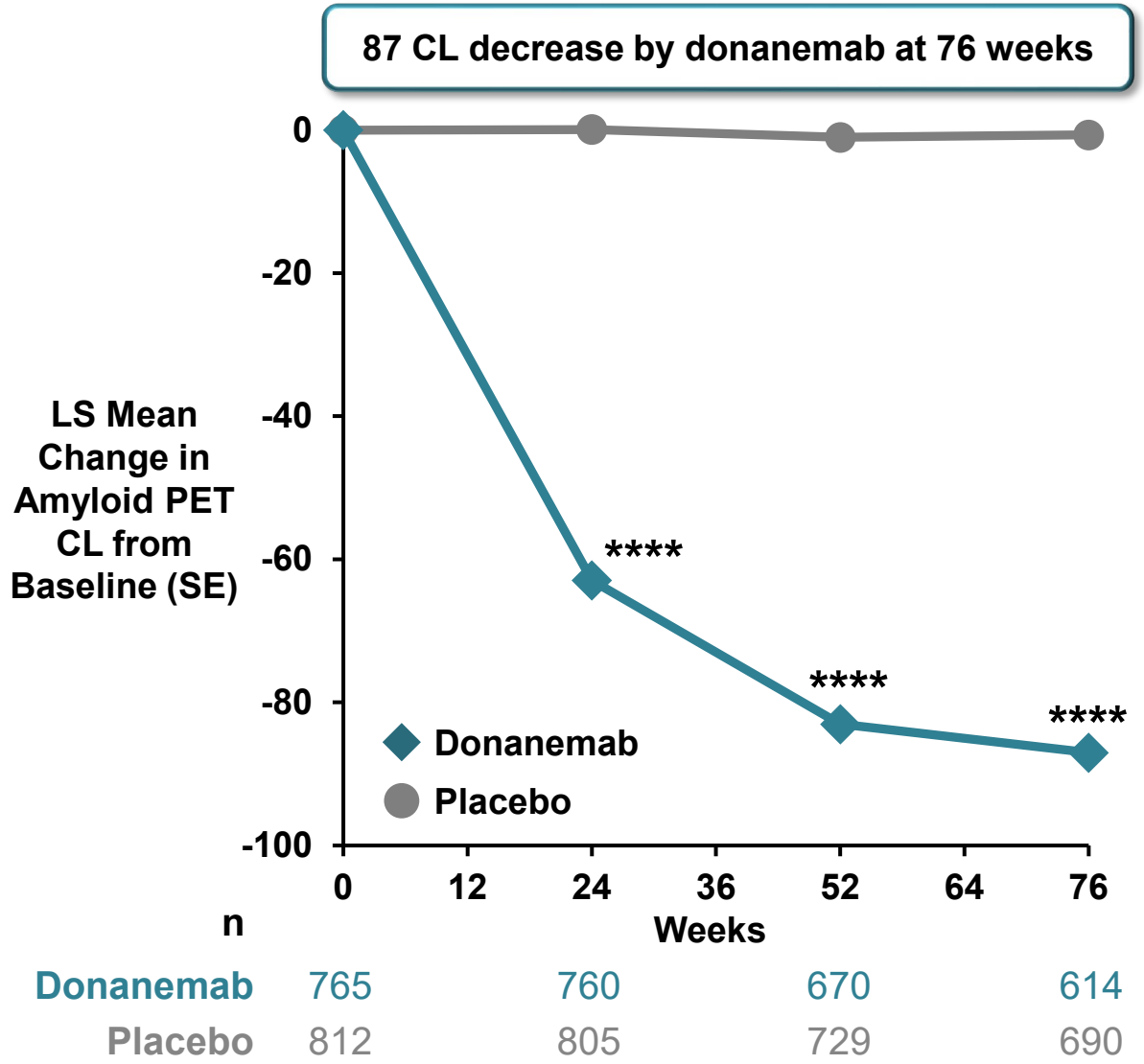


CDR-SB: Consistent Efficacy Observed Across Subgroups (Overall Population)

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



Amyloid Clearance and Effect in Disease-Relevant Biomarkers Support Donanemab in All Baseline Tau Participant Groups



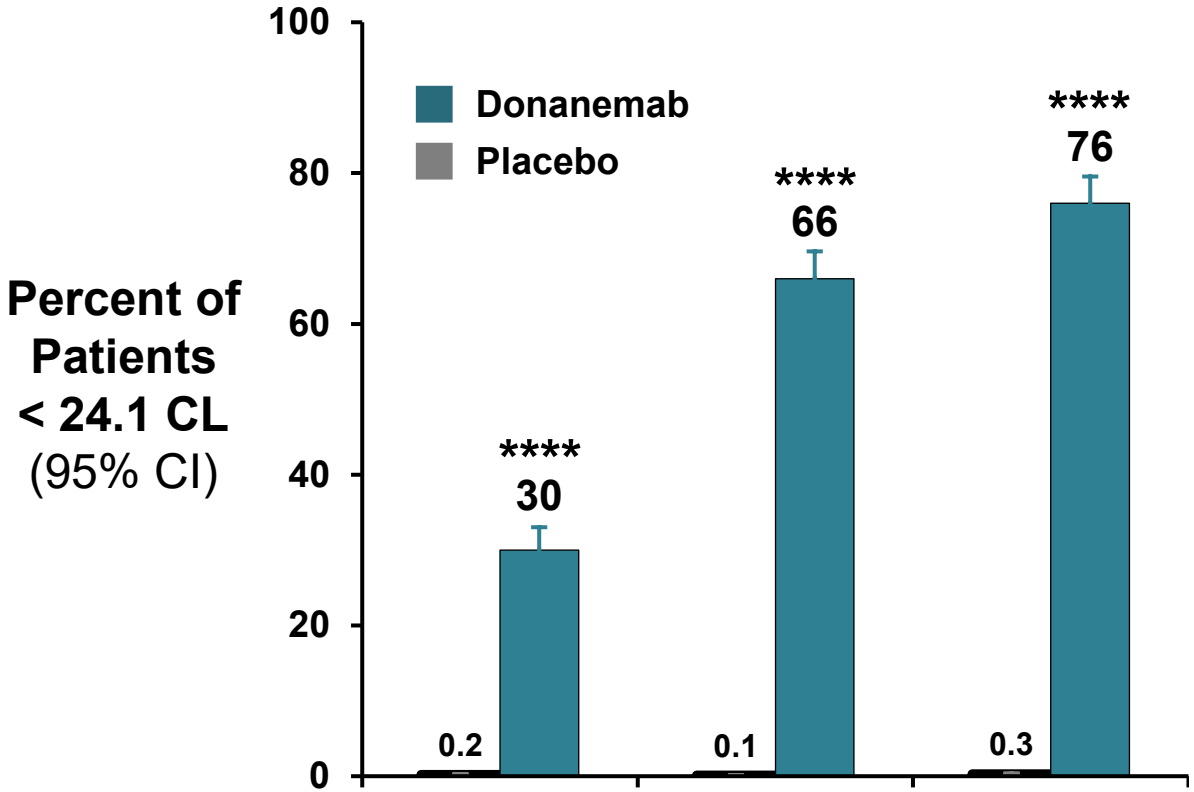
Percent change from baseline at 76 weeks	No / Very-Low Tau†	Low – Medium Tau	High Tau
Amyloid reduction	86%	85%	80%
P-tau217 reduction	56%	39%	33%
GFAP reduction	22%	21%	18%

†Data from AACI addendum

****p < 0.0001; Overall Population

Amyloid Results Support Dosing Recommendations

High Levels of Treatment-Related Amyloid Clearance Support Limited-Duration Dosing

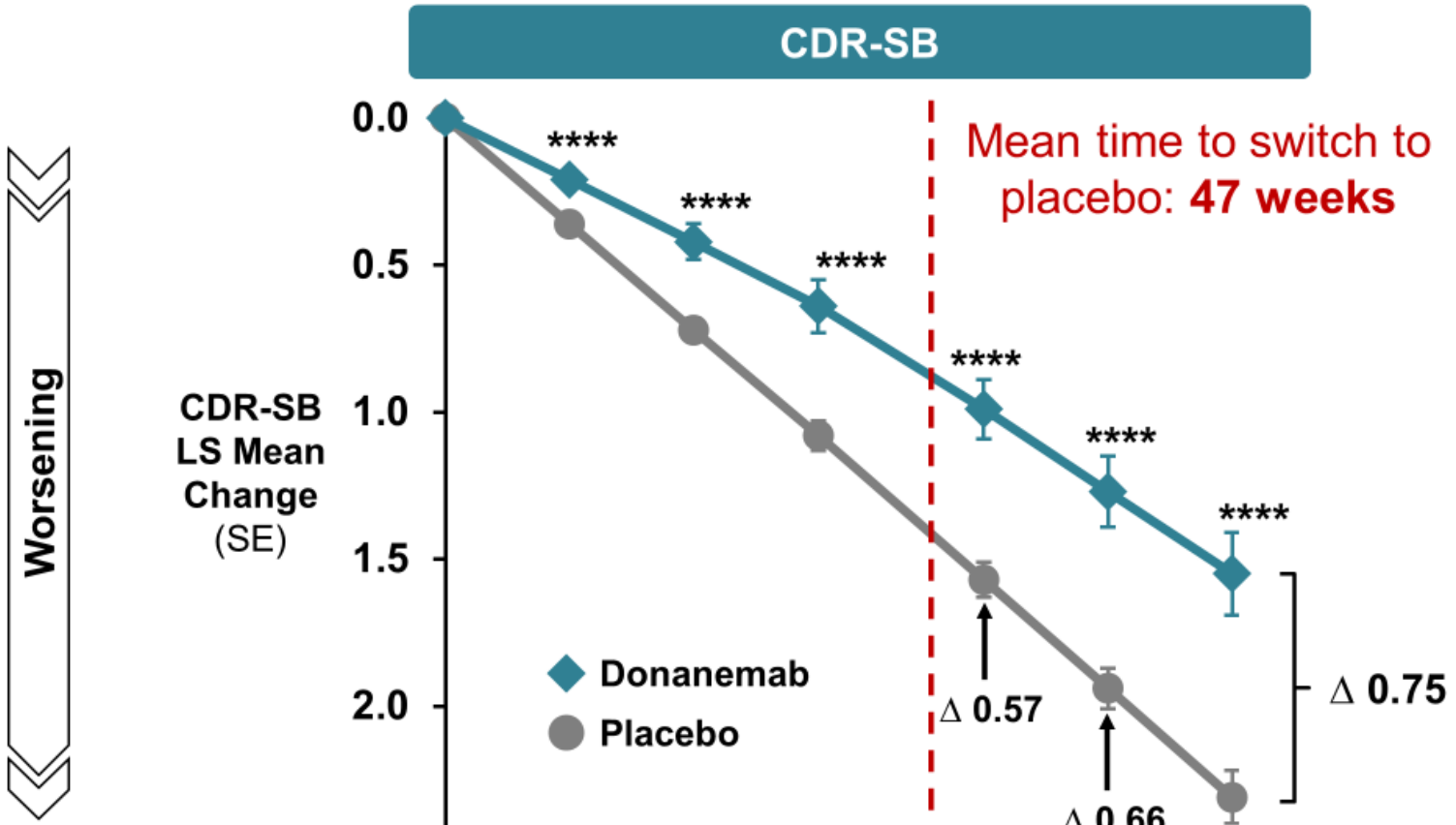


n	24	52	76
Donanemab	761	670	614
Placebo	805	730	690

76% reached treatment-related amyloid clearance by 76 weeks

****p < 0.0001; Overall Population

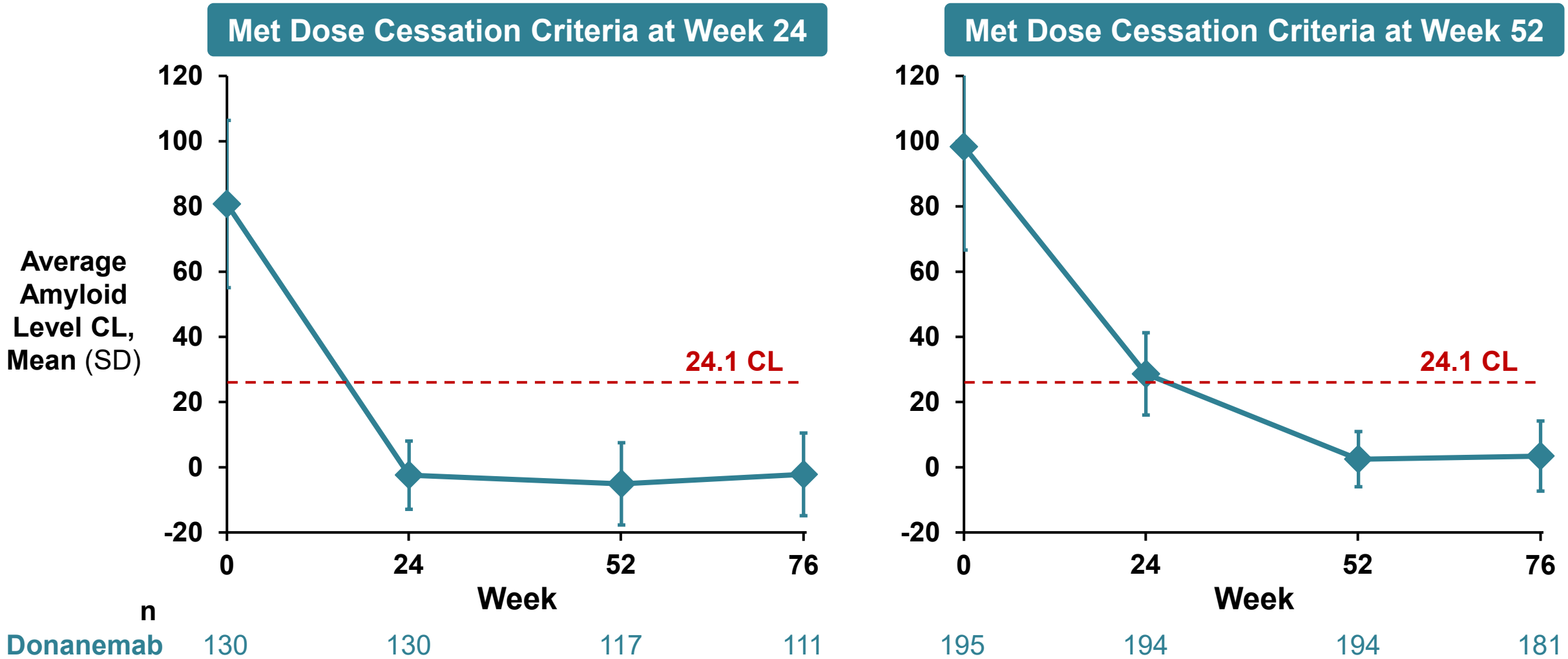
Widening Between Group Difference after Treatment Completion Supports Limited Duration Dosing



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

****p < 0.0001; Overall Population

Amyloid Levels Remain Low After Treatment Related Amyloid Clearance



Donanemab Significantly Slowed Cognitive and Functional Decline in Early Symptomatic Alzheimer's Disease

- Statistically significant and clinically meaningful data consistently demonstrated across
  - Secondary endpoints
  - Sensitivity analyses
  - Subgroups
  - Biomarkers
- Patients completing donanemab early continue to separate from placebo
- Treating early symptomatic disease should be considered across tau spectrum
- AACI Study replicated successful Phase 2 results

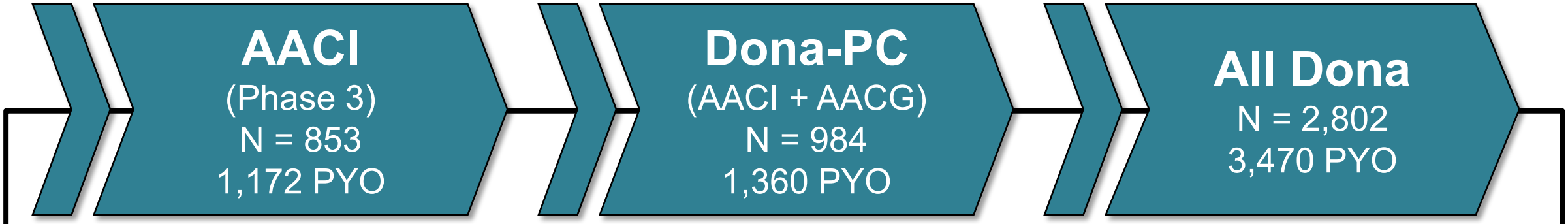
Safety

Melissa Veenhuizen, DVM, MS

Vice President-Global Patient Safety

Eli Lilly and Company

Safety Populations



- Pre-specified safety analysis plan
  - 1000 donanemab-exposed patients for ≥ 12 months, All Dona
  - Largest trial safety dataset compiled for amyloid-targeting therapy
  - First dose to end of treatment period + 57 days (~5 half-lives for donanemab) or day prior to long-term extension visit
- Data consistent regardless of population

Dona-PC = Placebo Controlled; PYO = Patient Years of Observation

Safety Overview

	Dona-PC		All Dona
	Donanemab N = 984	Placebo N = 999	Donanemab N = 2,802
Any AE	879 **(89%)**	831 **(83%)**	2,260 **(81%)**
SAE	170 **(17%)**	153 **(15%)**	463 **(17%)**
AE leading to treatment discontinuation	153 **(16%)**	46 **(5%)**	295 **(11%)**
Death, prespecified analysis*	18 **(1.8%)**	12 **(1.2%)**	36 **(1.3%)**
Death, updated analysis with vital status**	20 **(2.0%)**	17 **(1.7%)**	NA

*June 2023 datacut – pre-specified approach of pooled data, including AACG; **May 2024 datacut – updated approach with vital status

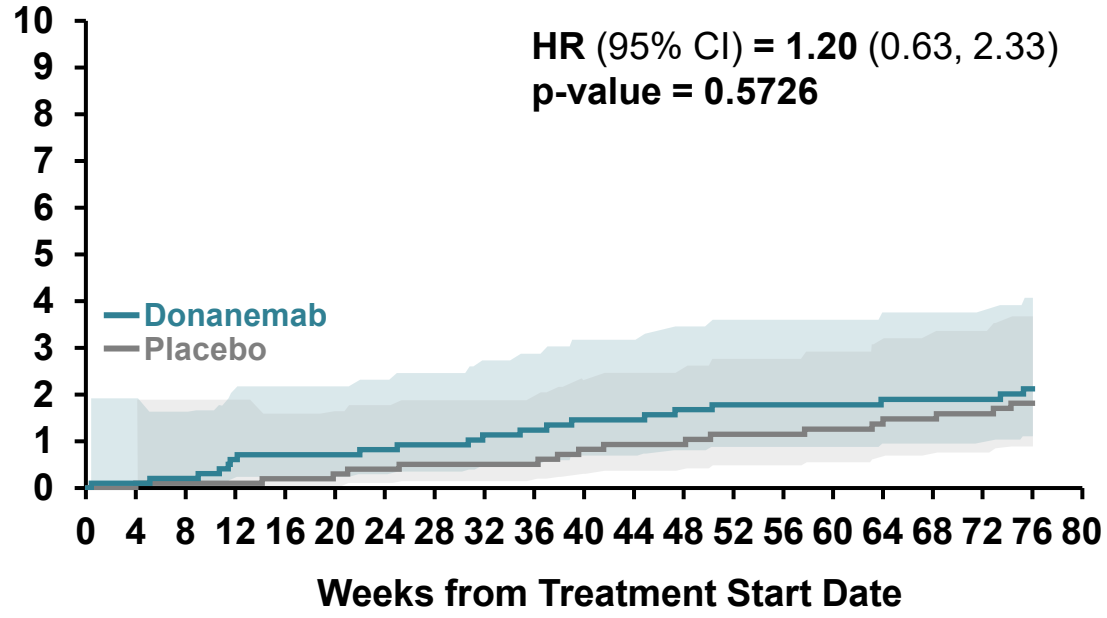
Placebo-Controlled Studies: Mortality Summary

	Dona-PC N = 1,983	
	Donanemab N = 984	Placebo N = 999
Total deaths by prespecified analysis*	18 **(1.8%)**	12 **(1.2%)**
ARIA	3 **(0.3%)**	0
Non-ARIA	15 **(1.5%)**	12 **(1.2%)**
Total deaths by updated analysis with vital status**	20 **(2.0%)**	17 **(1.7%)**
ARIA	3 **(0.3%)**	0
Non-ARIA	17 **(1.7%)**	17 **(1.7%)**

***June 2023 datacut – pre-specified approach; **May 2024 datacut – updated approach with vital status**

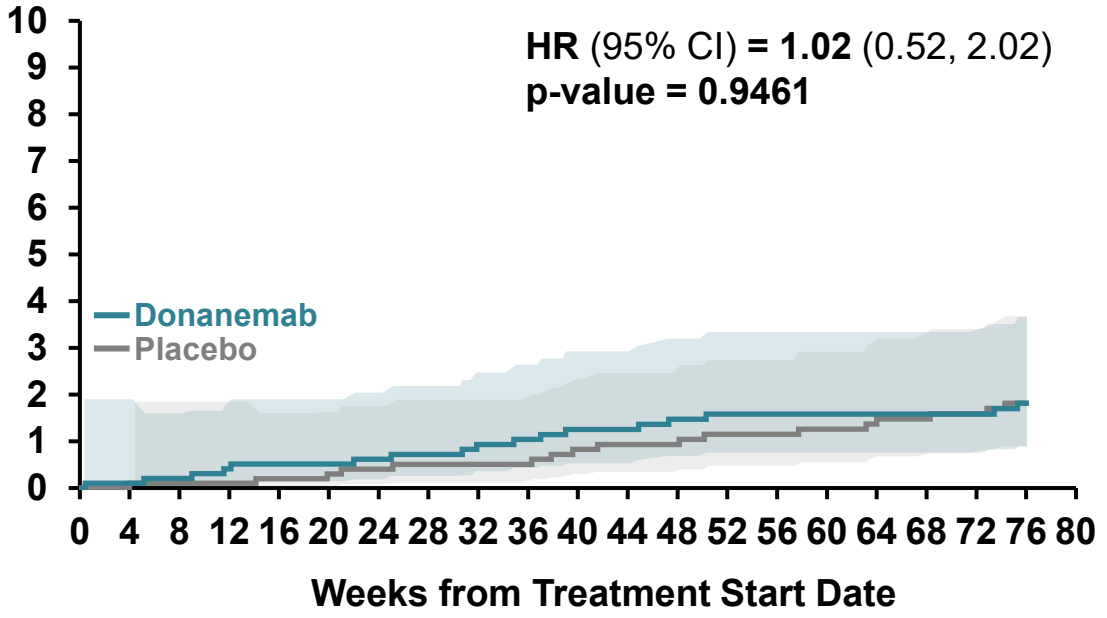
Updated Mortality Analysis According to Most Recent FDA Feedback

All Deaths



Event (n)									
Donanemab	2	7	8	11	14	16	17	18	18 20
Placebo	1	2	4	5	8	9	11	14	15 17

Non-ARIA Deaths



Donanemab	2	5	6	9	12	14	15	15	15 17
Placebo	1	2	4	5	8	9	11	14	15 17

May 2024 datacut – updated approach with vital status; Shading indicates 95% CI

Mortality Summary

- Overall frequency of death was low, difference related to ARIA
- Other than ARIA, no pattern of AEs leading to death
- Key learnings from development program have informed risk management recommendations
- Consistent with class, post-approval safety studies will further characterize risks, including ARIA

Adverse Events

Common AEs (≥ 5% of Patients)

Preferred Term	Dona-PC		All Dona
	Donanemab N = 984	Placebo N = 999	Donanemab N = 2,802
Any AE	89%	83%	81%
ARIA-E*	24%	2%	20%
ARIA-H**	18%	7%	17%
COVID-19	14%	16%	15%
Fall	13%	13%	12%
Headache	13%	10%	11%
Infusion related reaction	9%	0.4%	8%
Superficial siderosis of central nervous system	8%	1%	6%
Dizziness	7%	6%	6%
Urinary tract infection	6%	7%	6%
Arthralgia	6%	5%	4%
Nausea	5%	4%	3%

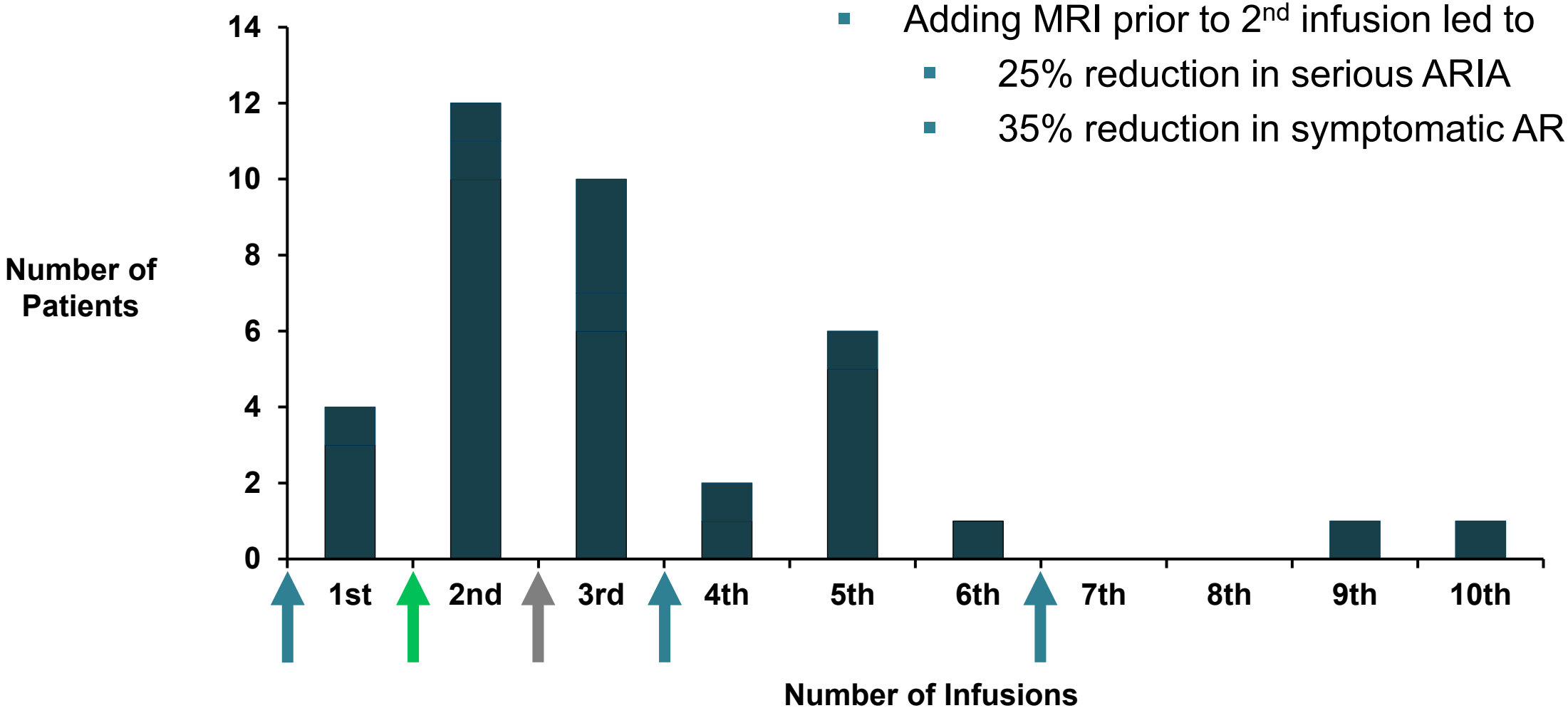
*Amyloid-related imaging abnormality – oedema/effusion; **Amyloid-related imaging abnormality – microhemorrhages and hemosiderin deposits

Overview of ARIA

Preferred term, n (%)	DONA-PC		All Dona
	Donanemab N = 984	Placebo N = 999	All Dona N = 2,802
ARIA-E	240 **(24%)**	19 **(2%)**	571 **(20%)**
SAE	15 **(2%)**	0	34 **(1%)**
Treatment discontinuations	28 **(3%)**	4 **(0.4%)**	54 **(2%)**
Symptomatic	57 **(6%)**	1 **(0.1%)**	127 **(5%)**
ARIA-H	309 **(31%)**	130 **(13%)**	778 **(28%)**
SAE	4 **(0.4%)**	0	9 **(0.3%)**
Treatment discontinuations	22 **(2%)**	4 **(0.4%)**	42 **(1.5%)**
Symptomatic	10 **(1%)**	3 **(0.3%)**	15 **(0.5%)**
Intracerebral hemorrhage > 1 cm	3 **(0.3%)**	2 **(0.2%)**	10 **(0.4%)**
SAE	1 **(0.1%)**	1 **(0.1%)**	3 **(0.1%)**
Treatment discontinuations	2 **(0.2%)**	1 **(0.1%)**	6 **(0.2%)**

All Dona: Most ARIA-Related SAEs Occurred Prior to 24 Weeks into Treatment (6th Infusion)

- Adding MRI prior to 2nd infusion led to
  - 25% reduction in serious ARIA
  - 35% reduction in symptomatic ARIA



All Dona safety set; = MRI per protocol; = Additional MRI added during study; = Additional MRI recommended in labeling

ARIA Risk Management Through Multi-Faceted Approach

- Risk management activities
  - Identifying higher risk patients prior to treatment
  - Targeted MRI monitoring
  - Dose titration, interruption, or discontinuation
  - Use of corticosteroids for serious or symptomatic ARIA
- Post-approval plan
  - Appropriate labeling
  - Patient card available for patients / caregivers
    - Includes ARIA-related information and emergency contact information
  - Patient / physician education
  - Observational post-approval safety studies proposed

Dona-PC: Infusion Related Reactions and Anaphylaxis

- 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
- Proposed label language warns of hypersensitivity and recommends monitoring for a minimum of 30 minutes

Summary of Safety

- Most common AE is ARIA, consistent with class
  - Generally asymptomatic and resolved
  - Serious and symptomatic ARIA was observed, uncommonly fatal
  - Clear labeling, targeted MRI monitoring, HCP education and a patient card help manage ARIA risk
- IRR are common, monitorable and most were mild to moderate
- No evidence of increased mortality beyond ARIA, post approval studies will further characterize risks
- Overall positive benefit / risk

Center for Alzheimer Research & Treatment

HARVARD AGING BRAIN

Massachusetts General Hospital ~ Harvard Medical School ~ Brigham and Women's Hospital

Treating Early Alzheimer's Disease

Reisa Sperling, MD
Brigham and Women's Hospital
Massachusetts General Hospital
Harvard Medical School

BWH VE RI TAS MGH 1811

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Alzheimer's Disease – The Unmet Challenge

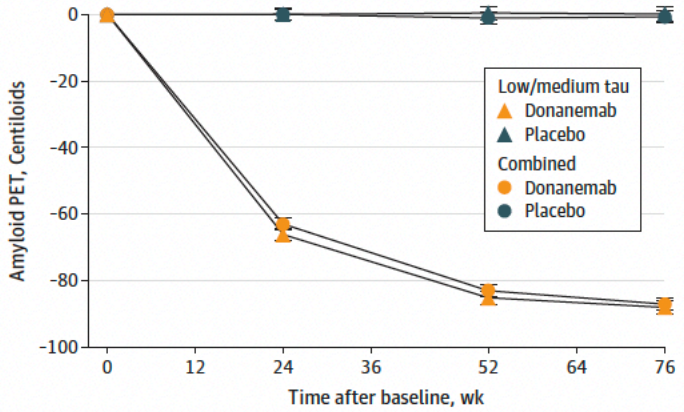
- Most common etiology contributing to late-life dementia
  - Prevalence increases exponentially by decade
  - 1 out of every 3 seniors will die with dementia, more than breast cancer and prostate cancer combined[1]
- Good news we can now:
  - Detect and monitor AD pathophysiological processes during life
  - Reliably decrease amyloid plaque build-up with biologically active treatments
  - Slow cognitive and functional decline if treatment is started at early symptomatic stage of AD

[1] Alzheimer's Association 2024 Facts and Figures

Consistency of Outcomes - Slowing Clinical Decline with Amyloid Removal

Donanemab Phase 3

Amyloid PET

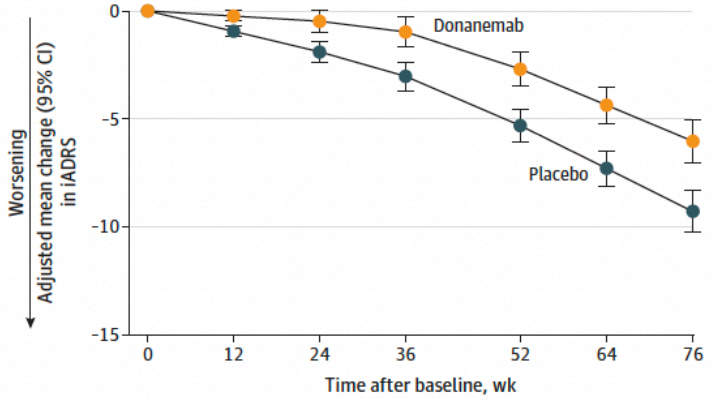


					76-wk value, Centiloids	Difference from baseline %
No. of participants						
Low/medium tau						
Donanemab	525	521	463	433	-88.0	-85.5
Placebo	556	552	498	470	0.2	0.2
Combined						
Donanemab	765	760	670	614	-87.0	-83.7
Placebo	812	805	729	690	-0.7	-0.7

Low/Medium Tau Group

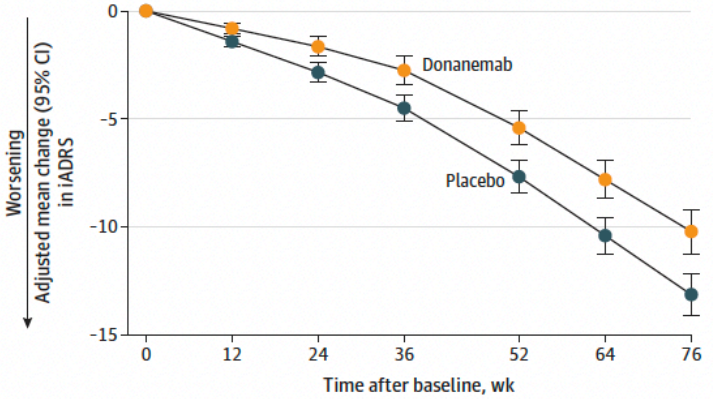
Overall Group

A iADRS in low/medium tau population



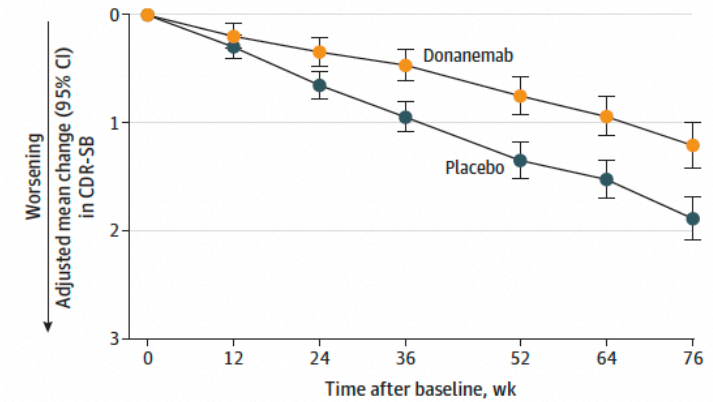
No. of participants							
Placebo	560	549	526	506	474	447	444
Donanemab	533	517	487	459	441	406	418

B iADRS in combined population



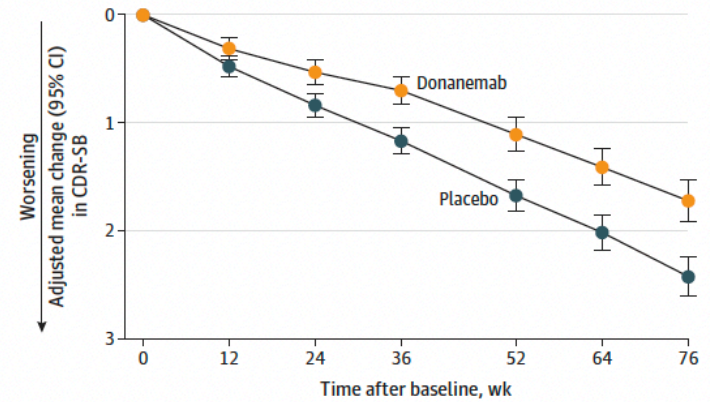
No. of participants							
Placebo	824	805	767	738	693	651	653
Donanemab	775	752	712	665	636	579	583

C CDR-SB in low/medium tau population



No. of participants							
Placebo	569	561	540	516	486	461	459
Donanemab	546	530	499	471	451	418	424

D CDR-SB in combined population

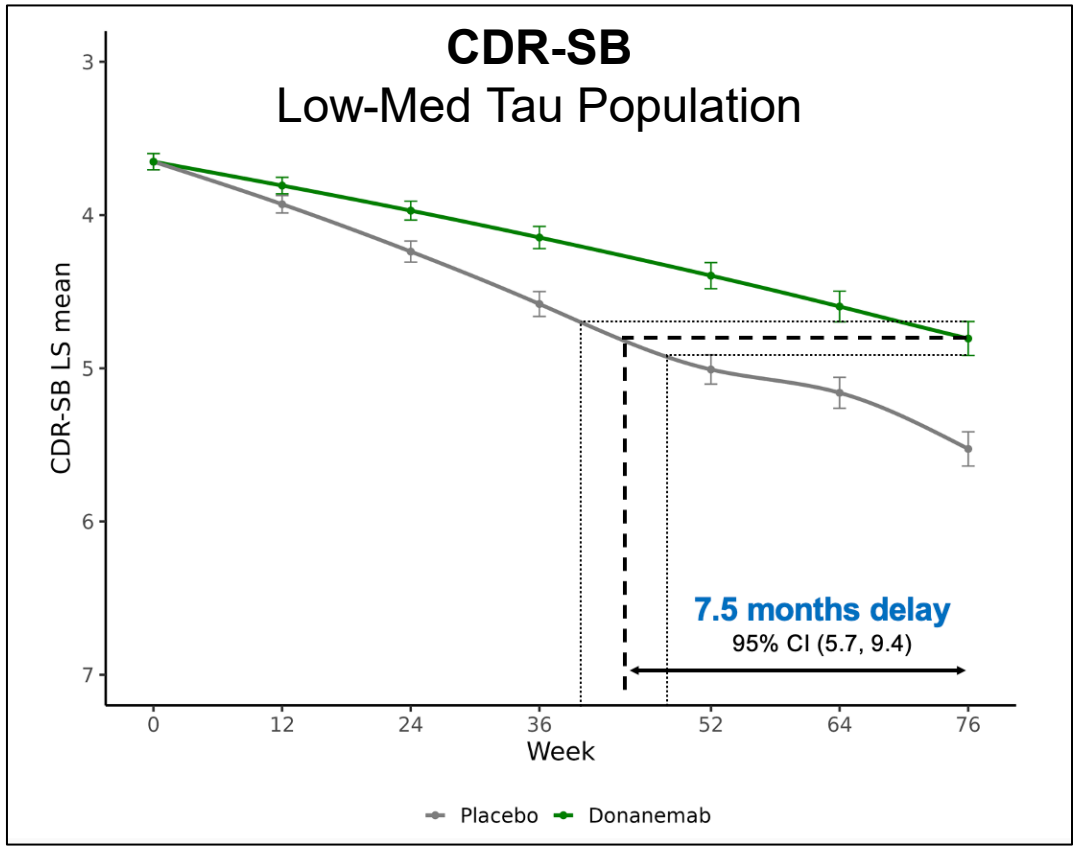


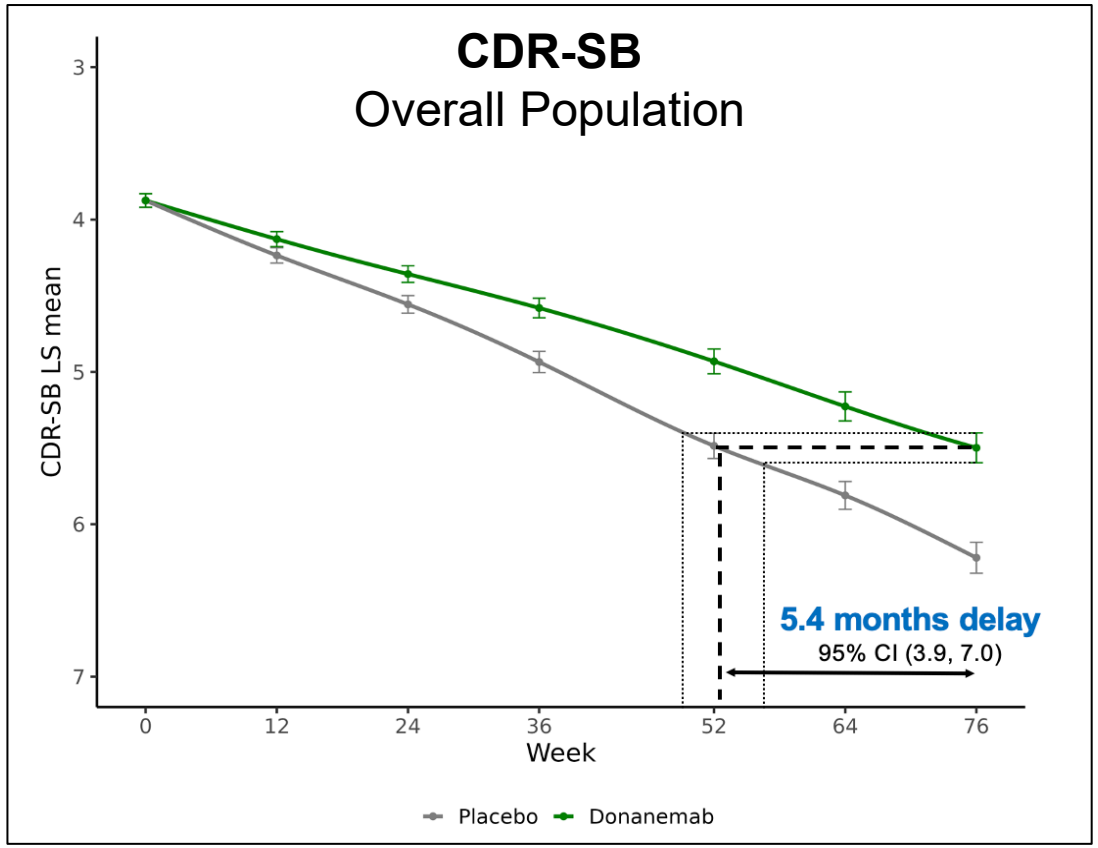
No. of participants							
Placebo	838	825	784	752	713	678	672
Donanemab	794	774	731	682	650	603	598

Sims J et al *JAMA* 2023

Gaining Valuable Time

Especially with Earlier Intervention

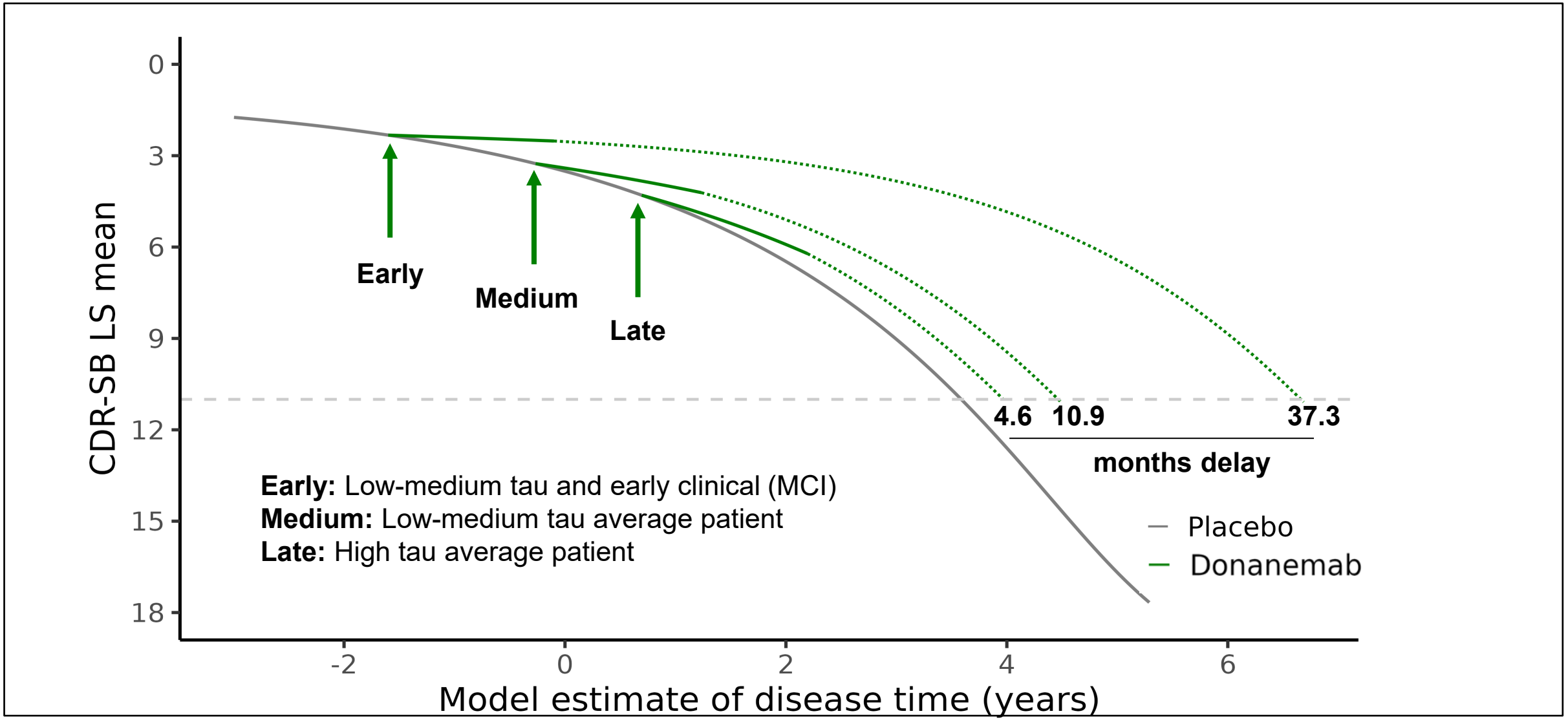




Proportional time slowing PMRM analysis
Error bars indicate +/- 1 standard error
PMRM = Progression Model for Repeated Measures, CI = Confidence Interval

Extending Valuable Time with Disease Modification

Extrapolation Model



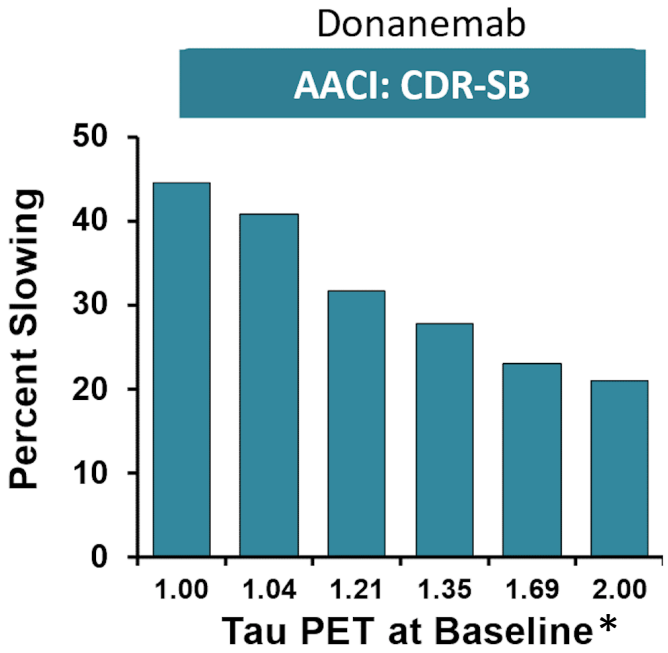
Latent-time disease progression model with proportional time slowing

Translation from Trial Design to Clinical Use

- Donanemab development program utilized novel clinical trial design elements
- Important to address implications for translating trial results into the clinic
  - Use of Tau PET to define eligibility
  - Cessation of treatment once amyloid “negative”
  - Risk-benefit considerations - ARIA

Tau PET

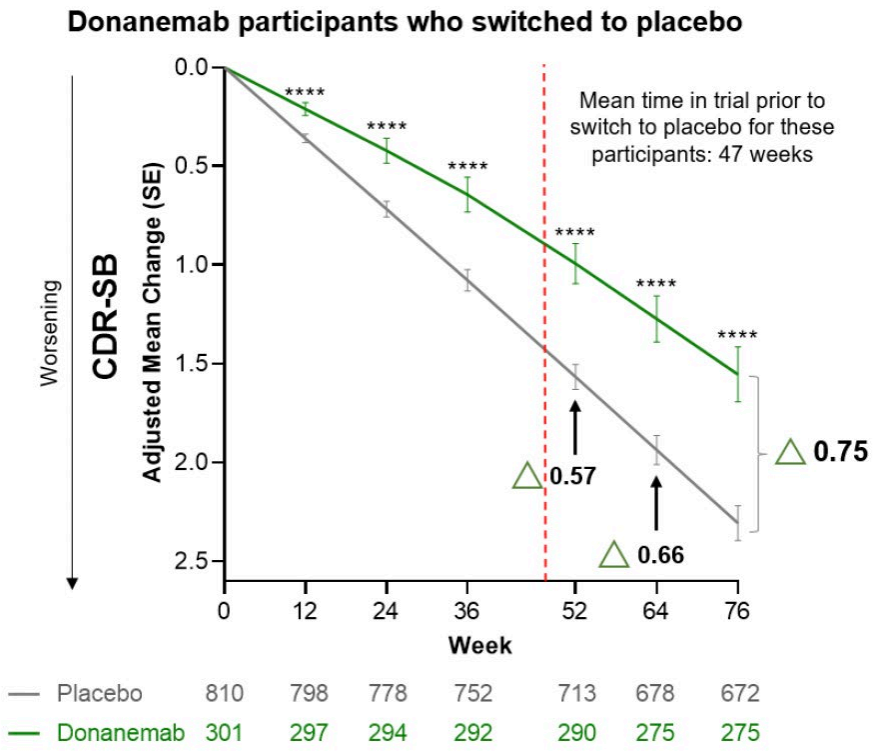
- Tau PET valuable tool in research studies to define anatomic location and levels of tau pathology to stage disease
- Greater treatment effect sizes observed with less tau pathology
- Not practical or necessary to require Tau PET for clinical use of donanemab
  - Limited availability and quantitative standardization of clinical Tau PET
  - Delay in starting therapy when every month may count
  - Further limit access to underserved communities
- Clinical benefit was observed across full range of tau



*Overall population at 76 weeks
Continuous measure based on modeling

Stopping Treatment Once Amyloid is Removed

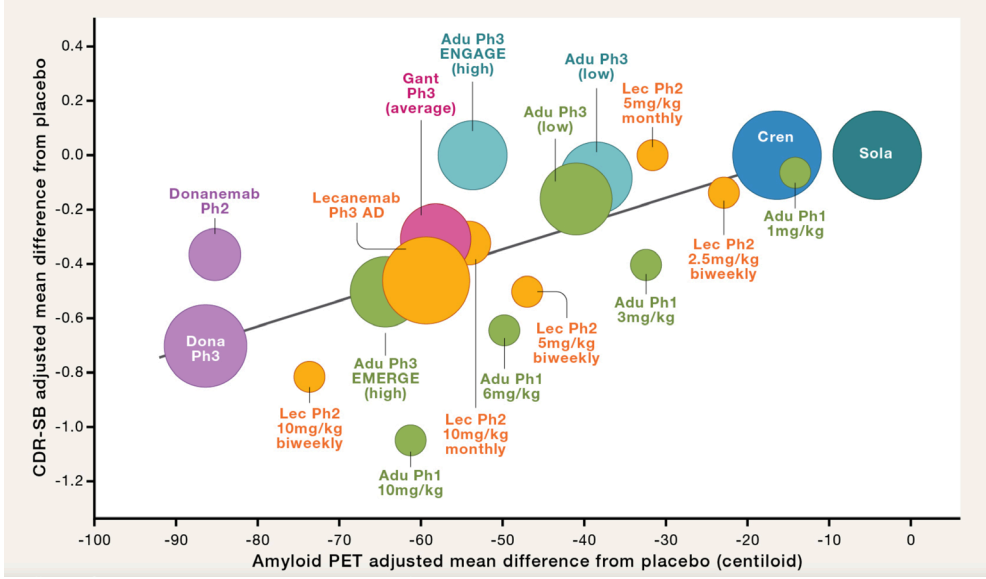
- Variable time to cessation of treatment mid-study added complexity to trial
- This approach is commonly used in other chronic diseases
  - Decreases patient burden
  - Decreases cost and other health care resources
- Ongoing studies to evaluate longer term outcomes once off-therapy for years
- Future approaches might include intermittent redosing



****p < 0.0001; Overall Population

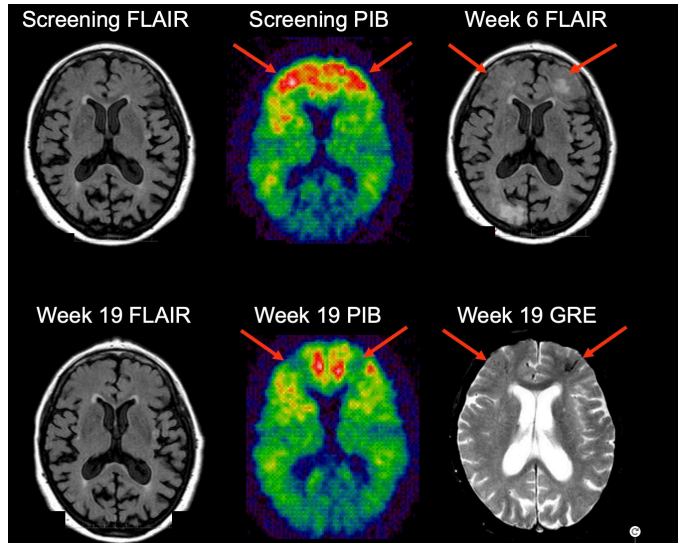
Amyloid Reduction and ARIA

- The totality of the data, both across the field and within programs, suggests that greater amyloid reduction is associated with greater clinical benefit



Boxer A and Sperling R *Cell* 2023

- ARIA is an “on-target” mechanistic side effect of amyloid removal
- Unlikely to be able to avoid ARIA and still achieve necessary levels of amyloid reduction



Sperling R et al Lancet Neurology 2012

Risk Benefit Considerations

- Overall ARIA is a manageable adverse event
  - Symptomatic ARIA is relatively uncommon
  - Serious adverse events are fortunately quite rare
- Important to minimize risk of ARIA with careful MRI monitoring
  - Particularly in APOE ε4 carriers
- Continue to inform broader medical community about ARIA detection and management
  - Post-approval “real world” data to improve understanding of ARIA risk
- Important to have detailed discussions with patients and care partners regarding individual risk-benefit
  - Allow people and their care partners to make informed decisions for themselves and their loved ones

Risk Benefit Considerations – Special Populations

- Risk of ARIA higher in APOE ε4/4
  - Higher amyloid load, greater CAA
- Similar directionality of benefit
  - Broader confidence interval with smaller group
  - Potentially related to lower exposure with ARIA dose suspensions
- APOE ε4/4 carriers desperately need treatment options
  - Have often seen AD in both parents
  - Risk of dementia extremely high
- Consider careful dosing for ε4/4 and close monitoring to minimize risk

nature medicine

Article

https://doi.org/10.1038/s41591-024-02931-w

APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease

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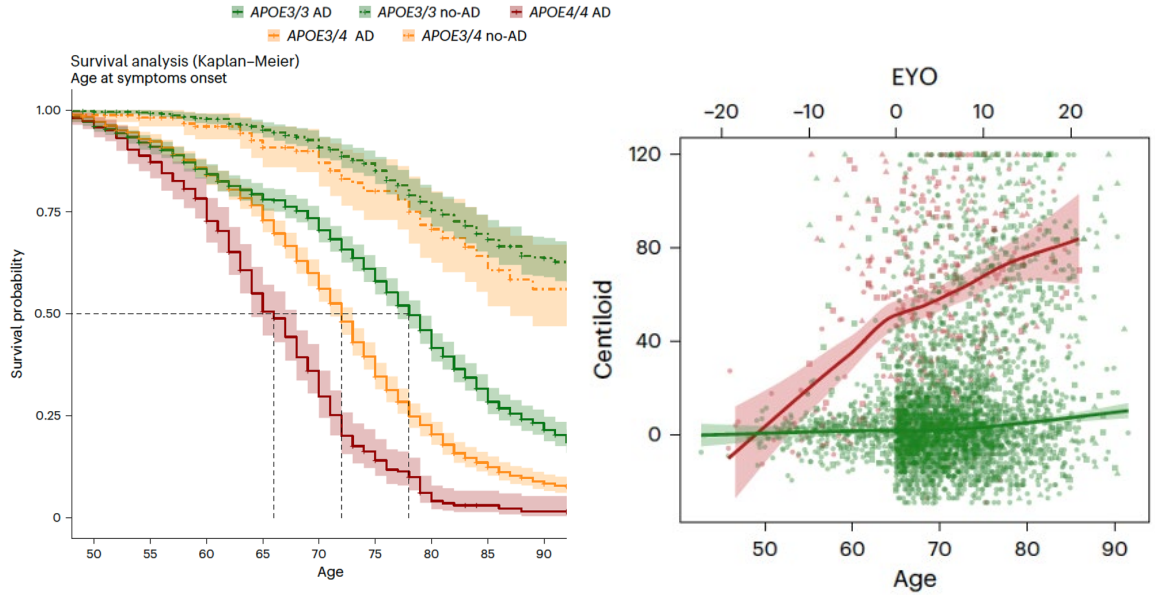
Check for updates

Juan Fortea[1,2,3,13], Jordi Pegueroles[1,2], Daniel Alcolea[1,2], Olivia Belbin[1,2], Oriol Dols-Icardo[1,2], Lídia Vaqué-Alcázar[1,4], Laura Videla[1,2,3], Juan Domingo Gispert[5,6,7,8,9], Marc Suárez-Calvet[5,6,7,8,9], Sterling C. Johnson[10], Reisa Sperling[11], Alexandre Bejanin[1,2], Alberto Lleó[1,2] & Víctor Montal[1,2,12,13]



AD symptom onset

Amyloid PET

Taking Alzheimer's Disease Seriously

- Serious diseases require aggressive treatments
  - Many older people fear Alzheimer's disease more than cancer
  - Commonly administer cancer treatments with debilitating side effects that are acceptable to gain months of life
- Historically, patients and doctors have believed there is nothing to slow Alzheimer's progression
  - After a quarter of a century, we finally have evidence that we can bend the curve of decline with substantial reduction of amyloid
- Valuable to have multiple treatment options for patients to consider
- Critical to make whatever impact we can to slow this terrible, inexorably progressive neurodegenerative disease

Donanemab for Treatment of Patients with Early Symptomatic Alzheimer's Disease

Eli Lilly and Company

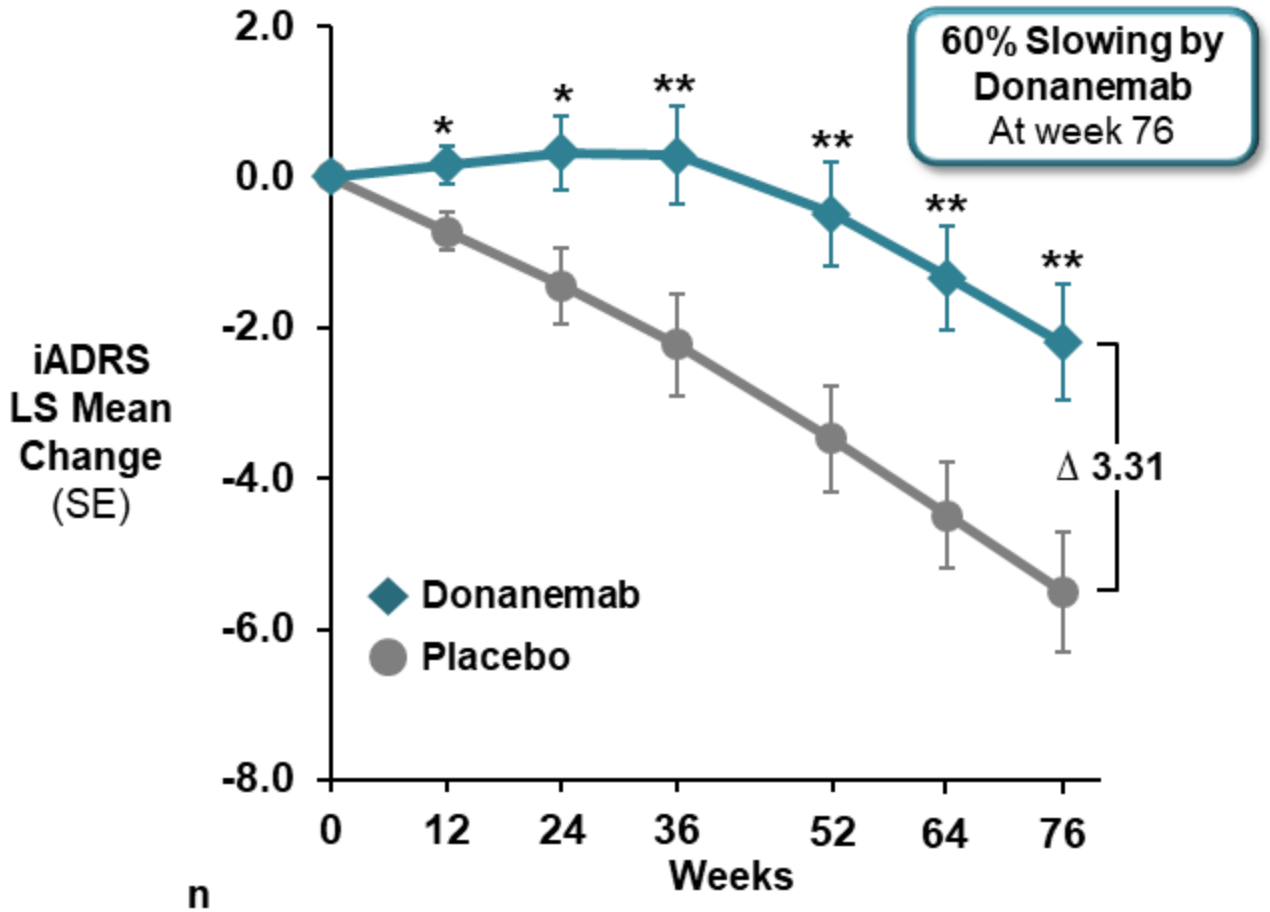
Peripheral and Central Nervous System Drugs Advisory Committee

June 10, 2024

Back Up Slides

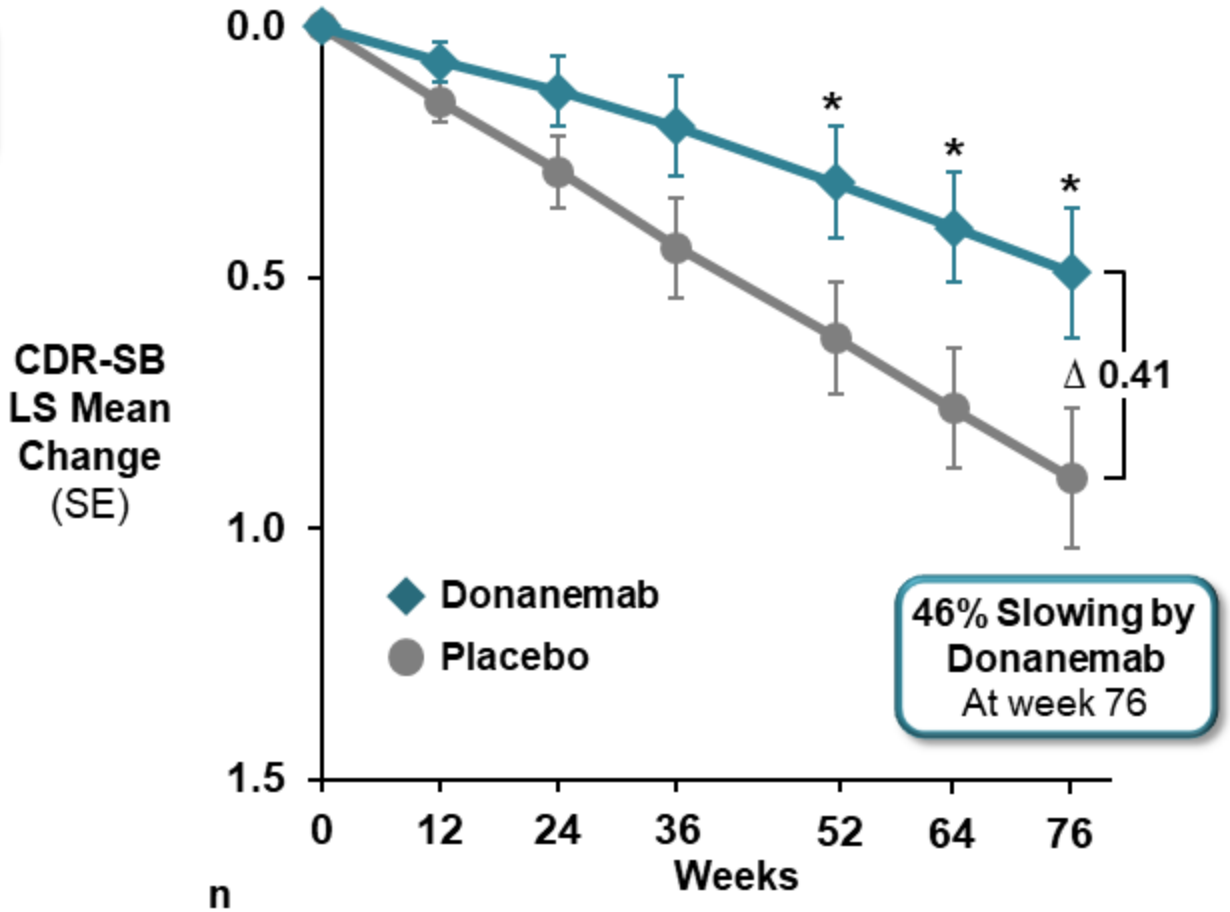
Patients Earlier in Disease May have Best Opportunity for Benefit Prespecified Subpopulation: MCI with Low-Medium Tau

iADRS



n							
Donanemab	112	110	103	101	96	91	92
Placebo	102	100	98	99	93	89	86

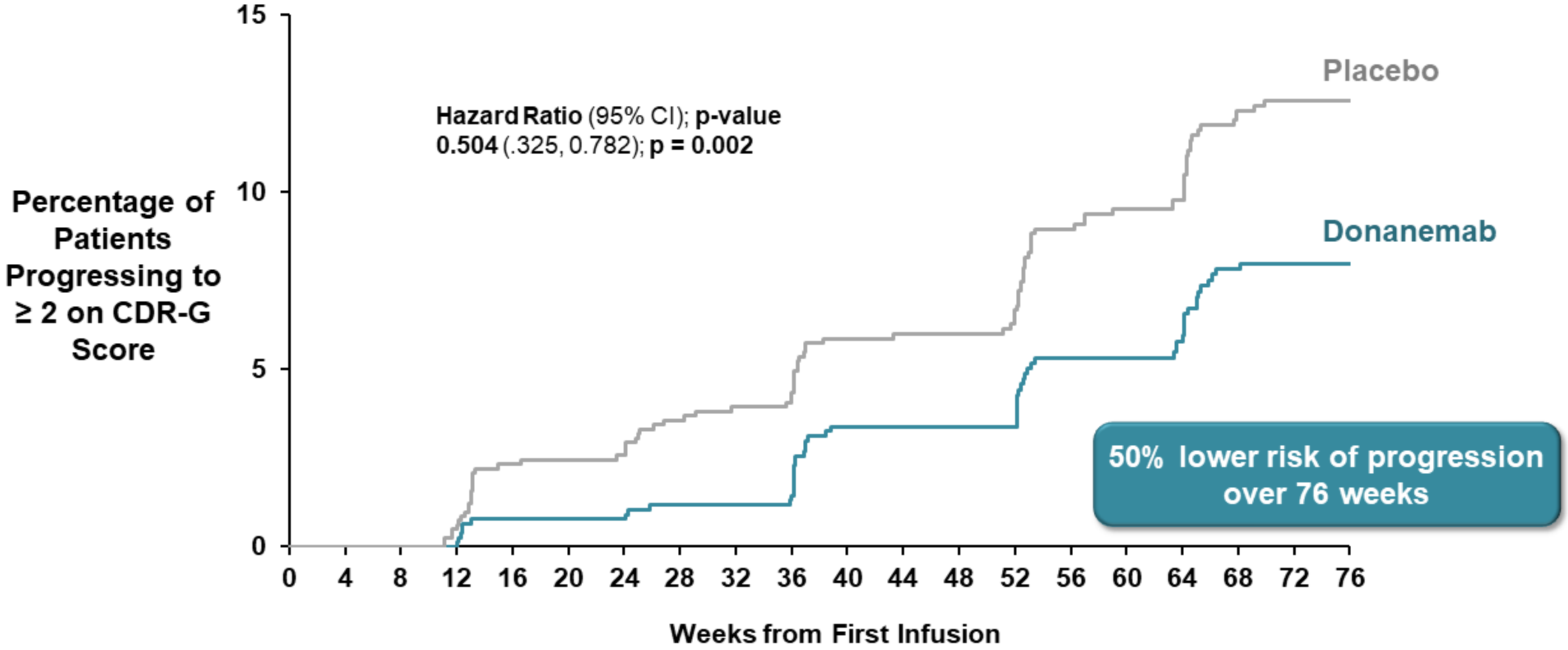
CDR-SB



n							
Donanemab	115	113	106	106	97	92	94
Placebo	104	102	100	101	95	91	89

*p < 0.05, **p < 0.01

Donanemab Lowers Risk of Progression to Moderate AD: CDR-Global Score, Overall Population

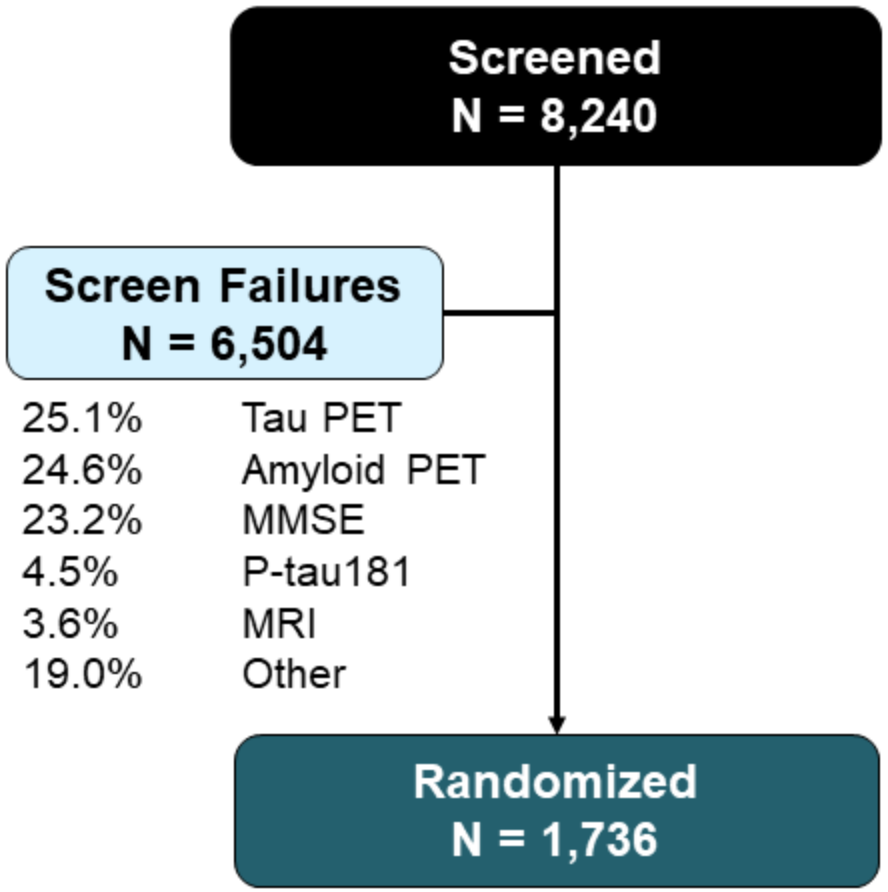


Patients Progressing to Next Clinical Stage (First CDR-G Worsening)

Shift CDR-G	Donanemab	Placebo
0 to 0.5	1	3
0.5 to 1	134	202
1 to 2	51	82
2 to 3	0	1

Shift represents change in CDR-G global score from baseline at 2 consecutive visits

Reasons for Screen Failure in Study AACI



Screen Failure Details	No. (%)
Screen Failure	6504 (78.9%)
Reasons for screen failure[a,b]	
Flortaucipir	1631 (25.1%)
Florbetapir	1601 (24.6%)
MMSE	1510 (23.2%)
Withdrawal by Subject	465 (7.1%)
P-tau 181[c]	295 (4.5%)
Reliability	259 (4.0%)
MRI	234 (3.6%)
Current Serious or Unstable Illness	76 (1.2%)
Clinically Important Abnormality	75 (1.2%)
Significant Neurological Disease	40 (0.6%)
Study Partner	38 (0.6%)
Physician Decision	32 (0.5%)
History of Cancer	29 (0.4%)
Age	28 (0.4%)
Poor Venous Access	23 (0.4%)
ALT/AST/TBL/ALP	21 (0.3%)
Withdrawal Due to Caregiver Circumstances	21 (0.3%)

Abbreviations: AD, Alzheimer's Disease; ALT, Alanine aminotransaminase; AST, aspartate aminotransferase; TBL, total bilirubin level; ALP, alkaline phosphatase; MMSE, Mini–Mental State Examination; MRI, magnetic resonance imaging; PET, positron emission tomography; P-tau181, phosphorylated tau 181; SUVR, standardized uptake value ratio

[a] Reasons for screen failure percentages are based on number of subjects screen failed rather than total number screened.

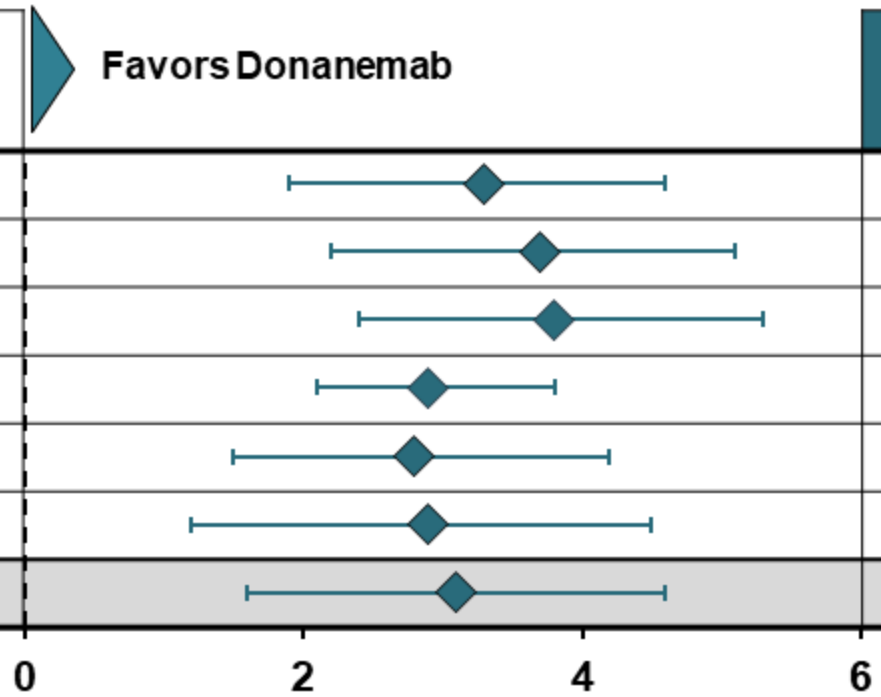
[b] Reasons for screen failure with a minimum of 20 participants are listed.

[c] Plasma P-tau181 exclusion applied to individuals who screened under the original protocol and amendment (a), but this criterion was removed in amendment (b) Feb 2021

Adapted from Sims et al. JAMA 2023

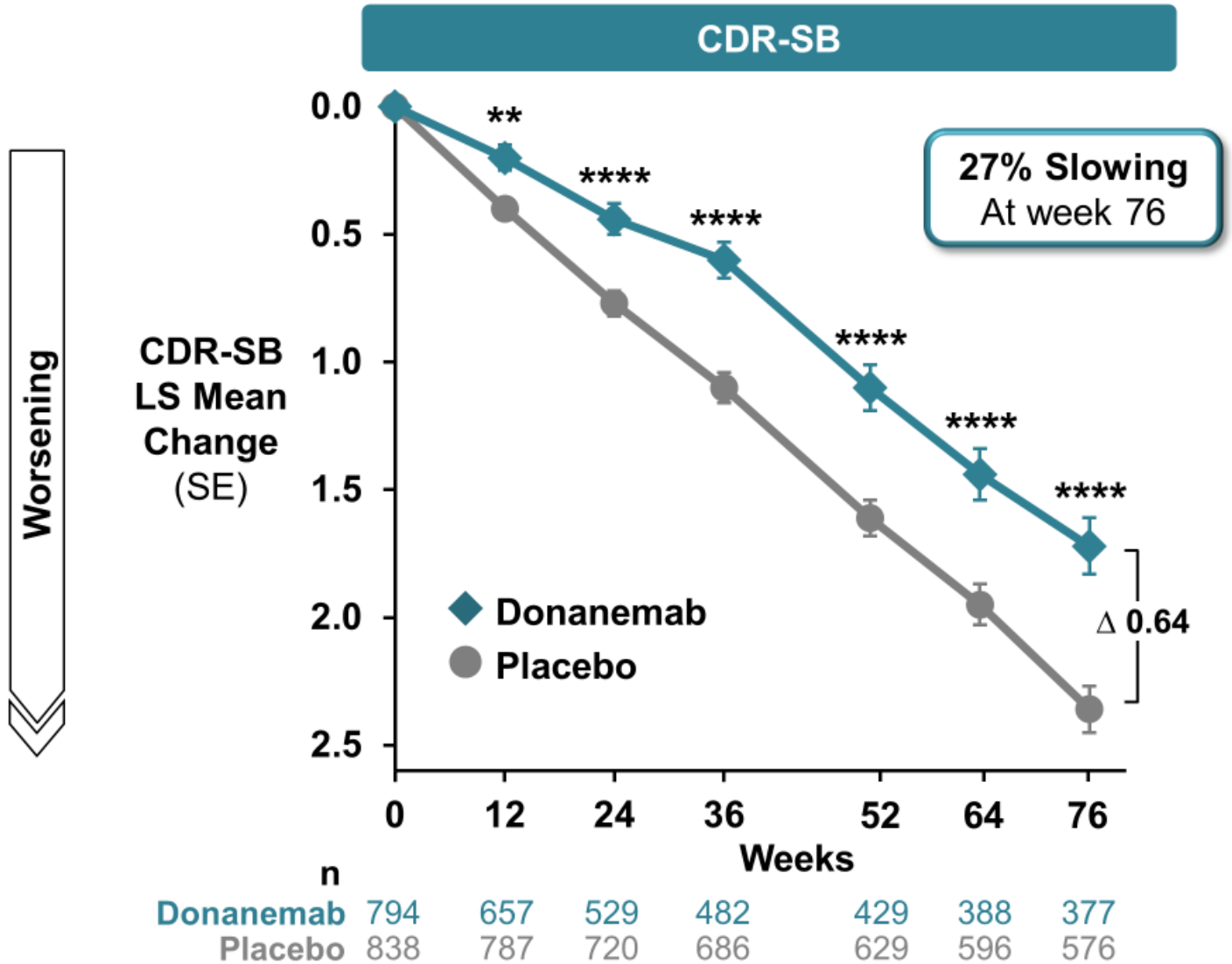
Donanemab Robustly Slowed Clinical Decline Censoring Clinical Scale Scores after ARIA and/or IRR

	Baseline N | N	Week 76 N | N	Favors Donanemab	Adjusted Mean Dif (Difference 95% CI)
NCS2	533 | 560	418 | 444		**3.3** (1.9, 4.6)
NCS3	533 | 560	418 | 444		**3.7** (2.2, 5.1)
MMRM	533 | 560	418 | 444		**3.8** (2.4, 5.3)
DPM	533 | 560	418 | 444		**2.9** (2.1, 3.8)
NCS2 in completers population	421 | 465	416 | 443		**2.8** (1.5, 4.2)
NCS2 – PP	268 | 275	268 | 275		**2.9** (1.2, 4.5)
NCS2 censored post ARIA-E/IRR	533 | 559	299 | 435		**3.1** (1.6, 4.6)



Overall population

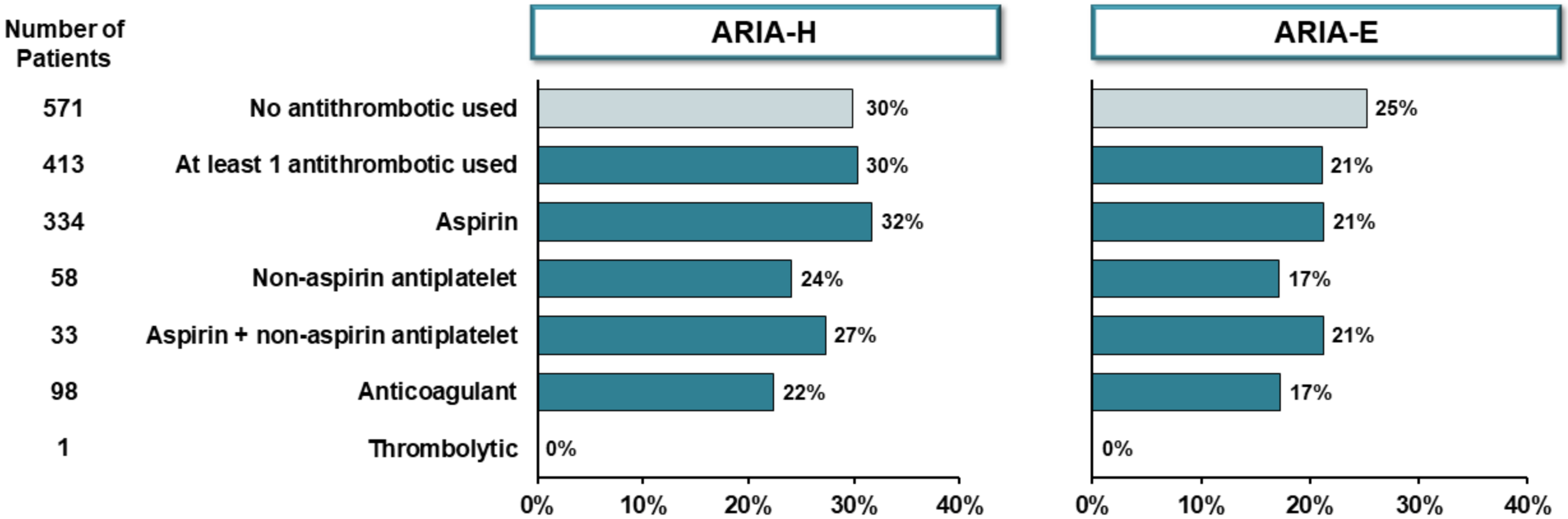
Censoring After First ARIA Occurence: Donanemab Slowed Progression of Clinical Decline



**p < 0.01; ****p < 0.0001; Overall population

Antithrombotics Did Not Increase Risk for ARIA

10% of Donanemab patients used anticoagulants, 40% used anti-platelets in Dona-PC



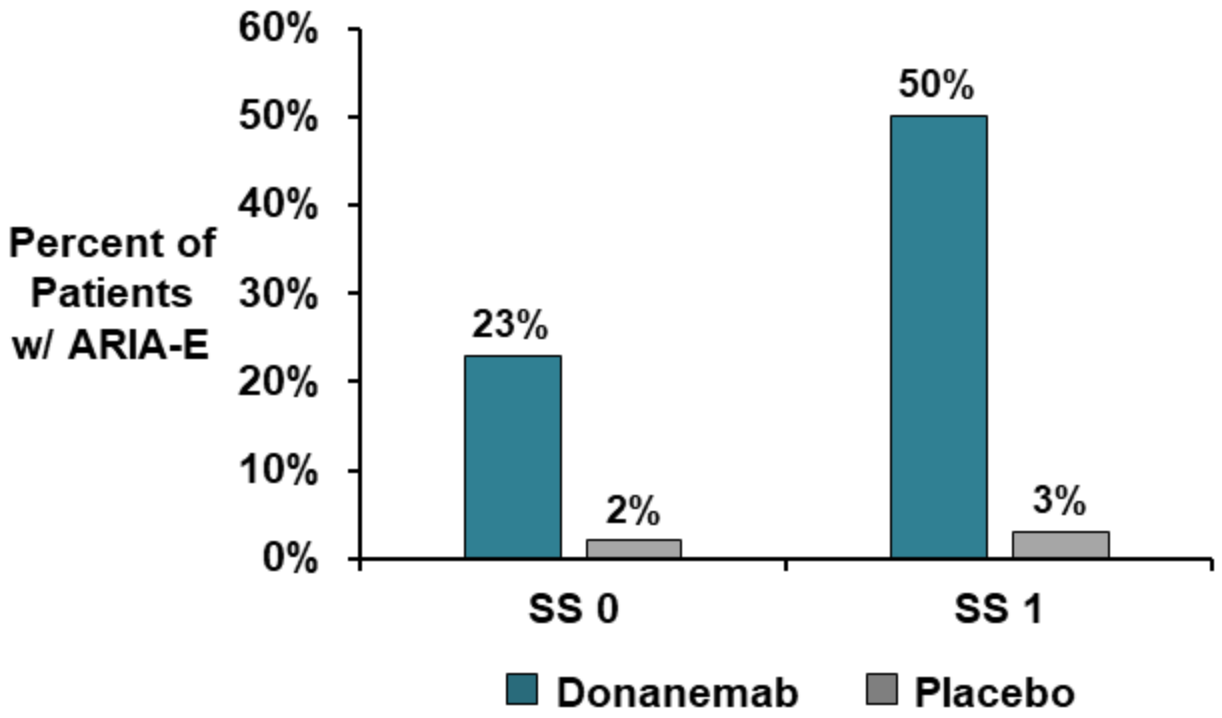
% of Patients in Dona Group with Specified Antithrombotic Use having ARIA Event w/in 30 Days

ARIA Related Deaths in All Dona: FDA - 0.18%

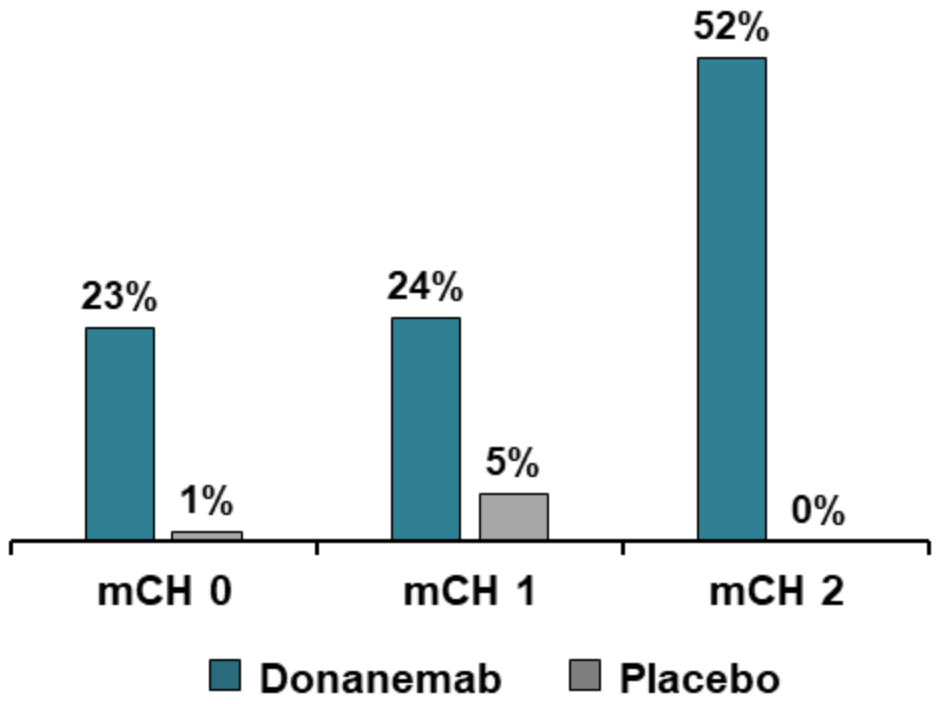
Fatal Event	Study	Patient Demographic	Death Study Day	Relevant Information
ARIA-H	**AACI**	**73, white, male**	**75**	**APOEε4 non-carrier, low-medium Tau, baseline superficial siderosis (50 mm), symptomatic headache. Donanemab infusions=2**
ARIA-E	**AACI**	**73, white, female**	**80**	**APOEε4 heterozygote, low-medium Tau, symptomatic confusion, agitation and speech abnormalities. Donanemab infusions=3**
Death (ARIA-E and ARIA-H)	**AACI**	**76, white, male**	**447**	**APOEε4 heterozygote, low-medium Tau, multiple episodes of ARIA-E and H on rechallenge, symptomatic nausea/vomiting. Donanemab infusions=10**
ARIA-E	AACI-LTE	77, white, male	730/164 (in LTE)	APOEε4 heterozygote, low-medium Tau, Switched to donanemab in LTE. Symptoms - confusion, headache, severe gait disturbance & loss of vision. Donanemab infusions=5
Intracranial Hemorrhage	**AACI-LTE**	**72, white, male**	**706/141 (in LTE)**	APOEε4 heterozygote, High Tau, Switched to donanemab in LTE. Symptoms of ischemic stroke treated with Tenecteplase developed intracranial hemorrhage. ARIA-E on central MRI. Donanemab infusion=5

Baseline mH and SS are Risk Factors for ARIA-E

Presence of Superficial Siderosis (SS)



Number of Microhemorrhages (mCH)



ARIA-E Risk Factors Assessed: All Dona

ARIA-E risk consistently driven by

APOE ε4 genotype
Number of baseline microhaemorrhages
Presence of superficial siderosis at baseline
+/- Baseline Amyloid

- **No Consistent Impact on ARIA**
  - Body weight
  - Mean arterial pressure
  - Time since onset of symptoms of AD
  - Time since diagnosis of AD
  - Baseline MMSE
  - Baseline C-reactive protein
  - Baseline tau PET
  - Baseline White matter disease
  - Baseline acetylcholinesterase use
  - Race
  - Age
  - Sex
  - Antithrombotic medication during study period
  - Antidrug antibodies titer
  - Initial rate of plaque removal
  - $C_{max,ss}$ and $C_{trough,ss}$

All Dona: Safety Overview in Black or African American and US Hispanic Populations

Preferred term, n (%)	All Dona N = 2,802	Black or African American N = 73	US Hispanic N = 163
Overview of AEs			
Deaths	36 **(1.3%)**	**0**	**0**
SAEs	463 **(17%)**	8 **(11%)**	15 **(9%)**
DCAE (treatment)	295 **(11%)**	9 **(12%)**	7 **(4%)**
TEAEs	2,260 **(81%)**	57 **(78%)**	122 **(75%)**
Overview of ARIA			
Any ARIA	917 **(33%)**	24 **(33%)**	47 **(29%)**
ARIA-E	571 **(20%)**	17 **(23%)**	26 **(16%)**
Symptomatic	127 **(5%)**	3 **(4%)**	5 **(3%)**
ARIA-H	778 **(28%)**	19 **(26%)**	41 **(25%)**
Intracerebral hemorrhage > 1 cm	10 **(0.4%)**	**0**	**0**
Infusion-related reaction	234 **(8%)**	6 **(8%)**	16 **(10%)**

Dona-PC: Safety Overview in Black / African American Patients (N = 24) by APOE-ε4 Genotype

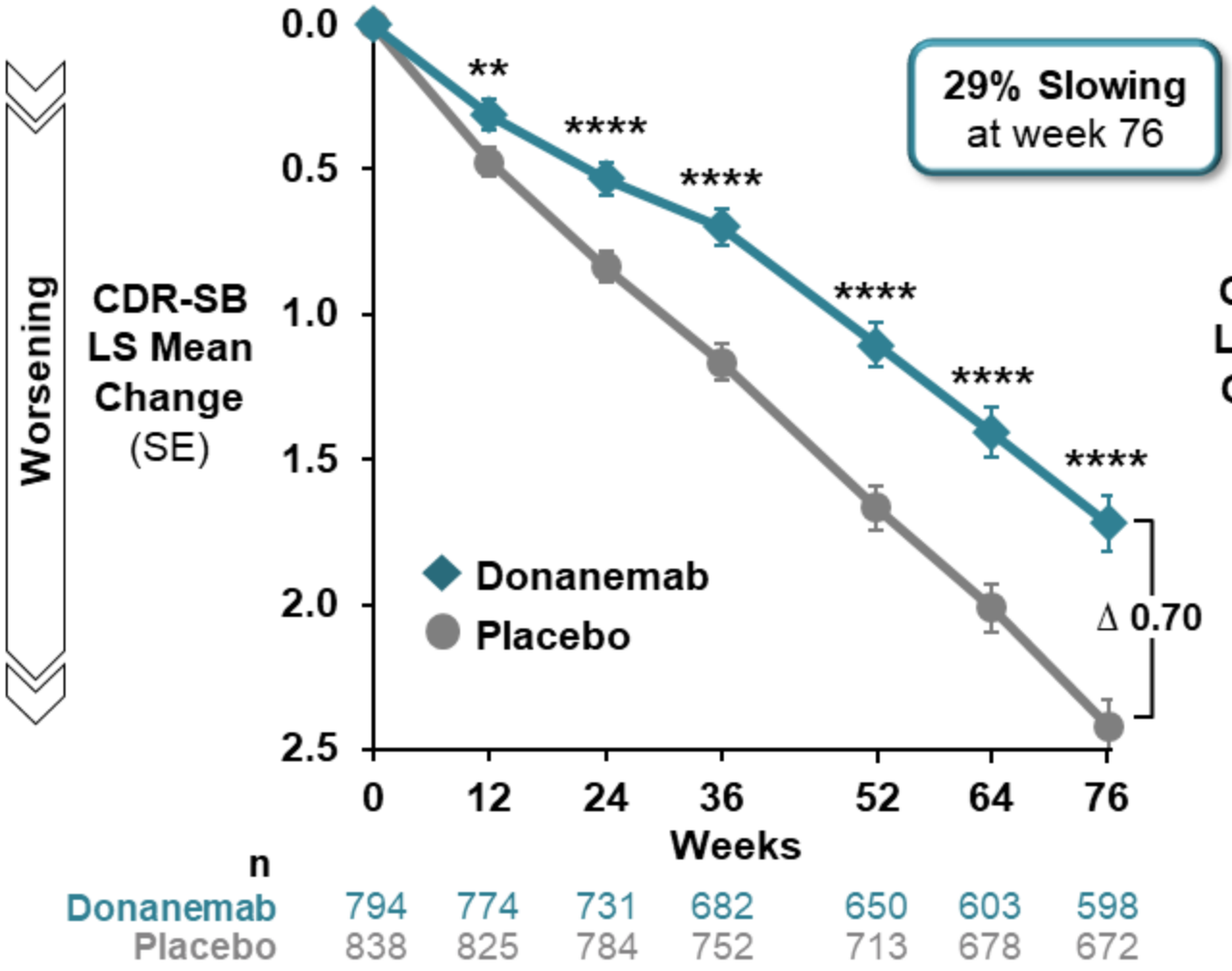
	Homozygote N = 3	Heterozygote N = 17	Non-carrier N = 4
TEAE	2 **(66.7%)**	15 **(88.2%)**	2 **(50.0%)**
SAE	1 **(33.3%)**	1 **(5.9%)**	**0**
AE leading to treatment discontinuation	**0**	6 **(35.3%)**	**0**
Death	**0**	**0**	**0**
Any ARIA	2 **(66.7%)**	6 **(35.3%)**	**0**
ARIA-E	1 **(33.3%)**	4 **(23.5%)**	**0**
Symptomatic	**0**	**0**	**0**
ARIA-H	2 **(66.7%)**	4 **(23.5%)**	**0**
Intracerebral Hemorrhage > 1 cm	**0**	**0**	**0**
Infusion Related Reaction	**0**	2 **(11.8%)**	1 **(25.0%)**

Dona-PC: Safety Overview in Hispanic Patients (N = 40) by APOE-ε4 Genotype

	Homozygote N = 7	Heterozygote N = 18	Non-carrier N = 15
TEAE	6 **(85.7%)**	16 **(88.9%)**	12 **(80.0%)**
SAE	**0**	1 **(5.6%)**	3 **(20.0%)**
AE leading to treatment discontinuation	1 **(14.3%)**	4 **(22.2%)**	2 **(13.3%)**
Death	**0**	**0**	**0**
Any ARIA	4 **(57.1%)**	6 **(33.3%)**	3 **(20.0%)**
ARIA-E	2 **(28.6%)**	3 **(16.7%)**	2 **(13.3%)**
Symptomatic	1 **(14.3%)**	**0**	1 **(6.7%)**
ARIA-H	4 **(57.1%)**	5 **(27.8%)**	2 **(13.3%)**
Intracerebral Hemorrhage > 1 cm	**0**	**0**	**0**
Infusion Related Reaction	1 **(14.3%)**	2 **(11.1%)**	**0**

CDR-SB in Overall Population and With Censoring

Overall Population (no censoring)



n							
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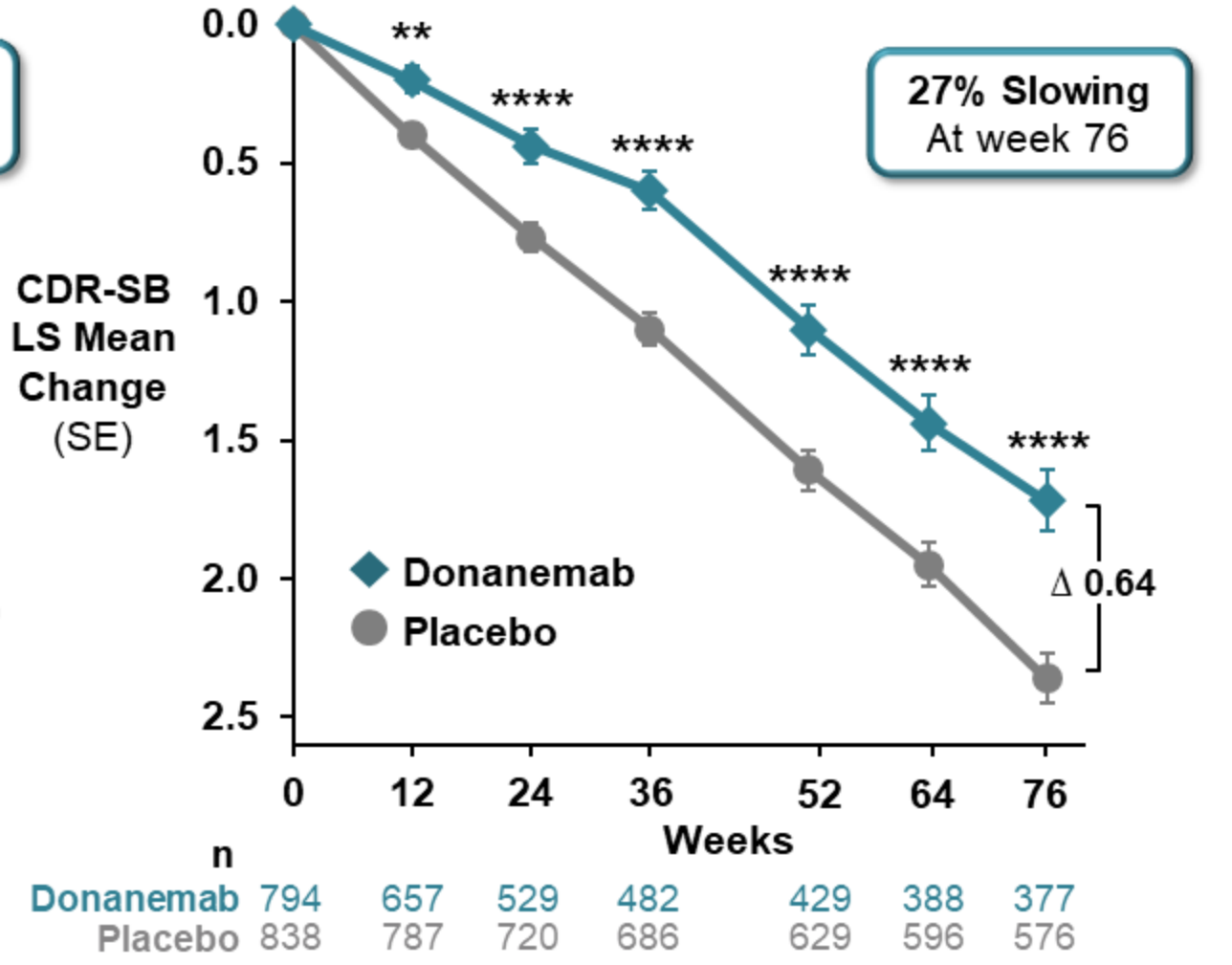
Placebo	838	825	784	752	713	678	672

With Censoring (at first ARIA occurrence)



n							
Donanemab	794	657	529	482	429	388	377
Placebo	838	787	720	686	629	596	576

Sensitivity Analysis by APOE Genotype: CDR-SB

		Non-Carrier	Heterozygotes	Homozygotes
No Censoring	Percent Slowing at Week 76	28.7%	33.6%	17.7%
	Treatment difference vs Placebo at week 76	0.76	0.73	0.41
	Baseline (N) / Week 76 (N)	238 / 181	423 / 320	131 / 97
Censoring After First ARIA-E / H Occurrence	Percent Slowing at Week 76	30.2%	30.5%	10.0%
	Treatment difference vs Placebo at Week 76	0.82	0.68	0.22
	Baseline (N) / Week 76 (N)	238 / 136	423 / 199	131 / 42