MOST RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF ALZHEIMER'S DISEASE

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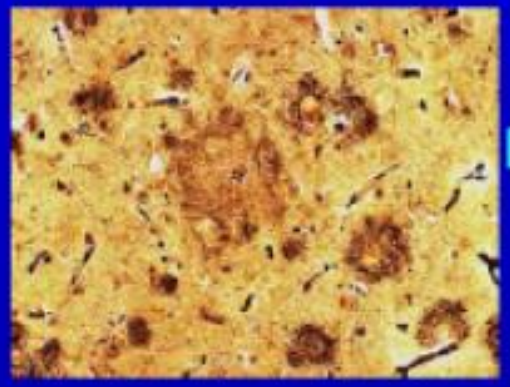
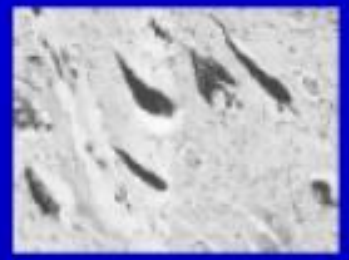
PATHOLOGY OF ALZHEIMER'S DISEASE

AMYLOID, TAU, NEURODEGENERATION



β-amyloid



Tau Pathology

Neurodegeneration:

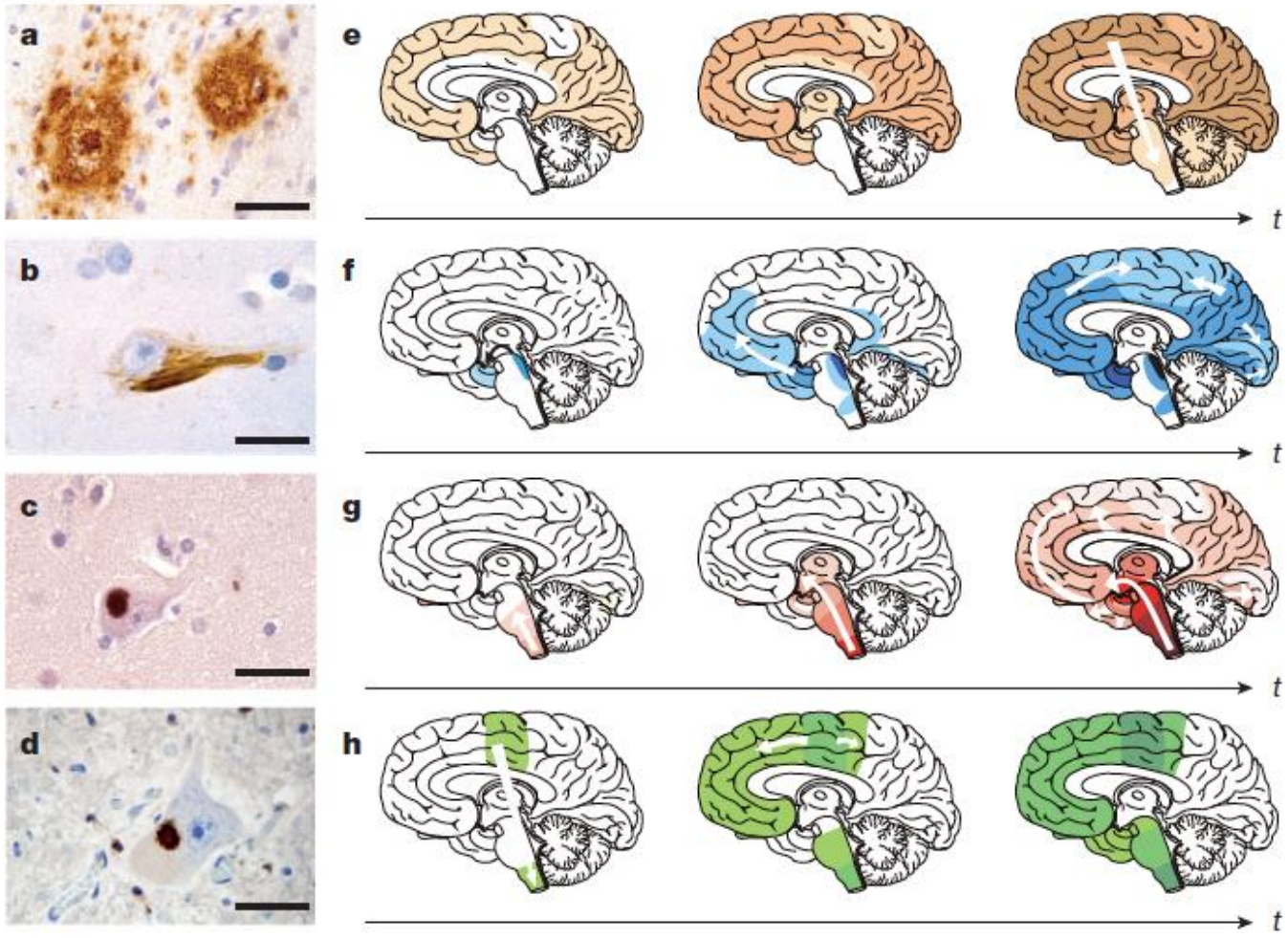
Cognitive Decline

and

Dementia

Age and Apoe-4 are major risk factors
Other pathologies contribute to neurodegeneration, cognitive decline, dementia

PROTEINS IN NEURODEGENERATIVE DISEASES



AD AMYLOID

AD TAU

PD ALPHA SYN

TDP 43 ALS

Cerebrovascular disease the most common comorbidity

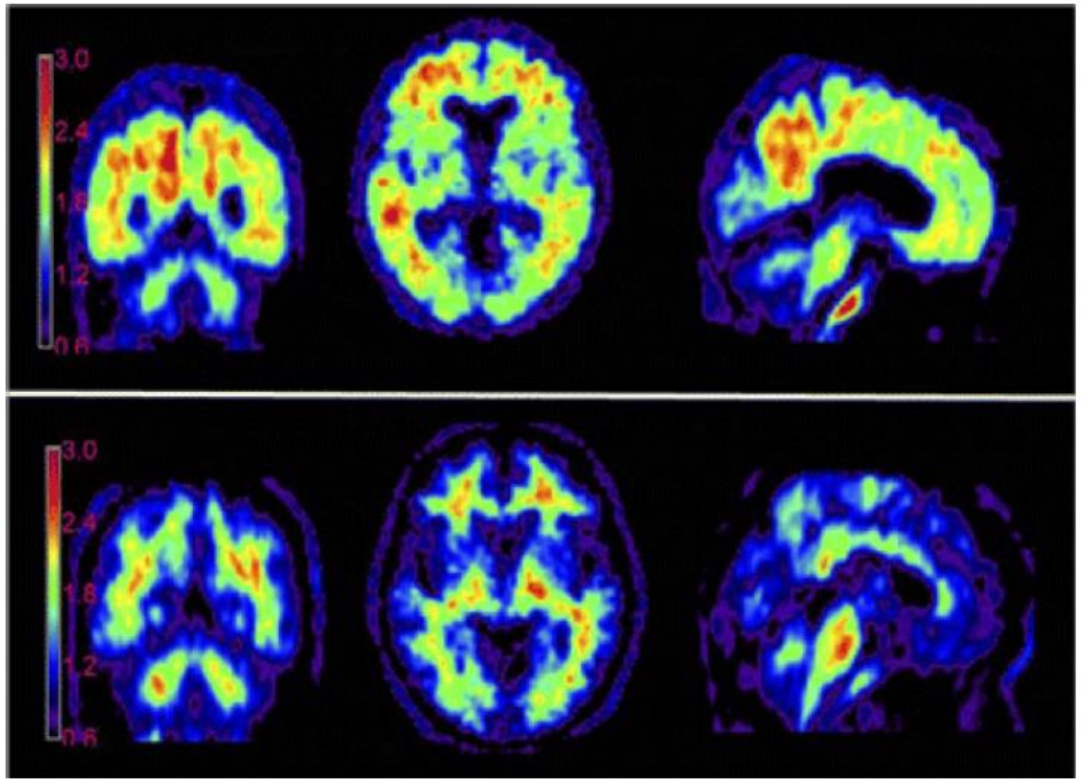
HOW TO DIAGNOSE AD

- Clinical diagnosis of MCI or dementia is not sufficient!
- Final AD diagnosis requires biomarker diagnosis
- Amyloid PET, Tau PET, MRI (neurodegeneration)
- Lumbar puncture: cerebrospinal fluid
  - Amyloid 42/40, phospho tau
- Plasma amyloid 42/40, phospho tau

Aβ PET in AD Compared to Cognitively Healthy Control

A

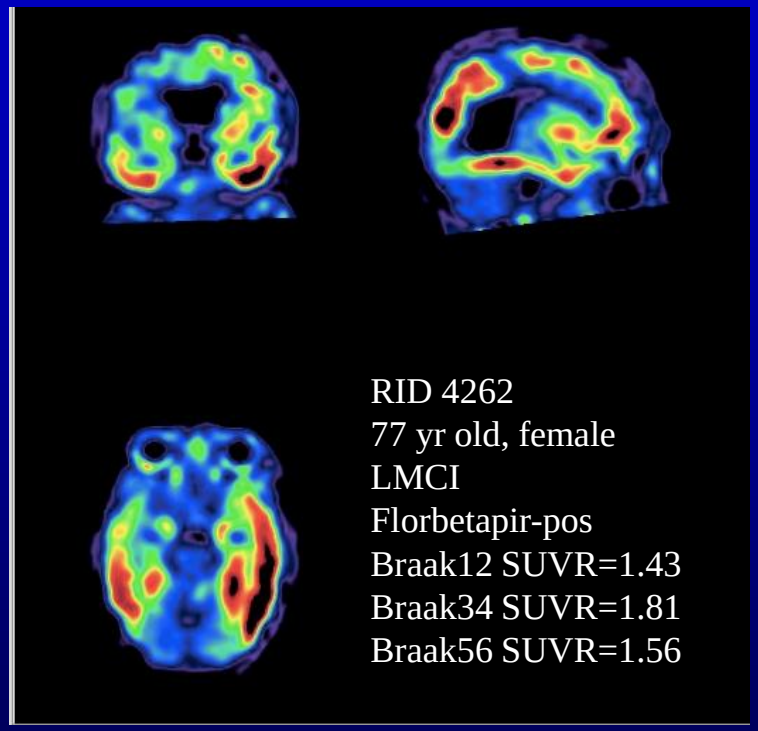
B



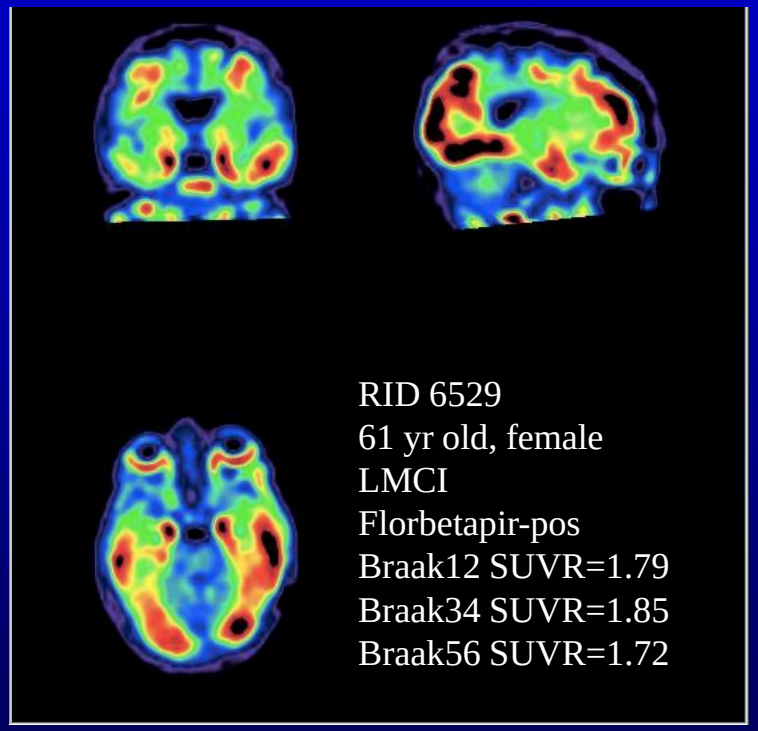
A. [18F]AV-45 PET: 77 year old female with mild AD patient with an MMSE of 24

B. [18F]AV-45 PET: 82 year old male cognitively healthy control with an MMSE of 30

TAU PET
AMYLOID POSITIVE SUBJECTS:
High Flortaucipir scans



RID 4262
77 yr old, female
LMCI
Florbetapir-pos
Braak12 SUVR=1.43
Braak34 SUVR=1.81
Braak56 SUVR=1.56

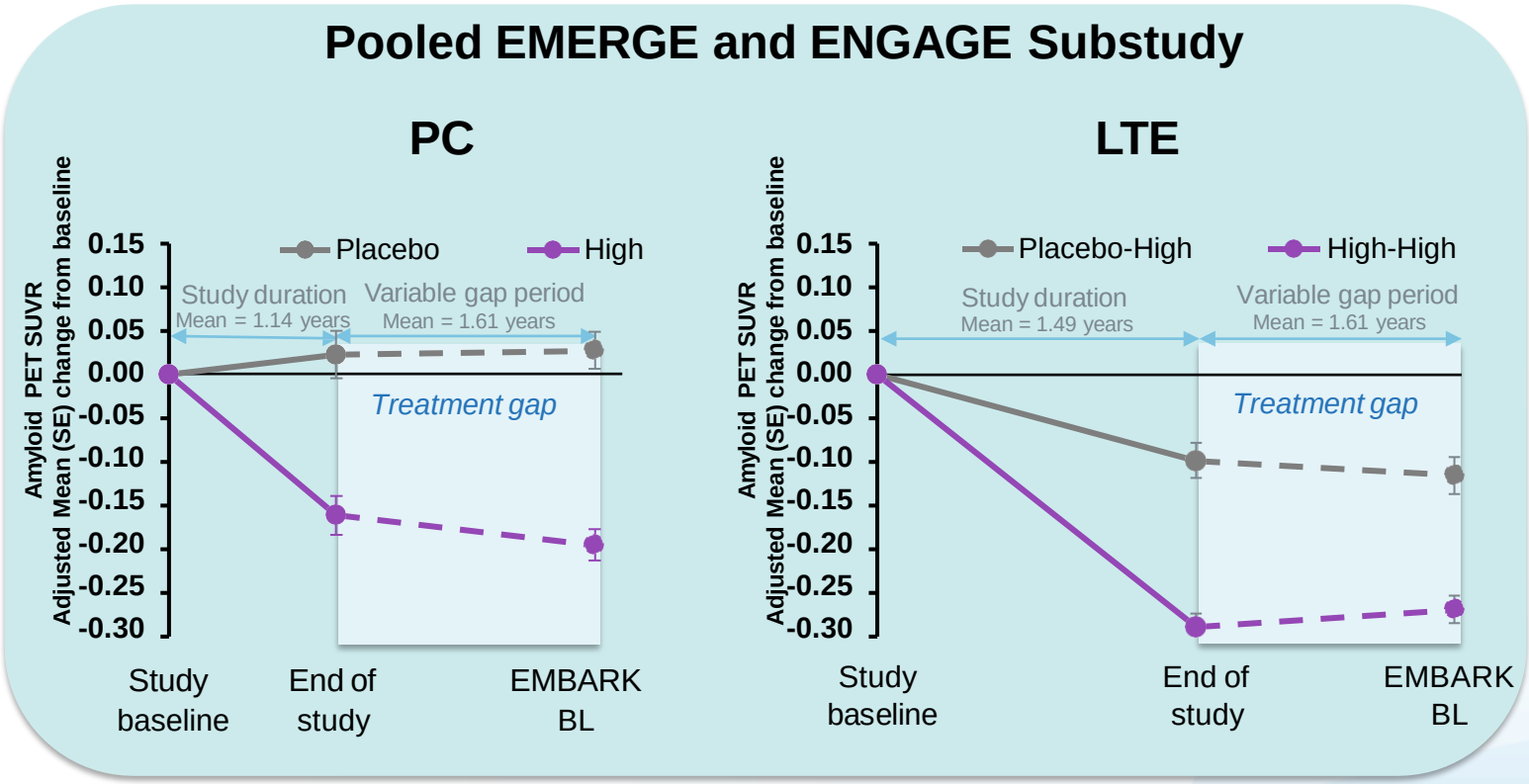


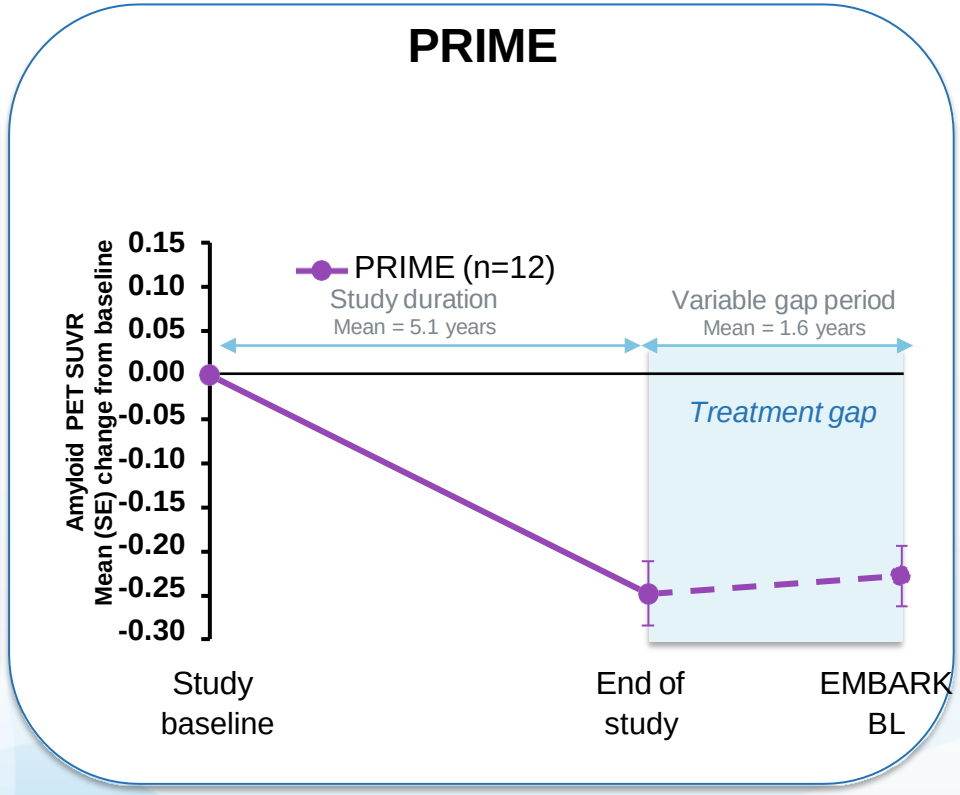
RID 6529
61 yr old, female
LMCI
Florbetapir-pos
Braak12 SUVR=1.79
Braak34 SUVR=1.85
Braak56 SUVR=1.72

ADUHELM (ADUCANUMAB)

- ADUHELM is an amyloid monoclonal antibody for AD (Biogen)
- Accelerated FDA approval based on reduction of plaques.
- Approval has been controversial for several reasons
  - Trial results mixed
    - One trial successful the other one negative
- US Medicare decided not to pay for Aduhelm

Reduction of amyloid plaque levels was maintained during the treatment gap from the end of feeder studies to EMBARK baseline: Pooled EMERGE/ENGAGE substudy data and PRIME data

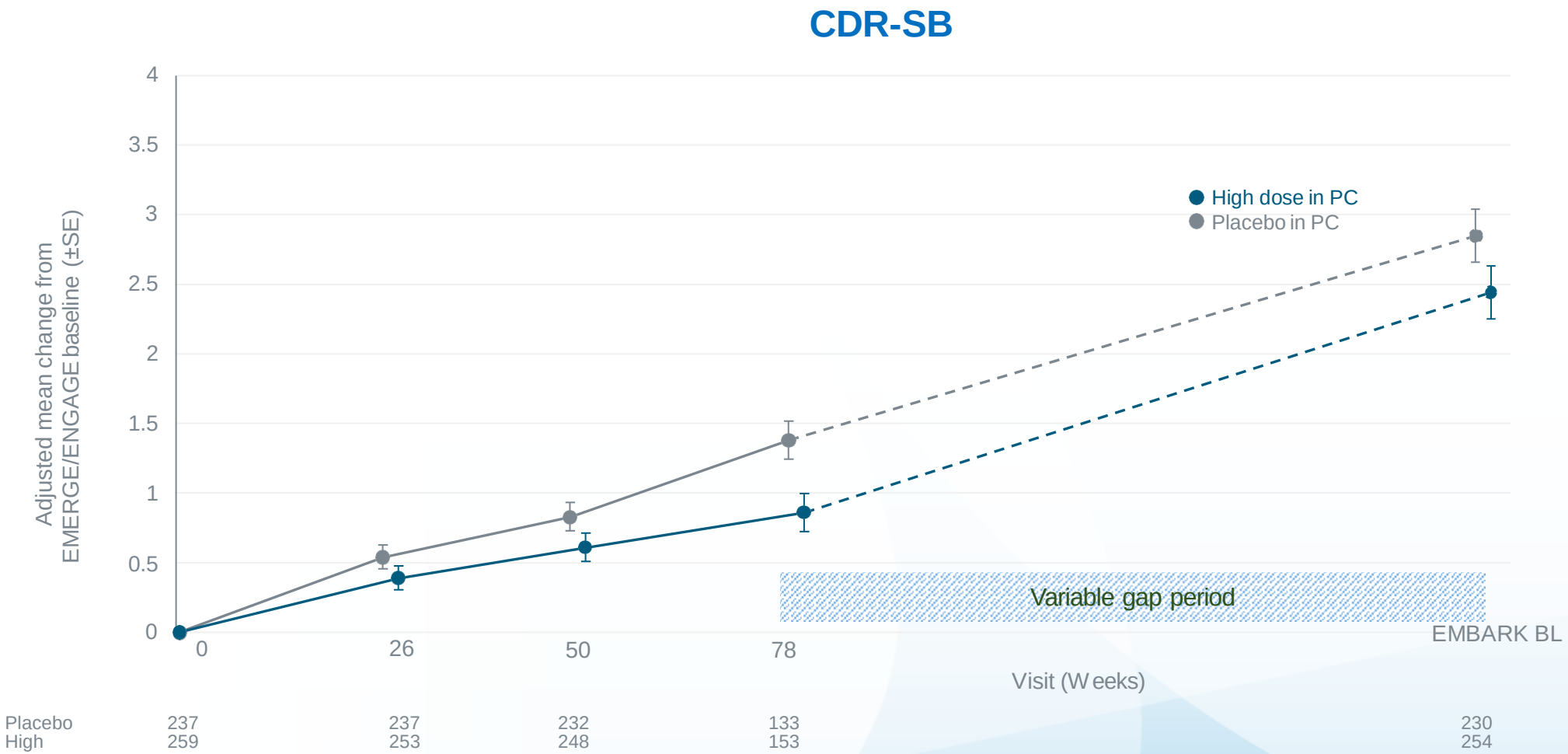




Placebo	18	16	18	Placebo-High	37	37	37	12	12	12
High	24	23	24	High-High	64	64	64			

The end-of-feeder-study amyloid PET SUVR was defined as the last non-missing post-baseline amyloid PET SUVR in the feeder study. Some subjects may receive aducanumab doses after the date of the last post-baseline amyloid PET in the feeder study. For the pooled EMERGE/ENGAGE analyses, adjusted mean changes were based on an MMRM with change from feeder-study baseline amyloid PET composite SUVR as outcomes using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, feeder-study baseline SUVR value, feeder-study baseline SUVR value by time interaction, feeder-study baseline MMSE, feeder-study baseline age, and laboratory ApoE status (carrier/noncarrier). ApoE, apolipoprotein E; BL, baseline; LTE, long-term extension; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; PC, placebo-controlled; PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.

Numerical differences for CDR-SB at the end of the PC period are maintained during the treatment gap from the end of EMERGE and ENGAGE to EMBARK baseline: Pooled PC cohort



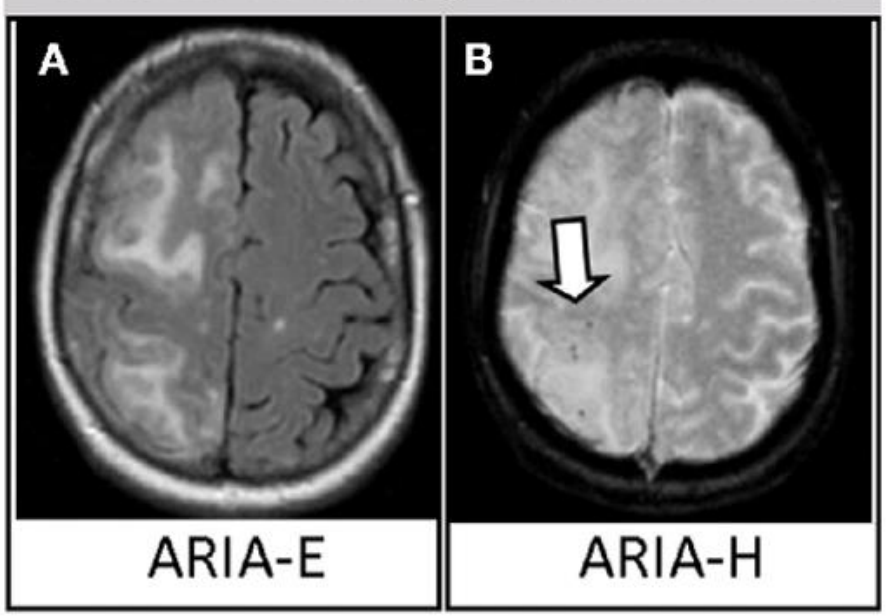
Adjusted mean and standard errors at each time point were based on an MMRM, with change from feeder-study baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, feeder-study baseline CDR-SB, feeder-study baseline CDR-SB by visit interaction, feeder-study baseline MMSE, AD symptomatic medication use at feeder-study baseline, region, and laboratory ApoE status. AD, Alzheimer's disease; ApoE, apolipoprotein E; BL, baseline; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; PC, placebo-controlled; SE, standard error.

Amyloid-related imaging abnormalities ARIA

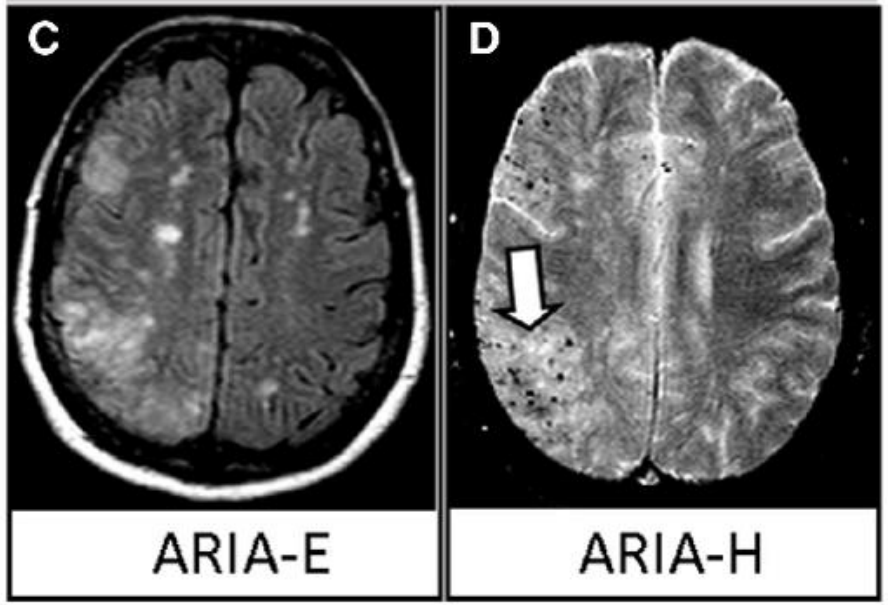
The major side effect of Aduhelm, and all monoclonal antibodies which remove amyloid plaques, is ARIA. Brain swelling (edema) and microbleeds

ARIA-Type	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and or cortex/subcortical white matter in one location < 5 cm	FLAIR hyperintensity 5 to 10 cm, or more than 1 site of involvement, each measuring < 10 cm	FLAIR hyperintensity measuring > 10 cm, often with significant subcortical white matter / sulcal involvement. May involve one or more separate sites
ARIA-H microhemorrhage	≤ 4 new microhemorrhages	5 to 9 new microhemorrhages	10 or more new microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 focal areas of superficial siderosis

Immunotherapy-induced ARIA



Spontaneous ARIA-like events



ARIA ASSOCIATED WITH ADUHELM

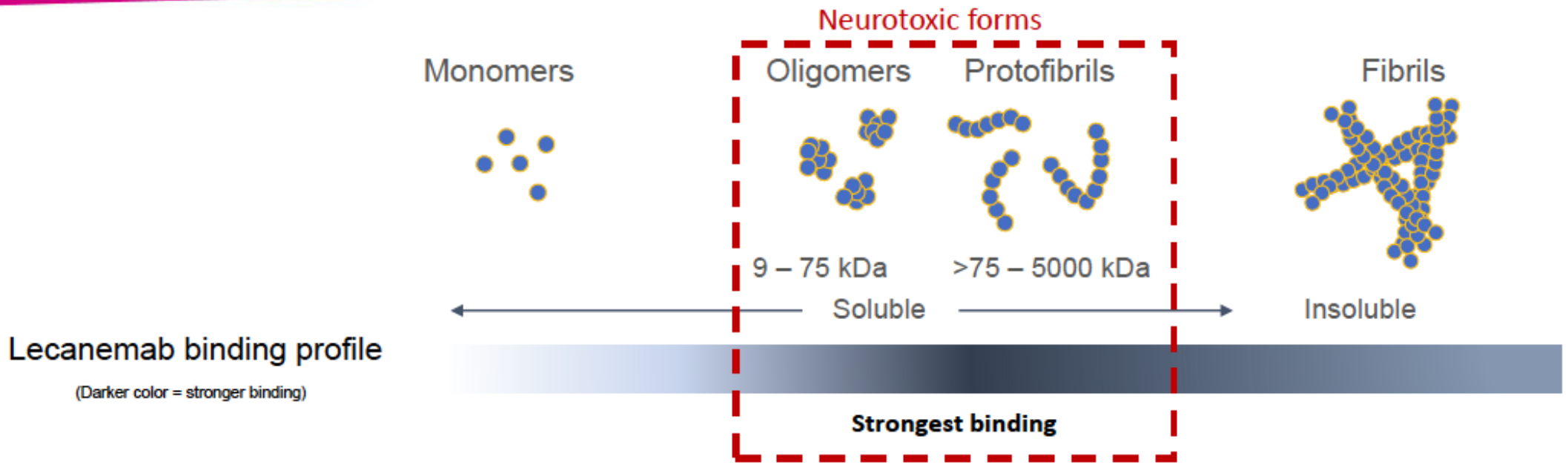
Participant Group	Placebo	Aducanumab
ARIA-E and ARIA-H (overall population)	10%	41%
ARIA-E (overall population)	2.7%	35.2%
ARIA-E with symptoms	10.3%	26%
ARIA-H (overall population)	8.7%	28.3%
Aria-E A APOE-4 carriers	2.2%	43%
Aria-E A APOE-4 noncarriers	3.9%	20.3%
Trial discontinuations due to ARIA	0.6%	6.2%

ARIA A MAJOR LIMITATION

- ARIA will be a limitation for monoclonal antibody treatment
  - More common and severe in Apoe4 homozygotes (4/4)
  - Also increased in Apoe4 carriers (3/4)
  - Anticoagulants are exclusionary
  - Amyloid angiopathy exclusionary
  - Severe CVD (more common in Japan) exclusionary
- In the future there will be efforts to reduce the ARIA complications

Lecanemab: Unique Selectivity Towards Toxic Soluble Species of Aβ

Highest Preference for Soluble Protofibrils/Oligomers Versus Monomeric and Fibrillar Forms of Aβ



- Lecanemab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody
- Selectively binds to soluble Aβ aggregate species
  - >1000-fold selectivity for protofibrils over Aβ monomers (low affinity for Aβ monomer[5])
  - Preferential activity for Aβ protofibrils over fibrils (>10x)[6-10]
- Initiates microglial mediated clearance of protofibrils and plaques

Aβ, amyloid-beta; kDa, kilodaltons. Source: Presented at CTAD 2021. Note: Illustration is based on data from Biacore, inhibition ELISA and immunoprecipitation.

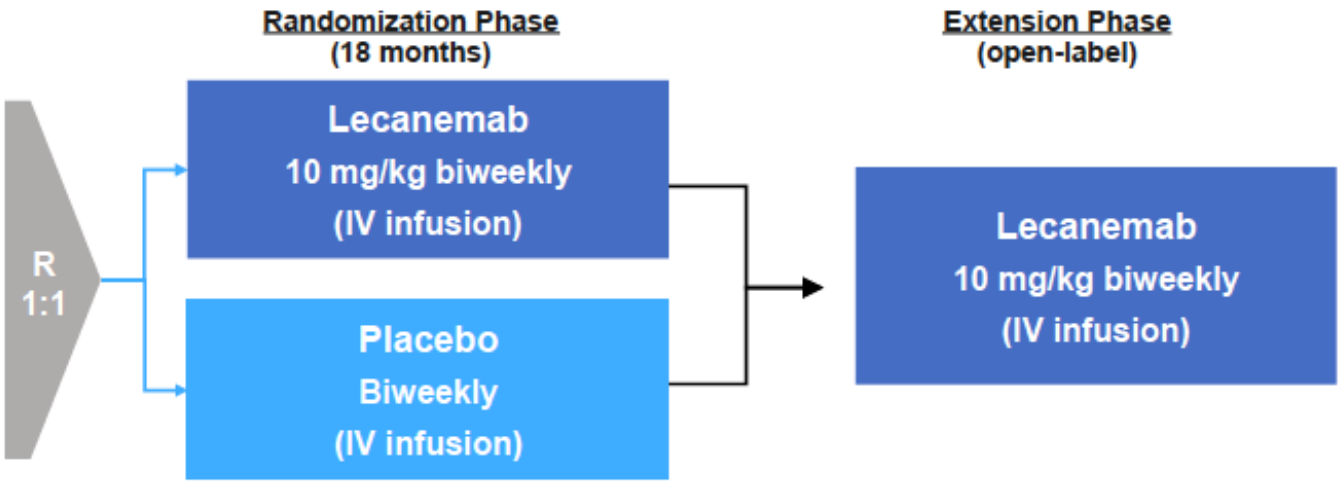
1. Walsh DM, et al. *J Biol Chem.* 1997;272:22364-22372. 2. Paranjape GS, et al. *ACS Chem Neurosci.* 2012;3:302-311. 3. Haass C, Selkoe DJ. Nat Rev Mol Cell Biol. 2007 Feb;8(2):101-12. 4. Stern AM, et al. bioRxiv 2022.10.18.512754. 5. Tucker S, et al. J Alzheimers Dis. 2015;43(2):575-88. 6. Lord A, et al. *Neurobiol Dis.* 2009;36:425–34. 7. Sehlin D, et al. *PLoS One.* 2012;7:e32014. 8. Sehlin D, et al. *Neurodegener Dis.* 2011;8:117–23. 9. Logovinsky V, et al. *Alzheimer's Research & Therapy.* 2016;8:14. Söderberg L, et al. *Neurotherapeutics.* 2022 Oct 17. Epub ahead of print.

Clarity AD Study Design

Clarity AD is a global, placebo-controlled, double-blind, parallel-group, randomized study

Patient Population

- 1,795 patients with Early AD
- MCI due to AD or mild Alzheimer's dementia
- Amyloid pathology confirmed
- MMSE score between 22 and 30 at screening and baseline
- WMS-IV LMSII ≥1 SD below age-adjusted mean at screening



Randomization Phase Primary Outcome Measure:

CDR: Change from Baseline at 18 months

Key Secondary Outcome Measures:

Change from Baseline at 18 months:
Amyloid PET
ADAS-Cog14
ADCOMS
ADCS MCI-ADL

Extension Phase Primary Outcome Measures

Number of Participants with TEAEs
Change from Core Study Baseline in CDR-SB

Diverse patient population

- Eligibility Criteria
- Site selection
- Community outreach
- Decentralized activities

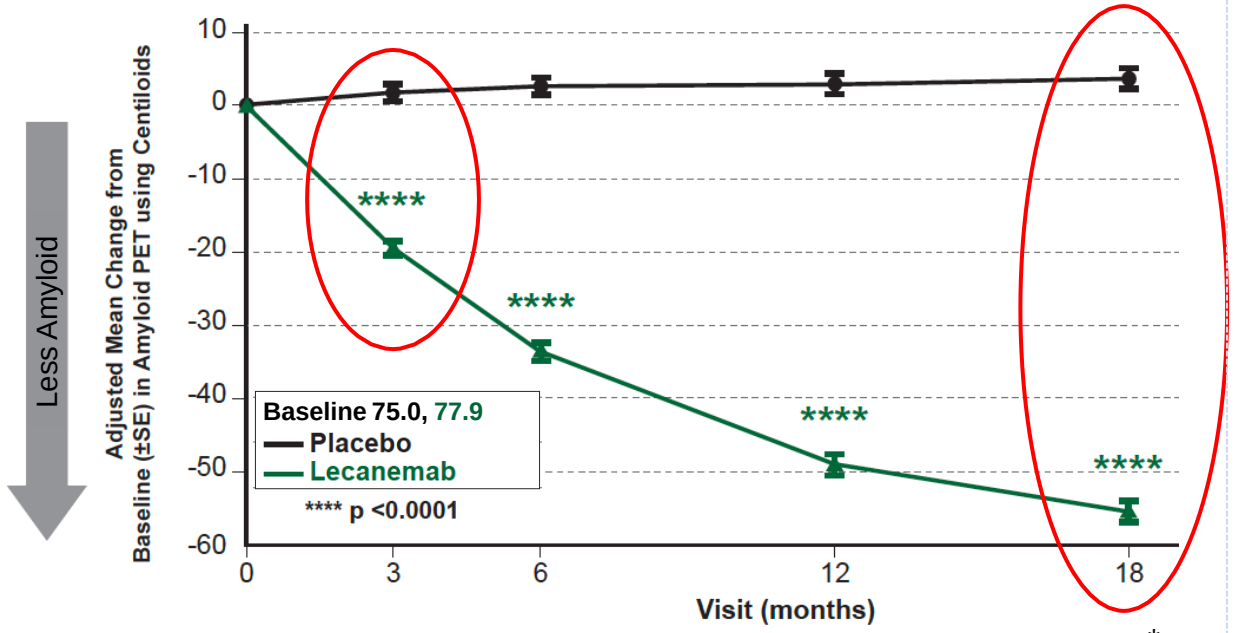
Optional longitudinal sub-studies

- Amyloid burden (amyloid PET)
- Brain tau pathology (tau PET)
- CSF biomarkers of neurodegeneration
- Subcutaneous formulation (OLE)

AD, Alzheimer's disease; ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating-sum of boxes; CSF, cerebrospinal fluid; IV, intravenous; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; OLE, open-label extension; PET, positron emission tomography; SD, standard deviation; TEAEs, treatment emergent adverse events; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II.

PET Centiloids and Amyloid PET SUVr Images at Baseline and 18 Months

Highly Significantly Reduced Amyloid Plaque (Centiloids) at All Time Points; Mean at 18 Months of 23 Centiloids (Below 30 Centiloid Threshold of Positivity)



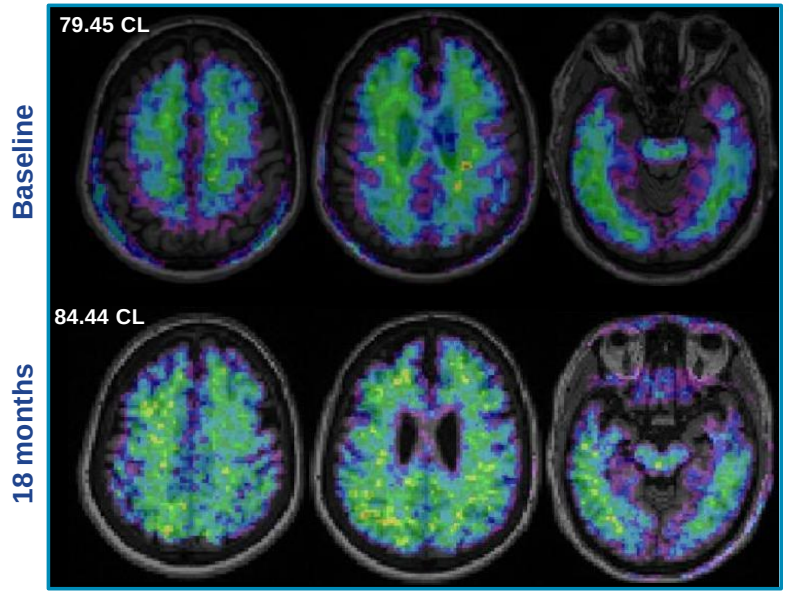
(N) Placebo:	344	303	286	259	205*
(N) Lecanemab:	354	296	275	276	210*

% Amyloid Negative (<30 CL)				
Placebo	15	14	15	16
Lecanemab	24	36	54	68

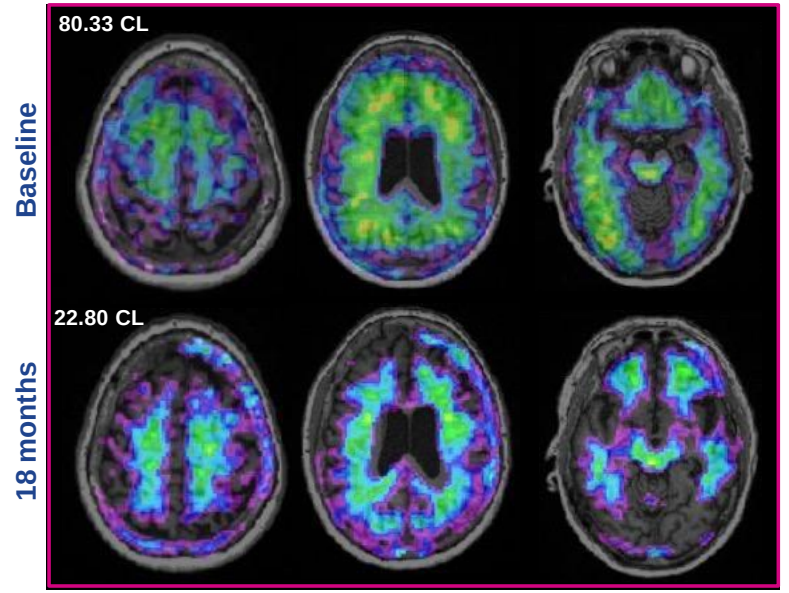
* 73 subjects were not included at 18 months (per SAP) since their PET assessments were performed after receiving lecanemab in the extension phase.

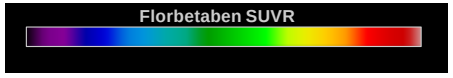
Note: Based on PD analysis population (PET substudy population). Adjusted mean change from baseline, SE and p-value are derived using MMRM with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of AD symptomatic medication at baseline, *ApoE4* carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

Placebo



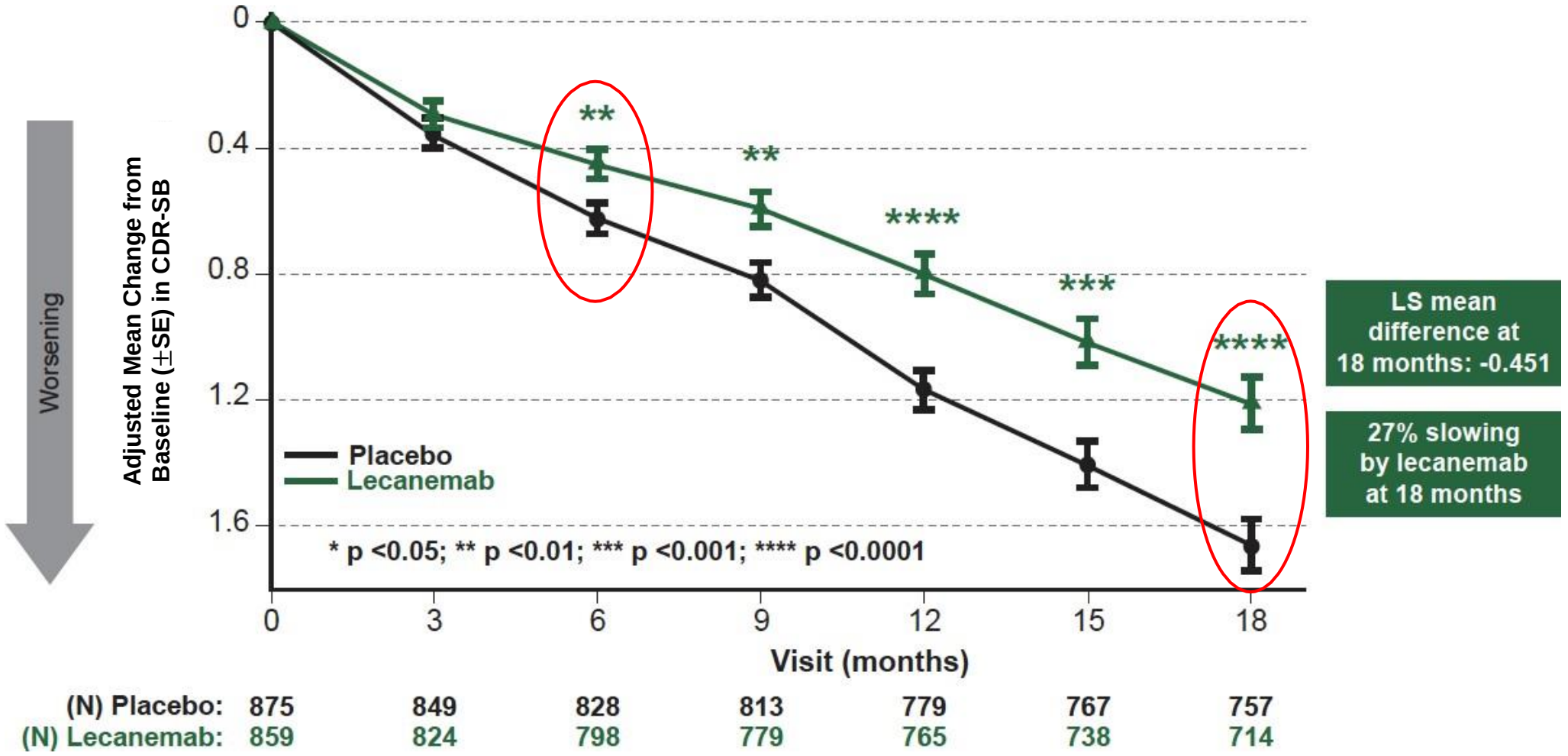
Lecanemab





Clarity AD Primary Endpoint: CDR-SB

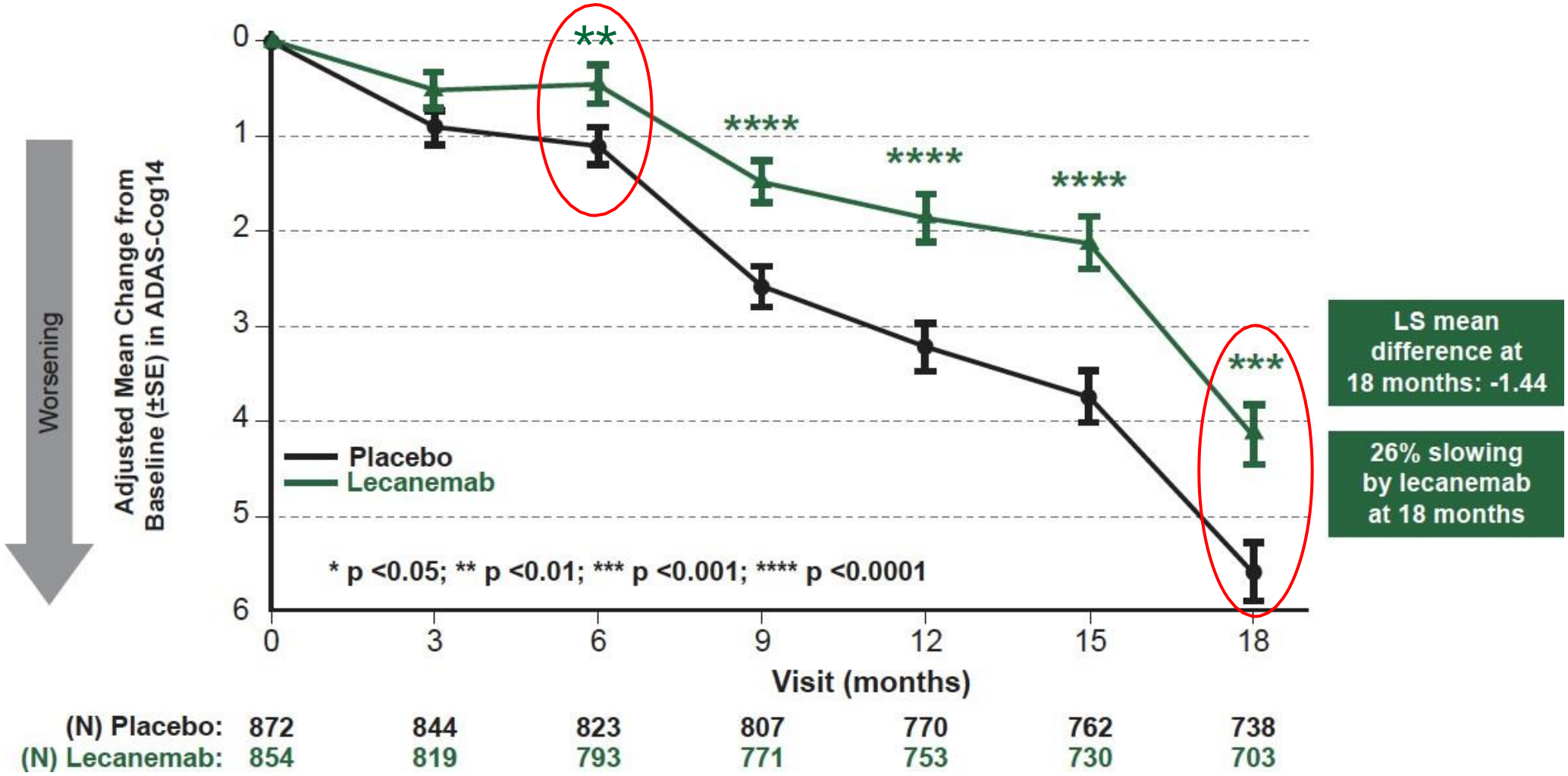
Lecanemab Significantly Slowed Disease Progression on CDR-SB by 27% at 18 Months and at All Time Points Beginning at 6 Months



Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.
CDR-SB, Clinical Dementia Rating, sum of boxes; LS, least squares; SE, standard error.

ADAS-Cog14:

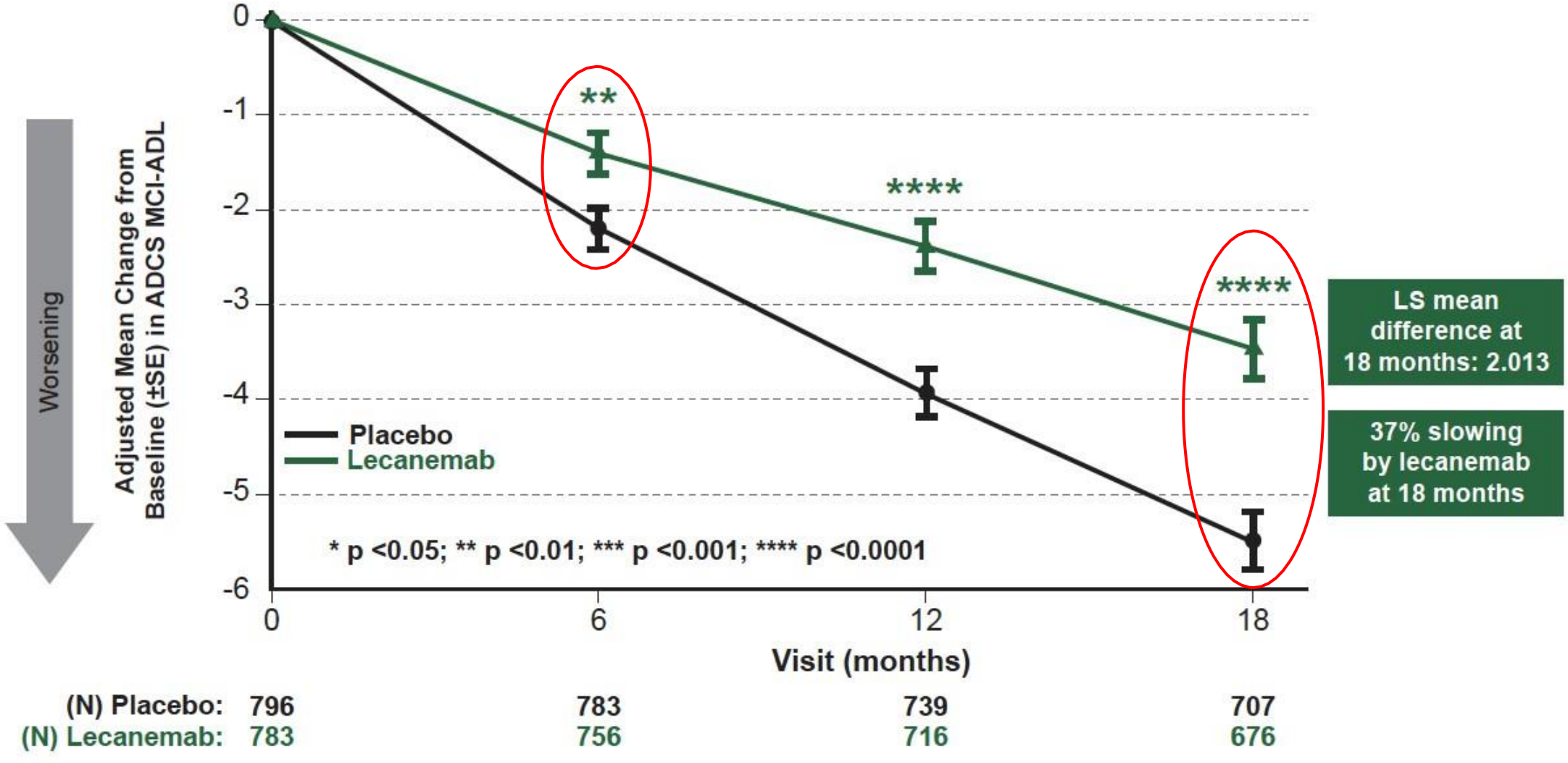
Lecanemab Significantly Slowed Disease Progression on ADAS-Cog14 by 26% at 18 Months and at All Time Points Beginning at 6 Months



Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.
ADAS-Cog14, Alzheimer's Disease Assessment Scale–cognitive subscale; LS, least squares; SE, standard error.

ADCS MCI-ADL:

Lecanemab Significantly Slowed Disease Progression on ADCS MCI-ADL by 37% at 18 Months and at All Time Points Beginning at 6 Months



Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.
ADCS ADL-MCI: Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for mild cognitive impairment (MCI) subjects; LS, least squares; SE, standard error.

Overall Adverse Event (AE) Summary

Core Study

	Placebo (n=897) n (%)	Lecanemab (n=898) n (%)
Deaths*	7 (0.8)	6 (0.7)
Serious adverse event (SAE)	101 (11.3)	126 (14.0)
SAE with ARIA-E	0	7 (0.8)
SAE with ARIA-H	1 (0.1)	5 (0.6)
SAE with infusion-related reactions	0	11 (1.2)
SAE without ARIA or infusion-related reactions	101 (11.3)	111 (12.4)
Treatment-emergent AE (TEAE)**	735 (81.9)	798 (88.9)
TEAE without ARIA or infusion-related reactions	719 (80.2)	746 (83.1)
TEAE leading to drug withdrawal	26 (2.9)	62 (6.9)
TEAE leading to drug withdrawal excluding AESI	24 (2.7)	28 (3.1)

*Cause of deaths in placebo group: death, acute respiratory failure, myocardial infarction, metastases to bone, hemorrhage intracranial, COVID-19, pancreatic cancer.
Cause of death in lecanemab group: death, cerebrovascular accident, myocardial infarction, respiratory failure, metastases to meninges, COVID-19. No participants died with or from ARIA in Core study.
**AE rates are similar between placebo and lecanemab when ARIA and infusion-related reactions are excluded.
AESI, adverse event of special interest; ARIA-E, amyloid related imaging abnormalities - edema; ARIA-H, ARIA-H, ARIA with hemosiderin deposits.

Most Common Adverse Events

Adverse Events Of Special Interest (Pooled preferred terms [PTs])	Placebo (n=897) %	Lecanemab (n=898) %
Infusion-related reaction	7.4	26.4
ARIA-E	1.7	12.6
ARIA-H (pooled PTs)	9.0	17.3
Isolated ARIA-H (pooled PTs)	7.8	8.9

Other Adverse Events >5%	Placebo (n=897) %	Lecanemab (n=898) %
Headache	8.1	11.1
Fall	9.6	10.4
Urinary tract infection	9.1	8.7
COVID-19	6.7	7.1
Back pain	5.8	6.7
Arthralgia	6.9	5.9
Dizziness	5.1	5.5
Diarrhea	6.5	5.3
Anxiety	4.2	5.0

- There were no significant trends in mean changes over time or shifts from baseline for any of the laboratory, ECG or vital sign parameters and no notable differences between groups

ARIA-E, amyloid related imaging abnormalities - edema; ARIA-H, ARIA-H, ARIA with hemosiderin deposits; COVID-19, coronavirus disease of 2019, ECG, electrocardiogram.

ARIA-E

	Placebo (N=897) n/N (%)	Lecanemab (N=898) n/N (%)
ARIA-E	15/897 (1.7)	113/898 (12.6)
ARIA-E by ApoE4 genotype		
ApoE4 noncarrier	1/286 (0.3)	15/278 (5.4)
ApoE4 carrier	14/611 (2.3)	98/620 (15.8)
ApoE4 heterozygote	9/478 (1.9)	52/479 (10.9)
ApoE4 homozygote	5/133 (3.8)	46/141 (32.6)
Symptomatic ARIA-E*	0	25/898 (2.8)
ApoE4 noncarrier	0	4/278 (1.4)
ApoE4 carrier	0	21/620 (3.4)
ApoE4 heterozygote	0	8/479 (1.7)
ApoE4 homozygote	0	13/141 (9.2)

*Symptomatic concurrent ARIA-E and ARIA-H were included under ARIA-E.

- ARIA-E events were largely mild-to-moderate radiographically (91%) and asymptomatic (78%)
- In the 2.8% of subjects with symptomatic ARIA-E, commonly reported symptoms were headache, visual disturbance, and confusion
- Recurrent ARIA-E
  - Placebo: 1 (0.1%)
  - Lecanemab: 28 (3.1%)

ApoE4, apolipoprotein E4; ARIA-E, amyloid related imaging abnormalities - edema; ARIA-H, ARIA-H, ARIA with hemosiderin deposits.

ARIA-H

- Isolated ARIA-H was similar between lecanemab (8.9%) and placebo (7.8%) with low rates of clinically symptomatic ARIA-H
- Timing of isolated ARIA-H occurs randomly during treatment course, while ARIA-H that occurs with ARIA-E tended to occur early in the course of lecanemab treatment

	Total		Isolated ARIA-H (no ARIA-E)	
	Placebo (N=897) n (%)	Lecanemab (N=898) n (%)	Placebo (N=897) n (%)	Lecanemab (N=898) n (%)
ARIA-H (micro, macro, superficial)	81 (9.0)	155 (17.3)	70 (7.8)	80 (8.9)
Microhemorrhage	68 (7.6)	126 (14.0)	63 (7.0)	60 (6.7)
Superficial siderosis	21 (2.3)	50 (5.6)	13 (1.4)	23 (2.6)
Cerebral macrohemorrhage	1 (0.1)	5 (0.6)	1 (0.1)	4 (0.4)
Symptomatic ARIA-H	2 (0.2)	13 (1.4)	2 (0.2)	4 (0.4)
ARIA-H by ApoE4 genotype				
ApoE4 noncarrier, n/N (%)	12/286 (4.2)	33/278 (11.9)	11/286 (3.8)	23/278 (8.3)
ApoE4 carrier, n/N (%)	69/611 (11.3)	122/620 (19.7)	59/611 (9.7)	57/620 (9.2)
ApoE4 heterozygote, n/N (%)	41/478 (8.6)	67/479 (14.0)	35/478 (7.3)	40/479 (8.4)
ApoE4 homozygote, n/N (%)	28/133 (21.1)	55/141 (39.0)	24/133 (18.0)	17/141 (12.1)

ApoE4, apolipoprotein E4; ARIA-E, amyloid related imaging abnormalities - edema; ARIA-H, ARIA-H, ARIA with hemosiderin deposits.

Cerebral Macrohemorrhage in Lecanemab Studies

Data Cutoff October 22, 2022 for Open-Label Extension (OLE; Ongoing)

Study	Total		Anticoagulant Use	
	Placebo n/N (%)	Lecanemab 10 mg/kg q2wk n/N (%)	Placebo n/N (%)	Lecanemab 10 mg/kg q2wk n/N (%)
201 Core Phase	0/245 (0%)	1/161 (0.6%)	0/20 (0%)	0/11 (0%)
201 OLE	N/A	1/180 (0.6%)	N/A	0/18 (0%)
301 Core Phase	2/897 (0.2%) [1]	6/898 (0.7%) [2]	0/74 (0%)	2/83 (2.4%) [2]
301 Core + OLE (includes cases in 301 Core above)	N/A	10/1608 (0.6%) [2, 3]	N/A	5/140 (3.6%) [2, 3]
301 Core & OLE Deaths with concurrent macrohemorrhage	1/897 (0.1%) [4]	2/1608 (0.1%) [3]	0/74 (0%)	2/140 (1.4%) [3]

[1] Includes one non-treatment emergent case in placebo (event > 30 days after discontinuing study medication)
[2] Includes one non-treatment emergent case on anticoagulation (event > 30 days after discontinuing study medication)
[3] 1 case of macrohemorrhage in 65F E4 homozygous after tPA for left MCA occlusion (OLE) and 1 case in 87M E4 non-carrier on apixaban (stopped) then received heparin for MI (OLE, cause of death cardiopulmonary)
[4] In core phase

AD, Alzheimer's disease; ApoE4, apolipoprotein E4; MRI, magnetic resonance imaging; NA, Not applicable; q2wk, every 2 weeks.

Cerebral Macrohemorrhage in AD

- Lobar macrohemorrhage in AD in the absence of arteriovenous malformation, hemorrhagic cerebral infarction, or tumor is usually caused by cerebral amyloid angiopathy (CAA)
- Risk factors for lobar macrohemorrhage include ApoE4 genotype, presence of microhemorrhages (which is evidence of CAA), and anticoagulant medications
- Background rates of macrohemorrhage in placebo arms of prior AD clinical trials is 0.4% (*JAMA Neurol*. 2022;79:13-21)

Safety Assessment

- There is a low rate of macrohemorrhage with lecanemab therapy (0.6-0.7%), which is higher than placebo (0.2%)
- **Rate of macrohemorrhage for subjects on both anticoagulants and lecanemab was 2.4-3.6%.** Background rate of macrohemorrhage in AD patients on anticoagulation is not known but is expected to be higher than in non-AD patients due to CAA; therefore, comparative risk is difficult to assess.
- No clear relationship of macrohemorrhage to ApoE4 status, baseline MRI, or timing of treatment
- Subjects allowed to continue on anticoagulation in OLE with informed consent language regarding increased risk of cerebral hemorrhage with concomitant anticoagulant use

Clarity AD Results

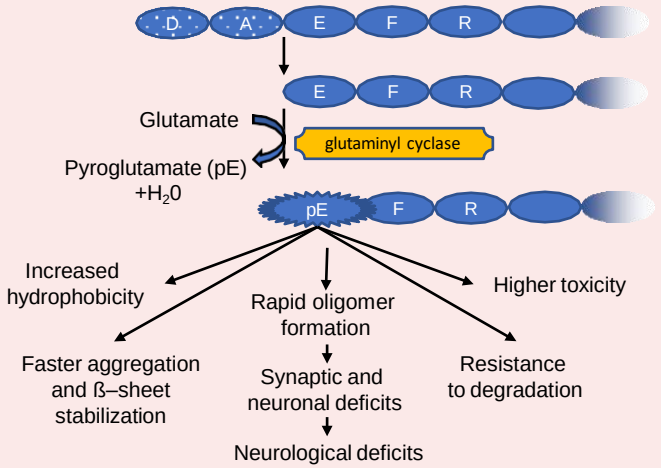
- Clarity AD met all primary and secondary efficacy endpoints ($p<0.001$)
- Benefit-risk supported by convergence of comprehensive Clarity AD assessments:
  - Consistency of results across scales of cognition and function (27-37% slowing) and subgroups (race, ethnicity, comorbidities)
  - Delay in progressing to later stages of the disease (HR 0.69)
  - Preservation relative to placebo of health-related quality of life and caregiver burden (23-56% slowing)
  - Effects on A/T/N+ biomarkers that provide a biological basis for the treatment effects
  - Safety profile with important AEs of infusion related reactions (26.4%), ARIA-E (12.6% overall; 2.8% symptomatic) and uncommon intracerebral hemorrhage (0.6%)

van Dyck CH, et al. N Engl J Med. 2023;388:9-21.
Van Dyck CH, et al. Presented at the 15th Annual CTAD Meeting. November 29 – December 2, 2022. San Francisco, CA

Donanemab is being investigated for the treatment of symptomatic AD, including TRAILBLAZER-ALZ (completed) and TRAILBLAZER-ALZ2 (ongoing)

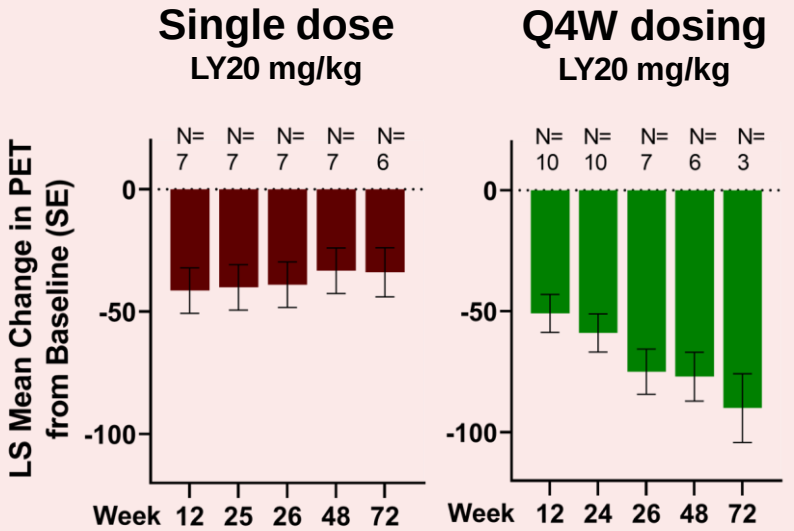
Donanemab is an immunoglobulin G1 antibody specific for an N-terminal pyroglutamate amyloid-β epitope that is present only in mature brain amyloid plaques

Formation of N3 pyroglutamate:



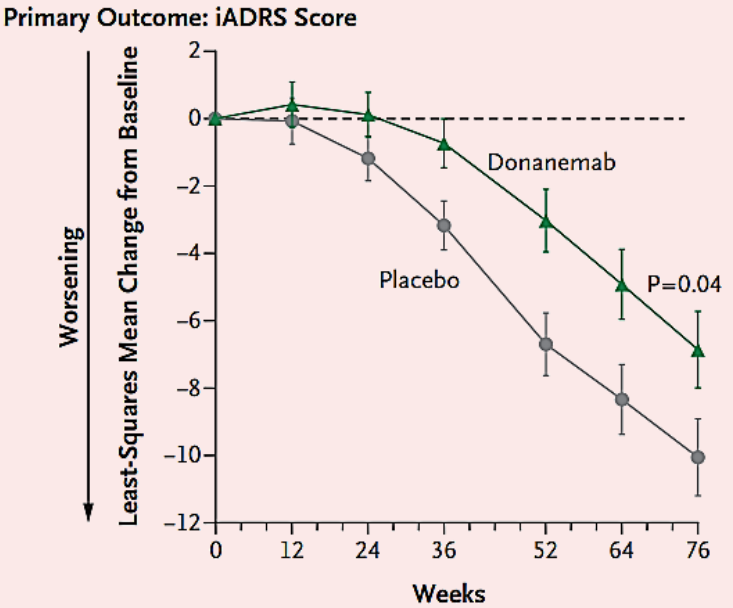
Adapted from Jawhar et al. J Biol Chem, 2011

In Phase 1, donanemab significantly reduced amyloid plaque, even with a single dose, in participants with amyloid positive AD



Lowe et al. CTAD, 2019

In Phase 2, donanemab significantly slowed disease progression on iADRS at 76 weeks, compared with placebo



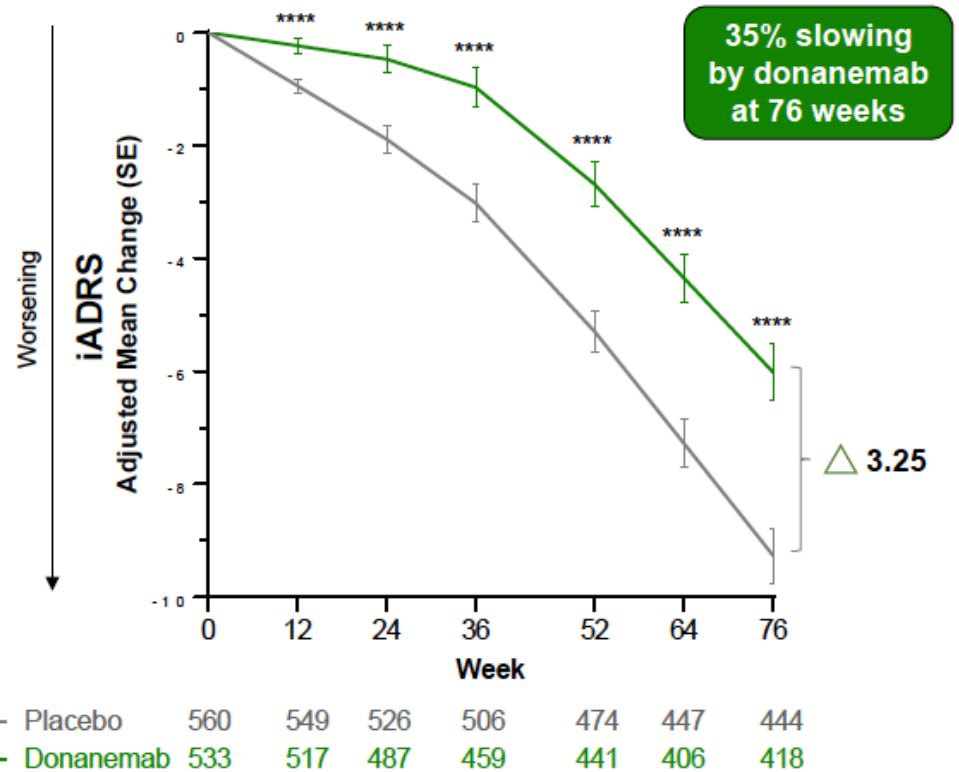
Mintun et al. NEJM, 2019

AD = Alzheimer's disease; iADRS = Integrated Alzheimer's Disease Rating Scale; Q4W = every 4 weeks

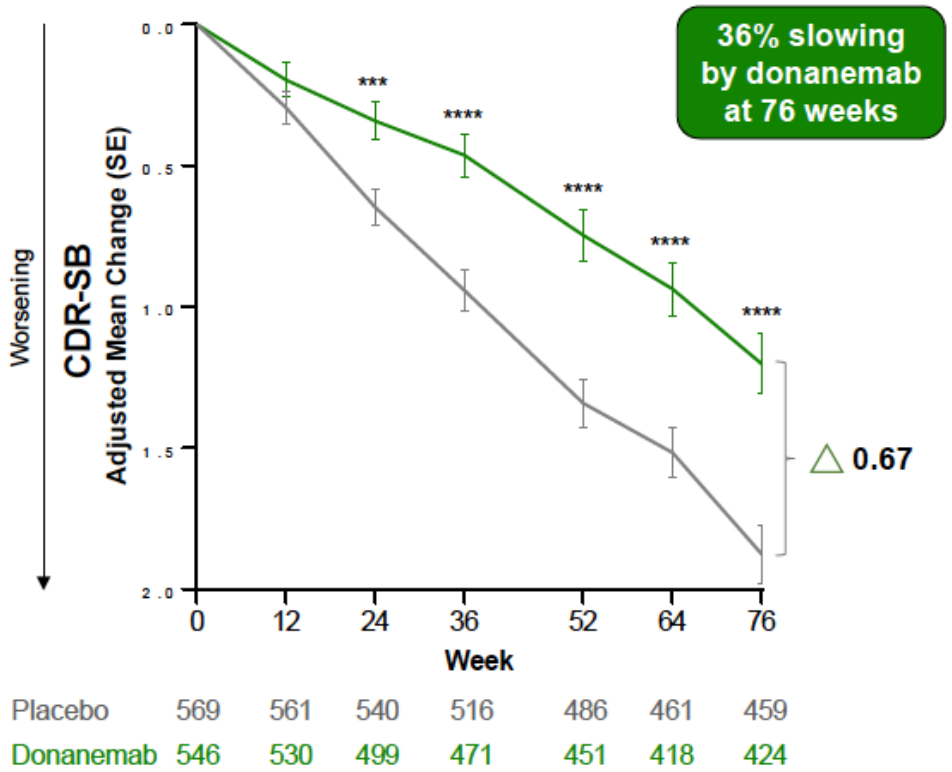
Phase 3 Primary Outcome: iADRS

Consistent with Key Secondary outcome on CDR-SB

iADRS: Low-medium Tau Population



CDR-SB: Low-medium Tau Population

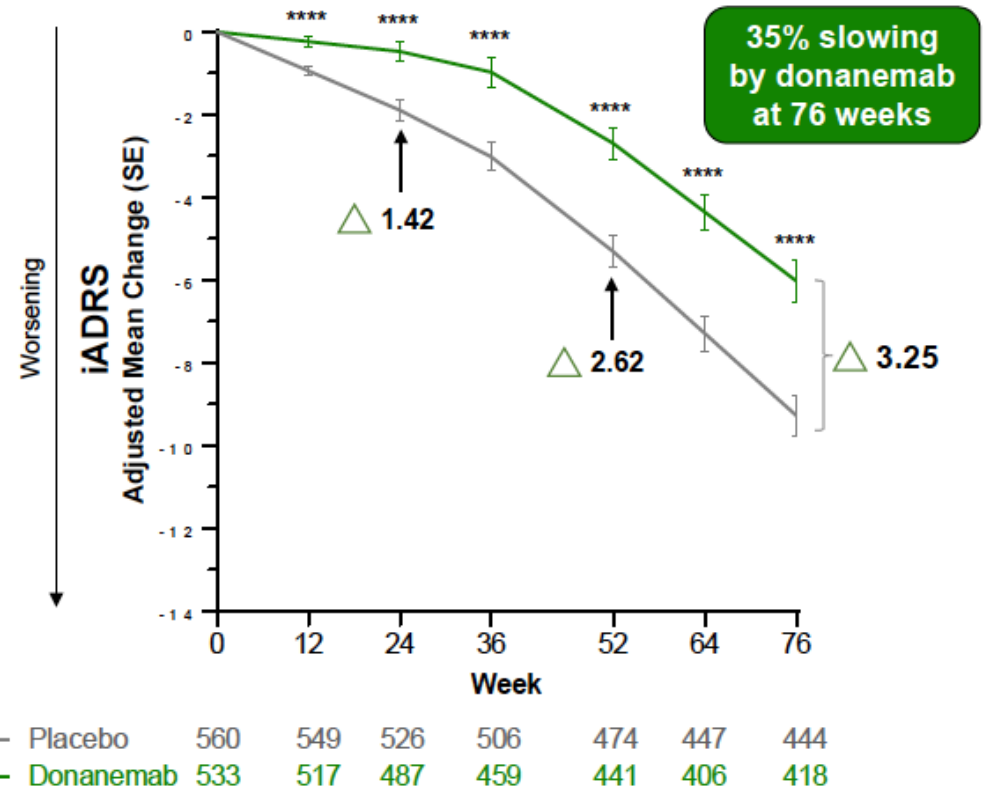


TRAILBLAZER-ALZ 2 primary (iADRS) used the NCS model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level (overall model only), and baseline acetylcholinesterase inhibitor/memantine use. For CDR-SB: adjusted mean change from baseline, SE, 95% CI and p-value are derived using pre-specified mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, age at baseline, pooled investigator, and baseline acetylcholinesterase inhibitor/memantine use. * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: CDR-SB=Clinical Dementia Rating–Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; NCS=natural cubic spline; SE=Standard Error

Phase 3 Primary Outcome: iADRS

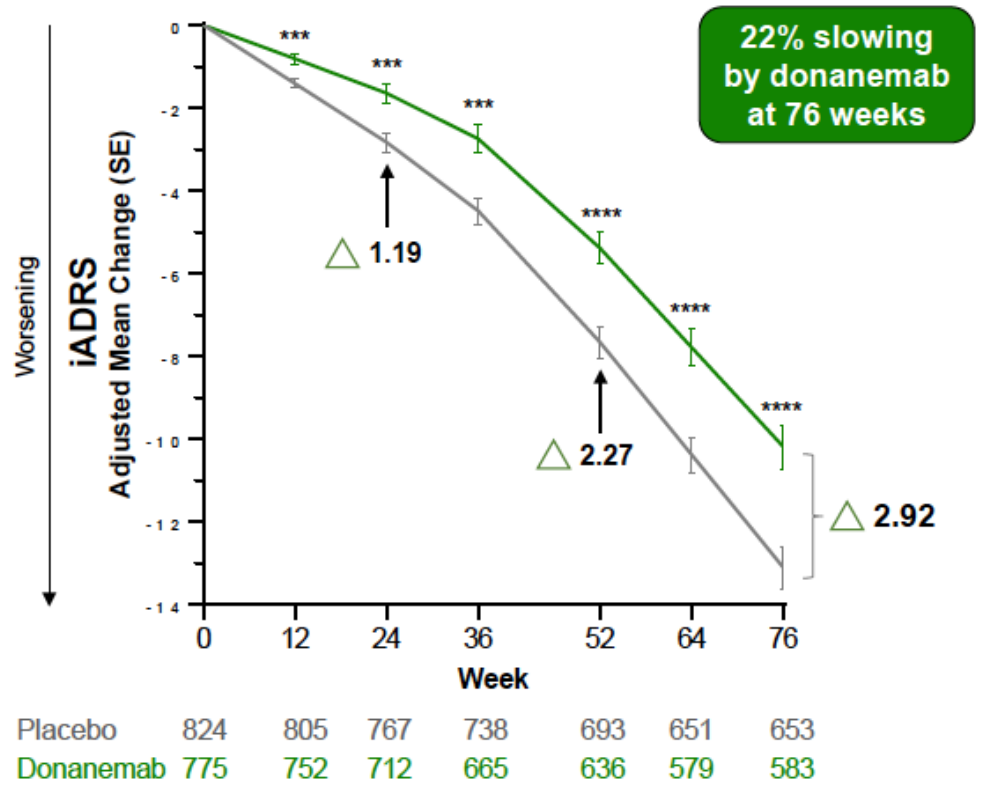
Both Populations Show Treatment Effect which Widens over Time

iADRS: Low-medium Tau Population



Placebo	560	549	526	506	474	447	444
Donanemab	533	517	487	459	441	406	418

iADRS: Combined Tau Population



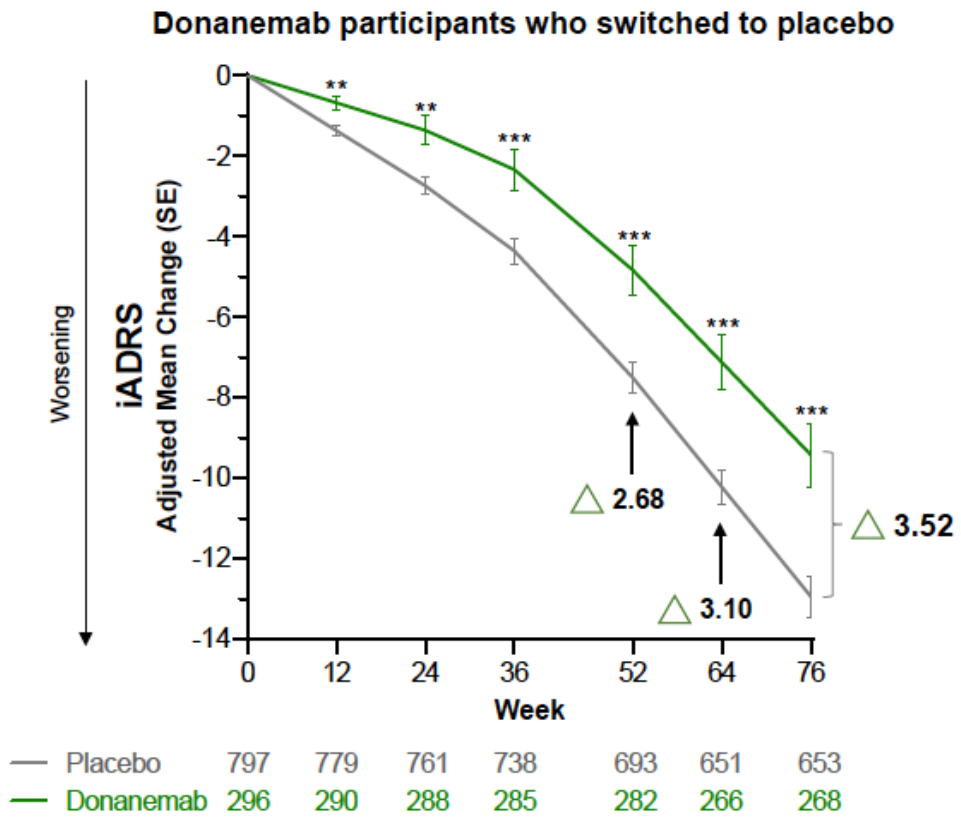
Placebo	824	805	767	738	693	651	653
Donanemab	775	752	712	665	636	579	583

TRAILBLAZER-ALZ 2 primary analysis (iADRS) used the NCS model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level (Combined model only), and baseline acetylcholinesterase inhibitor/memantine use. * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: iADRS=Integrated Alzheimer's Disease Rating Scale; NCS=natural cubic spline; SE=Standard Error

Treatment Effect Continues to Widen Even After Participants are Switched to Placebo Based on 6- or 12-Month PET Scan

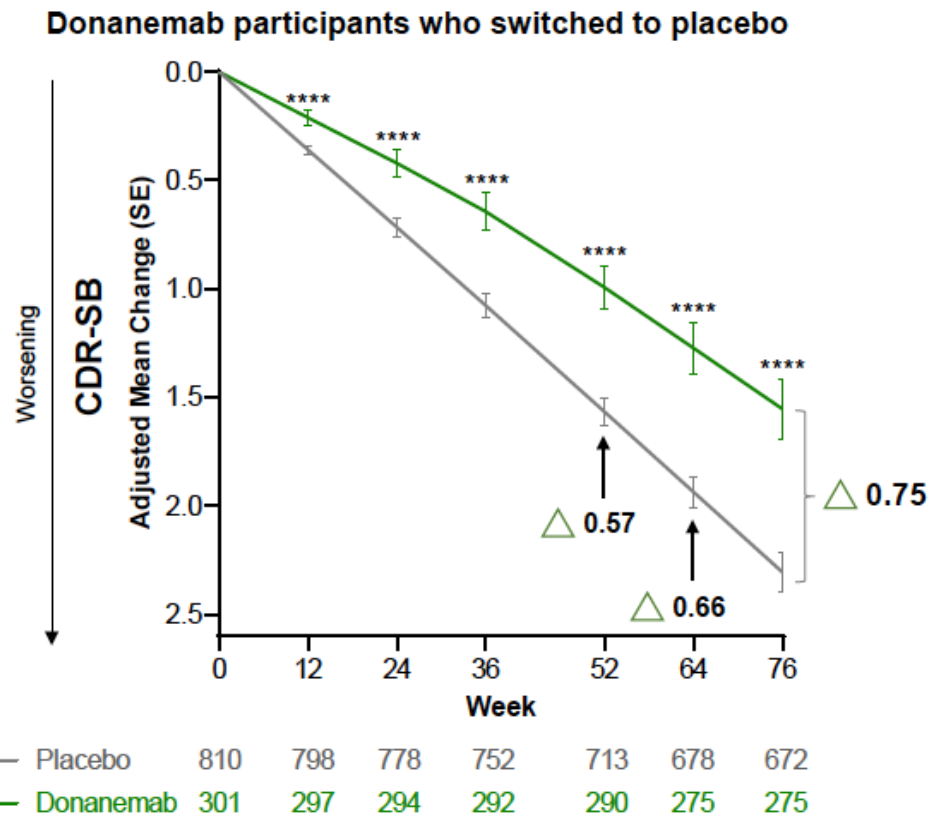
Mean time in trial prior to switch to placebo for these participants: 47 weeks

iADRS: Combined Tau Population



Placebo	797	779	761	738	693	651	653
Donanemab	296	290	288	285	282	266	268

CDR-SB: Combined Tau Population



Placebo	810	798	778	752	713	678	672
Donanemab	301	297	294	292	290	275	275

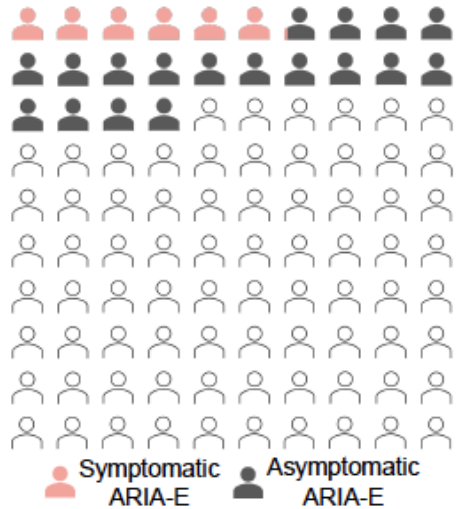
iADRS and CDR-SB used the NCS model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level, and baseline acetylcholinesterase inhibitor/memantine use. Participants that did not stop treatment were also included in the model but are not plotted here. Nominal P-values: ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: CDR-SB=Clinical Dementia Rating–Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; NCS=natural cubic spline; SE=Standard Error

Summary of ARIA and macrohemorrhage

Event[a], 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)[b]	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)

[a] ARIA and macrohemorrhage events based on MRI or TEAE cluster
[b] One placebo-treated participant had ARIA-E during the placebo-controlled period; however, the participant developed symptoms during the long-term extension period

24% of donanemab-treated participants experienced ARIA-E



- ARIA-E events were largely mild to moderate radiographically (94%)
- Commonly reported symptoms of symptomatic ARIA-E were headache and confusion

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

ARIA and *APOE*

ARIA by *APOE* ε4 Carrier Status

No./Total No. (%)[a,b]	Placebo (N=870)	Donanemab (N=850)
ARIA-E		
Non-carrier	2/250 (0.8)	40/255 (15.7)
Heterozygous carrier	9/474 (1.9)	103/452 (22.8)
Homozygous carrier	5/146 (3.4)	58/143 (40.6)
ARIA-H[c]		
Non-carrier	28/250 (11.2)	48/255 (18.8)
Heterozygous carrier	57/474 (12.0)	146/452 (32.3)
Homozygous carrier	30/146 (20.5)	72/143 (50.3)

[a] Based on MRI.
[b] Participants with missing *APOE* ε4 carrier status are excluded.
[c] Treatment-emergent microhemorrhage is based on new incidents of microhemorrhages. Treatment-emergent superficial siderosis is based on new or worsening superficial siderosis.

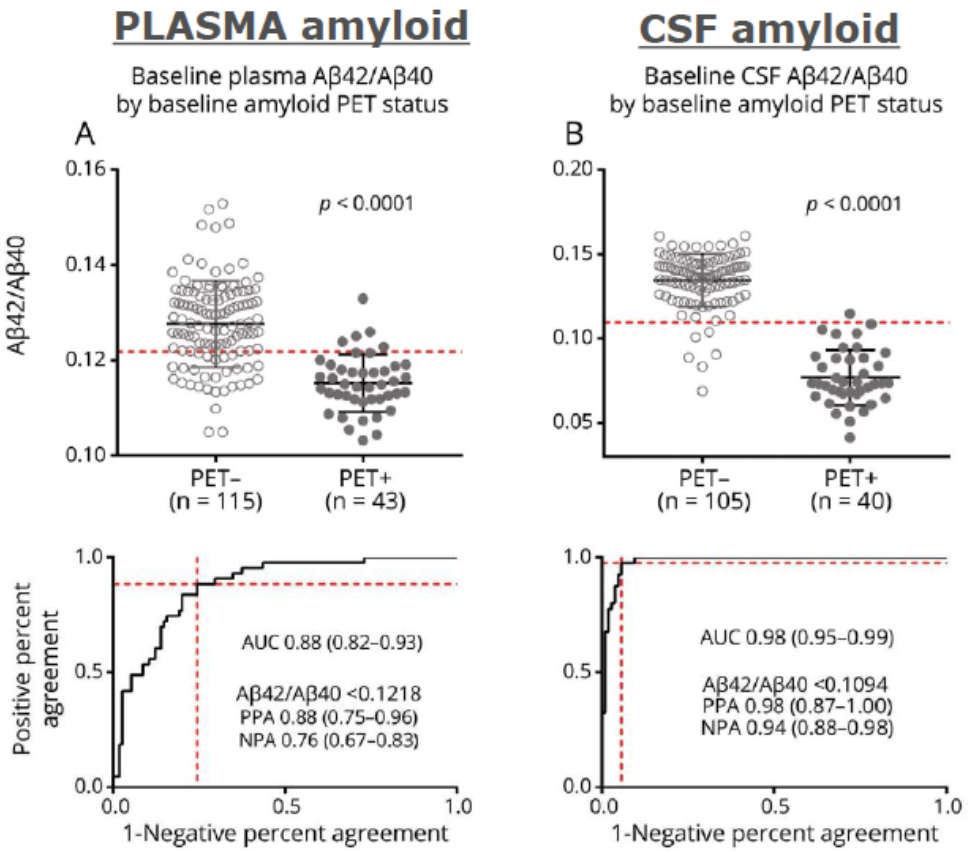
- Participants with at least 1 serious ARIA event[d]
  - ARIA-E: 12 *APOE* ε4 carriers and 1 non-carrier
  - ARIA-H: 3 *APOE* ε4 carriers and 1 non-carrier

[d] SAEs are by AE reporting

Abbreviations: *APOE*=apolipoprotein E; 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

Predicting A status from blood

plasma Aβ42/40 ratio is lower in amyloid PET + vs -, as in CSF



High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis

Suzanne E. Schindler, MD, PhD, James G. Bollinger, PhD, Vitaliy Ovod, MS, Kwasi G. Mawuenyega, PhD, Yan Li, PhD, Brian A. Gordon, PhD, David M. Holtzman, MD, John C. Morris, MD, Tammie L.S. Benzinger, MD, PhD, Chengjie Xiong, PhD, Anne M. Fagan, PhD, and Randall J. Bateman, MD

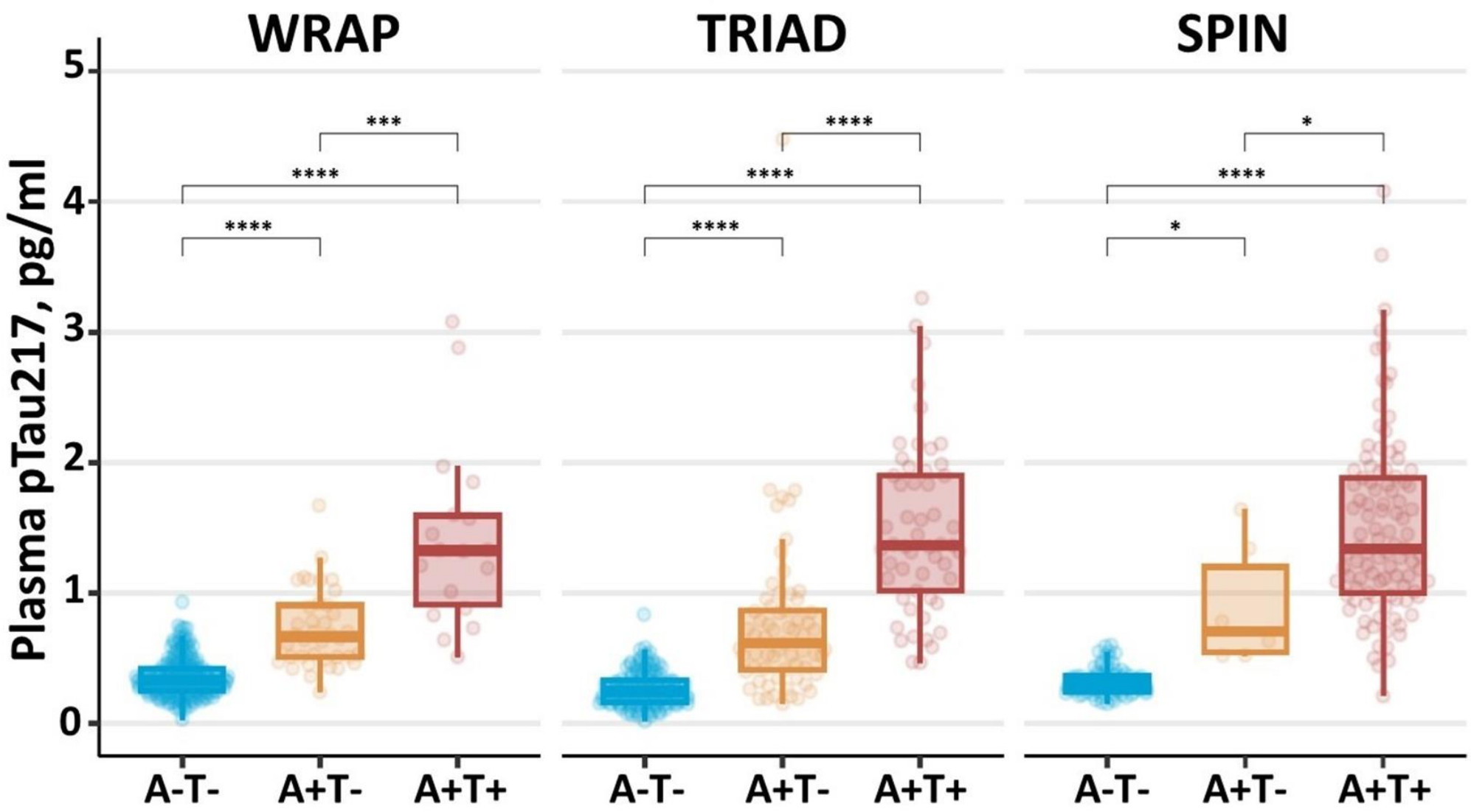
Correspondence
Dr. Bateman
batemanr@wustl.edu

Neurology® 2019;93:e1647-e1659. doi:10.1212/WNL.0000000000008081

Plasma Phosphotau

- There are many species of phospho tau
- Initial studies were with Ptau 181, but Ptau 217 appears superior
- Ptau 217 can be measured with mass spectroscopy (C2N) or immuno-assay (Fujirebiro, Alzpath, Quanterix using antibodies from Lilly, Janssen)

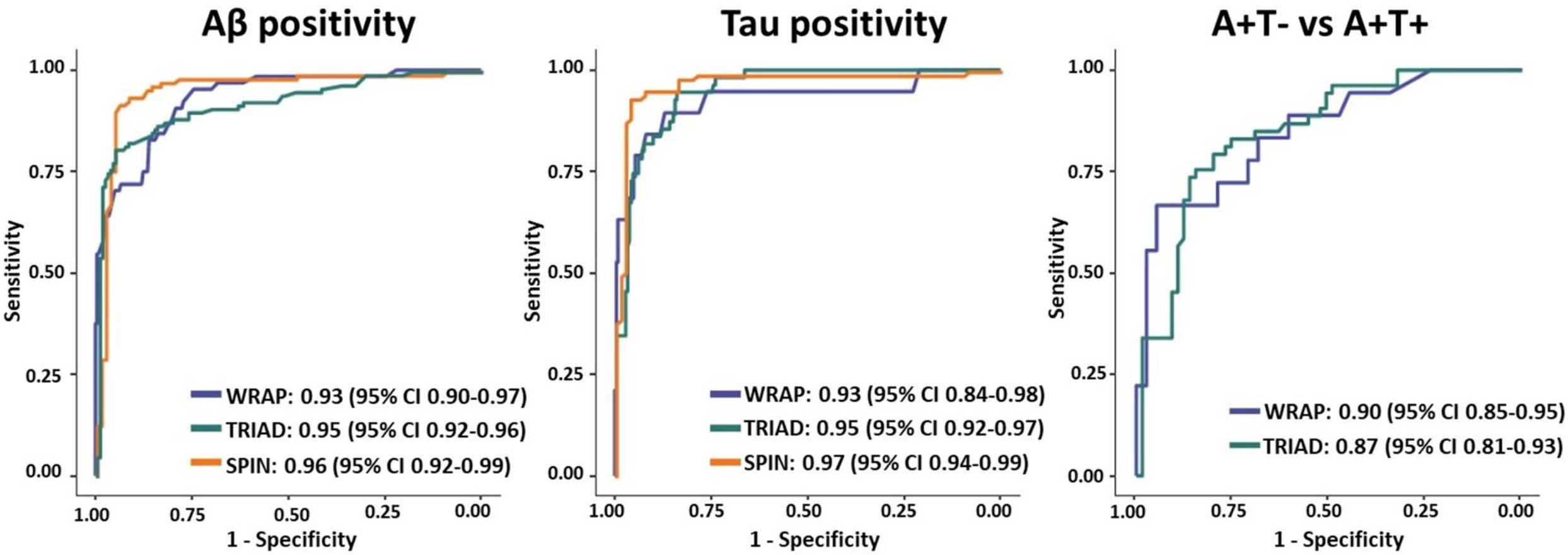
ALZpath pTau217 levels by AT profile for WRAP, TRIAD & SPIN cohorts



Reproduced from Ashton et al., 2023, *MedRxiv*

ALZpath

ALZpath pTau217 ROC (Sensitivity X Specificity) Curves



Reproduced from Ashton et al., 2023, *MedRxiv*

ALZpath

SUMMARY

- Alzheimer's disease (AD) is amyloid, tau, neurodegeneration
- Brain amyloid, tau, and neurodegeneration can be detected in living participants
  - Amyloid and tau Pet scans, MRI
  - Blood tests for amyloid, tau, neurodegeneration
- Amyloid plaque clearing antibodies slow cognitive decline
- We are now in the era of blood tests and effective treatments!!!!
- **BUT ONLY 30-40% SLOWING! MUCH MORE TO DO**