Anti-Amyloid Therapies

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Disclosures

No relevant conflicts of interest

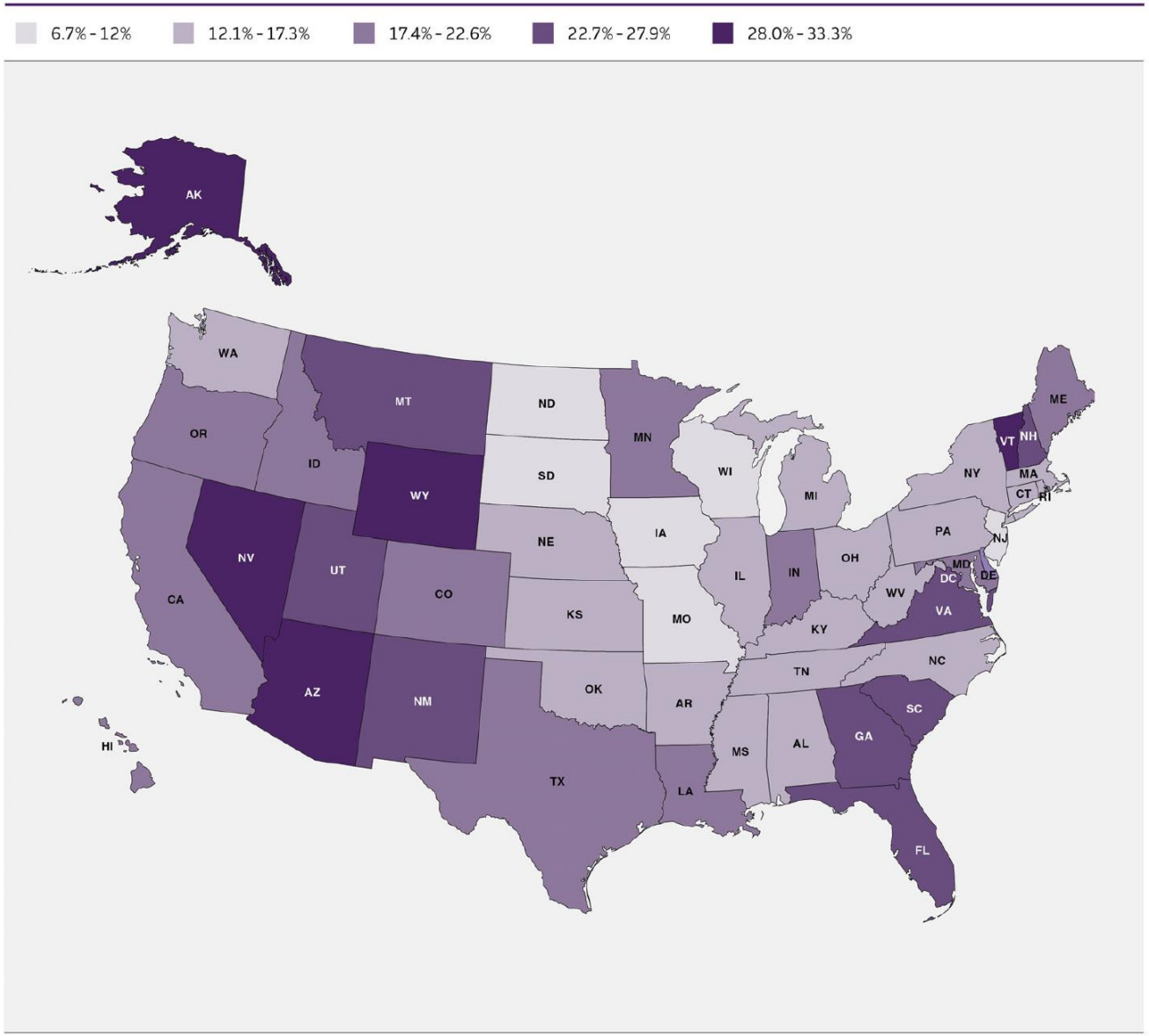
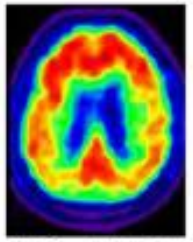


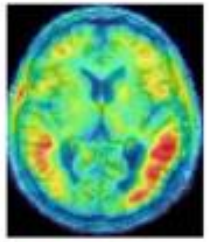
FIGURE 3 Projected increases between 2020 and 2025 in Alzheimer's dementia prevalence by state. Change from 2020 to 2025 for Washington, D.C.: 1.1%. Created from data provided to the Alzheimer's Association by Weuve et al.[A4,257]

- Estimated 6.7 million Americans
- 5% of adults 65-74
- 13.1% of adults 75-84
- 33.3% of adults >85
- Estimated 110 of 100,000 adults 30-64 have Alzheimer's Dementia

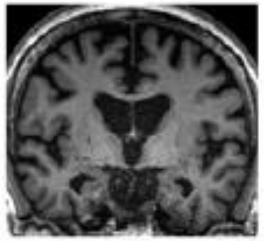
A → T → (N) → (C)



+Aβ PET



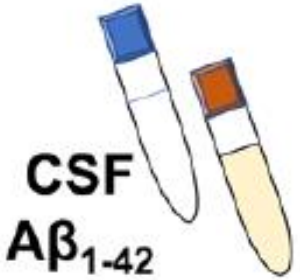
+Tau PET



Brain atrophy

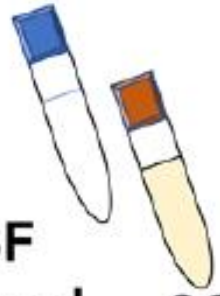
	Face	Velvet	Church	Daisy	Red
No cue	✓				
Category cue		✓			
Multiple choice					✓

Cognitive impairment



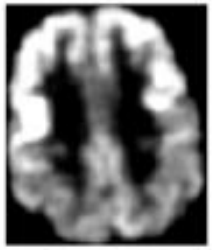
CSF $A\beta_{1-42}$

Plasma $A\beta_{40/42}$



CSF Tau and P-tau

CSF P-tau



Brain hypometabolism

Functional impairment

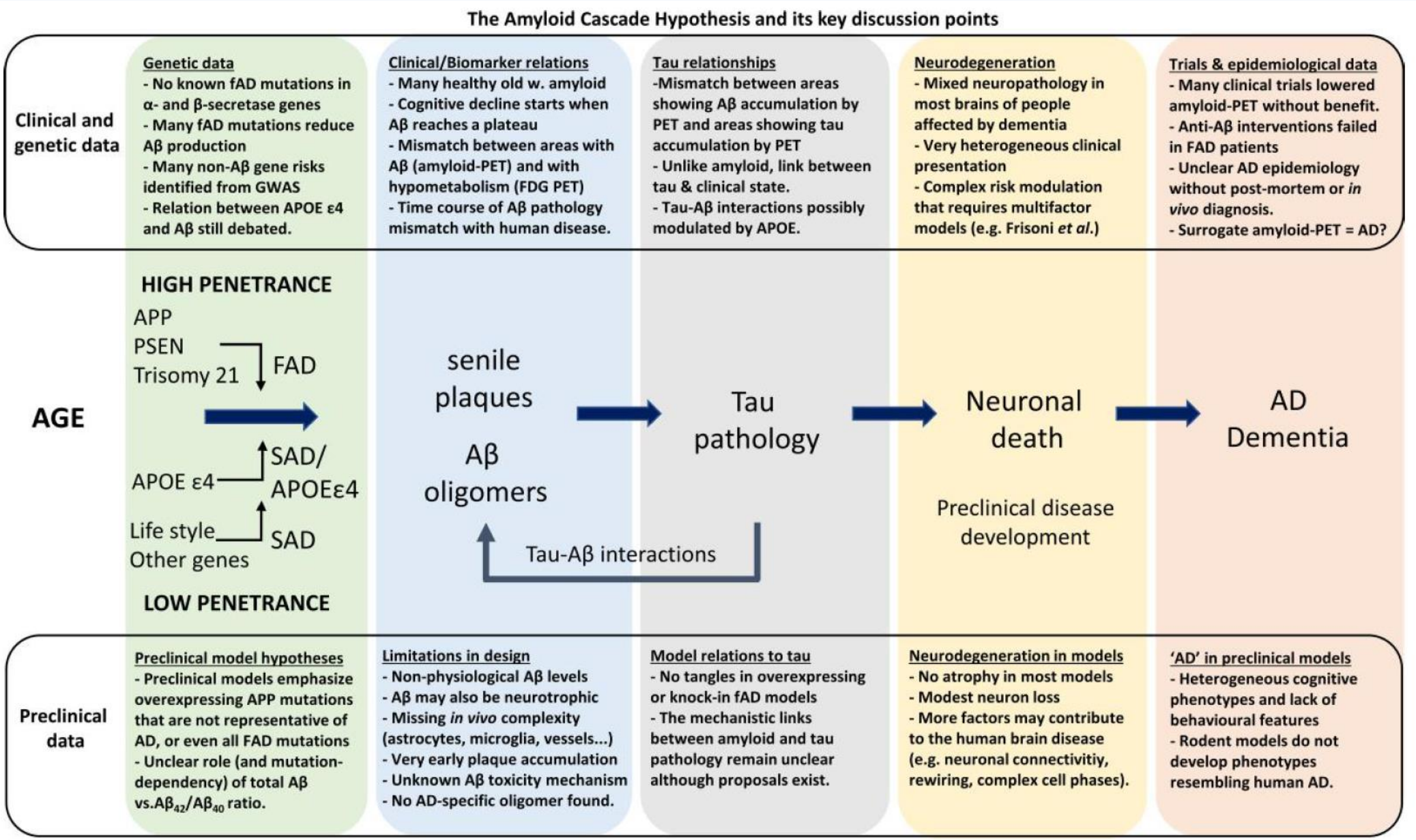


Figure 1 Overview of the amyloid cascade hypothesis and its related controversies. The amyloid cascade hypothesis[11,80,153] has been updated into a model in which APOE ε4 and tau pathology affect total penetrance (Frisoni *et al.*[154]).Aβ = amyloid-β; AD = Alzheimer's disease; FAD = familial Alzheimer's disease; GWAS = genome-wide association studies; SAD = sporadic Alzheimer's disease.

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Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

ABSTRACT

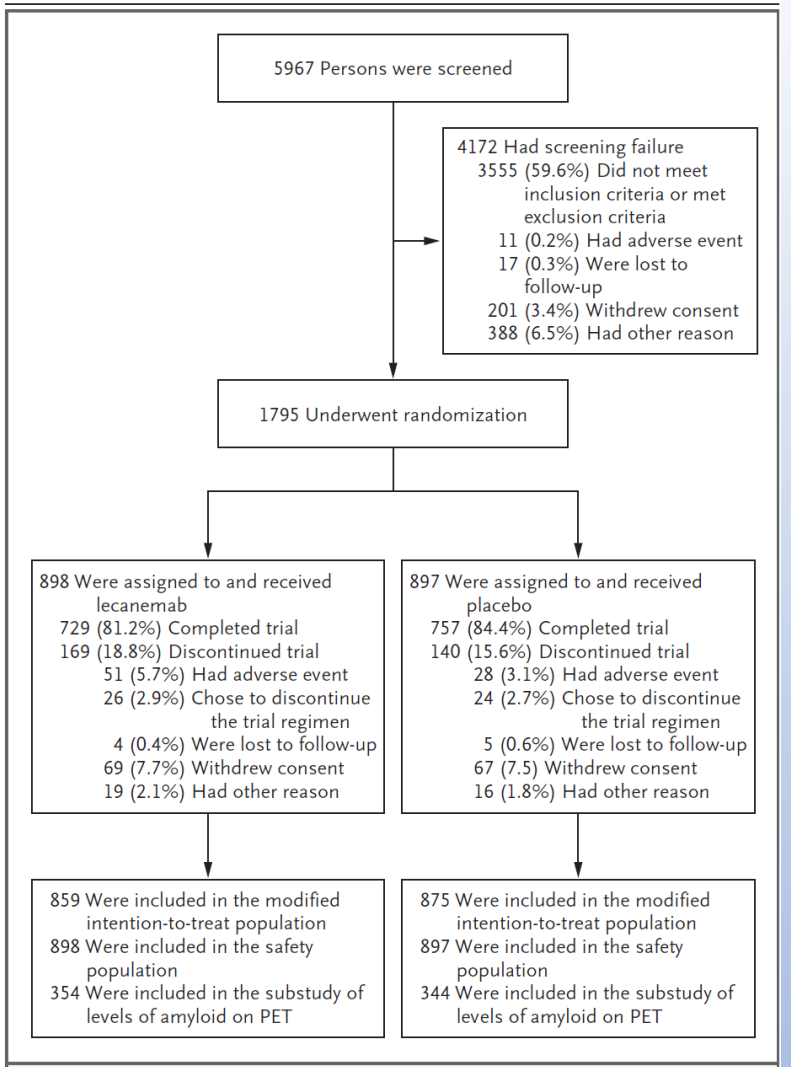


Figure 1. Screening, Randomization, and Follow-up.

Participants who completed visit 42 (at 18 months) are considered to have completed the trial. If the primary reason for trial discontinuation was missing, the participant was counted under "Other" for discontinuation reason. The modified intention-to-treat population included randomly assigned participants who received at least one dose of lecanemab or placebo and underwent assessment for the primary end point. PET denotes positron-emission tomography.

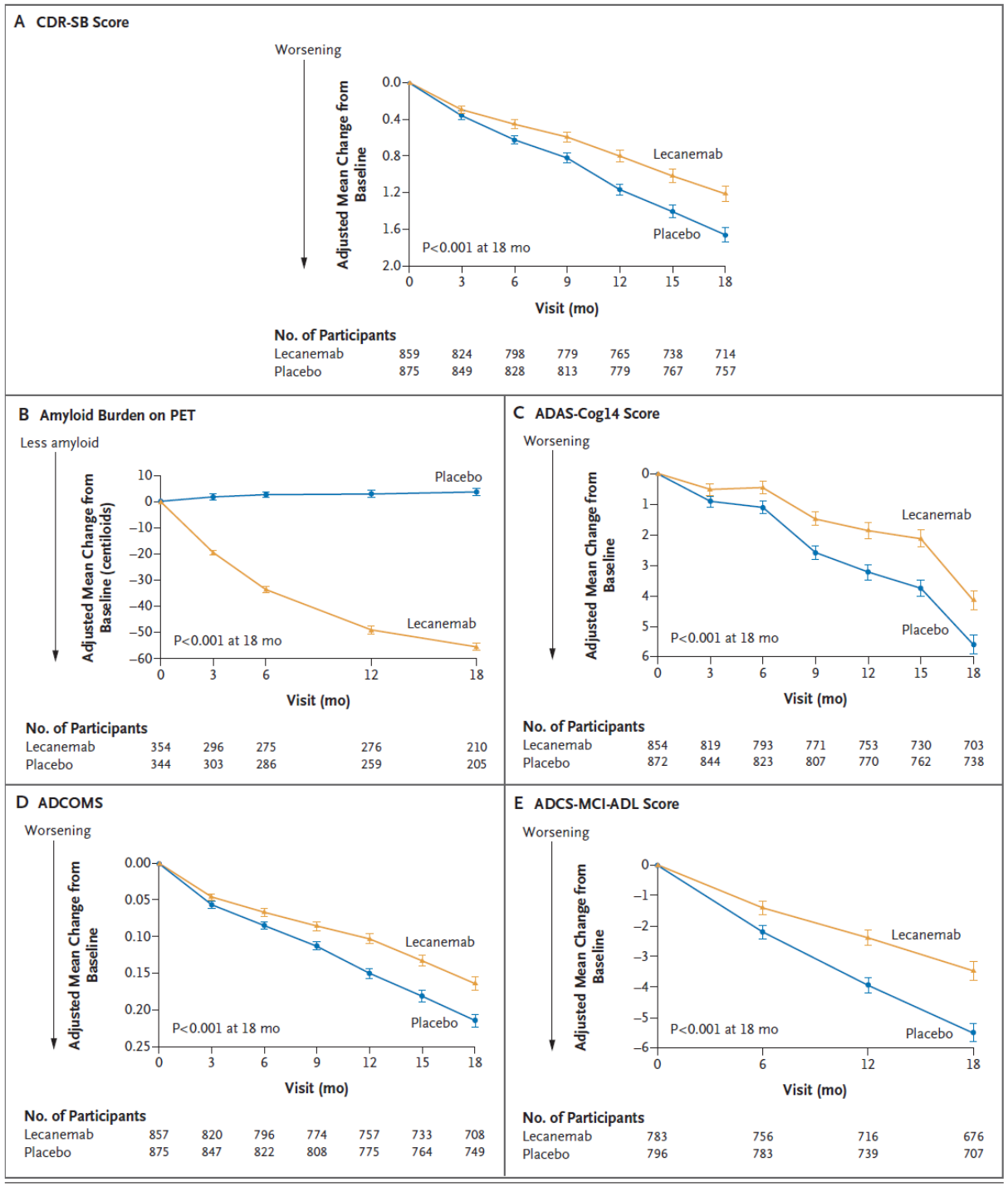


Table 2. Primary and Secondary End Points (Modified Intention-to-Treat Population).

End Point	Lecanemab (N=859)	Placebo (N=875)
Primary efficacy end point		
Change from baseline to 18 mo in the CDR-SB score		
No. of participants evaluated	859	875
Adjusted mean change	1.21	1.66
Adjusted mean difference vs. placebo (95% CI)	−0.45 (−0.67 to −0.23)	
P value vs. placebo	<0.001	
Secondary efficacy end points		
Change from baseline to 18 mo in amyloid burden on PET		
No. of participants evaluated	354	344
Adjusted mean change — centiloids	−55.48	3.64
Adjusted mean difference vs. placebo (95% CI) — centiloids	−59.12 (−62.64 to −55.60)	
P value vs. placebo	<0.001	
Change from baseline to 18 mo in the ADAS-cog14 score		
No. of participants evaluated	854	872
Adjusted mean change	4.14	5.58
Adjusted mean difference vs. placebo (95% CI)	−1.44 (−2.27 to −0.61)	
P value vs. placebo	<0.001	
Change from baseline to 18 mo in the ADCOMS		
No. of participants evaluated	857	875
Adjusted mean change	0.164	0.214
Adjusted mean difference vs. placebo (95% CI)	−0.050 (−0.074 to −0.027)	
P value vs. placebo	<0.001	
Change from baseline to 18 mo in the ADCS-MCI-ADL score		
No. of participants evaluated	783	796
Adjusted mean change	−3.5	−5.5
Adjusted mean difference vs. placebo (95% CI)	2.0 (1.2 to 2.8)	
P value vs. placebo	<0.001	

CDR™ Scoring Table

Subject Initials _____

CLINICAL DEMENTIA RATING (CDR™):	0	0.5	1	2	3

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

Table 3. Adverse Events.*

Event	Lecanemab (N=898)	Placebo (N=897)
Overall — no. (%)		
Any adverse event	798 (88.9)	735 (81.9)
Adverse event related to lecanemab or placebo†	401 (44.7)	197 (22.0)
Serious adverse event	126 (14.0)	101 (11.3)
Death	6 (0.7)	7 (0.8)
Adverse event leading to discontinuation of the trial agent	62 (6.9)	26 (2.9)
Adverse event that occurred in ≥5% of participants in either group		
Infusion-related reaction	237 (26.4)	66 (7.4)
ARIA with microhemorrhages or hemosiderin deposits	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)
Urinary tract infection	78 (8.7)	82 (9.1)
Covid-19	64 (7.1)	60 (6.7)
Back pain	60 (6.7)	52 (5.8)
Arthralgia	53 (5.9)	62 (6.9)
Superficial siderosis of central nervous system	50 (5.6)	22 (2.5)
Dizziness	49 (5.5)	46 (5.1)
Diarrhea	48 (5.3)	58 (6.5)
Anxiety	45 (5.0)	38 (4.2)
ARIA‡		
ARIA-E — no. (%)	113 (12.6)	15 (1.7)
Symptomatic ARIA-E — no. (%)§	25 (2.8)	0
ApoE ε4 noncarrier — no./total no. (%)	4/278 (1.4)	0/286
ApoE ε4 carrier — no./total no. (%)	21/620 (3.4)	0/611
ApoE ε4 heterozygote	8/479 (1.7)	0/478
ApoE ε4 homozygote	13/141 (9.2)	0/133
ARIA-E according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	15/278 (5.4)	1/286 (0.3)
ApoE ε4 carrier	98/620 (15.8)	14/611 (2.3)
ApoE ε4 heterozygote	52/479 (10.9)	9/478 (1.9)
ApoE ε4 homozygote	46/141 (32.6)	5/133 (3.8)
ARIA-H — no. (%)	155 (17.3)	81 (9.0)
Microhemorrhage	126 (14.0)	68 (7.6)
Superficial siderosis	50 (5.6)	21 (2.3)
Macrohemorrhage	5 (0.6)	1 (0.1)
Symptomatic ARIA-H§	6 (0.7)	2 (0.2)
Isolated ARIA-H: no concurrent ARIA-E	80 (8.9)	70 (7.8)

Table 3. (Continued.)

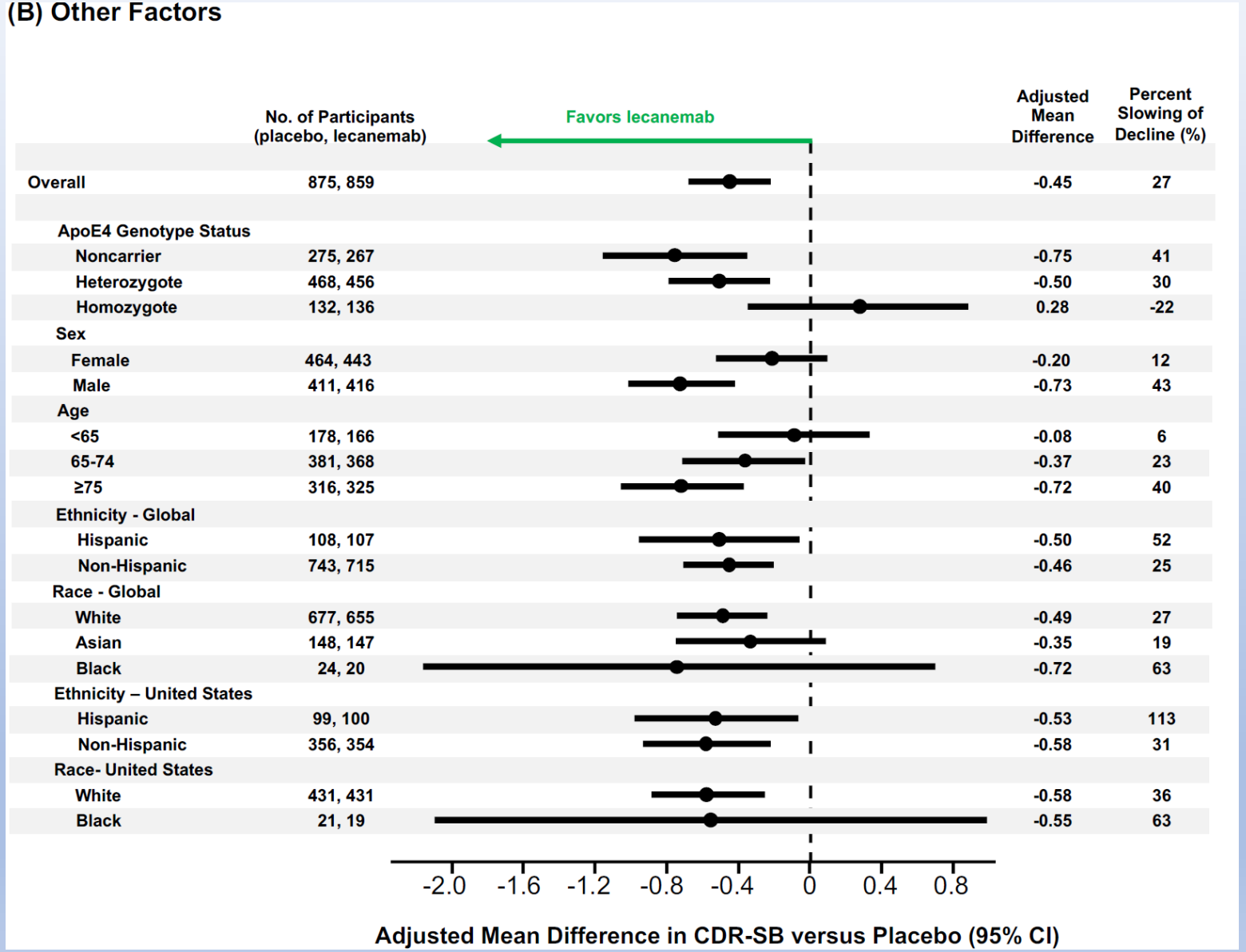
Event	Lecanemab (N=898)	Placebo (N=897)
ARIA-H according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	33/278 (11.9)	12/286 (4.2)
ApoE ε4 carrier	122/620 (19.7)	69/611 (11.3)
ApoE ε4 heterozygote	67/479 (14.0)	41/478 (8.6)
ApoE ε4 homozygote	55/141 (39.0)	28/133 (21.1)
ARIA-E or ARIA-H — no. (%)	193 (21.5)	85 (9.5)
Concurrent ARIA-E and ARIA-H — no. (%)	74 (8.2)	9 (1.0)

Any ARIA was 21.5%

- ARIA E – 12.6% of patients
  -- symptomatic cases – 2.8% total
  -- ApoE homozygous – 9.2%

- ARIA H – 17.3% of patients
  -- symptomatic cases – 6 cases total (0.7%)
  -- ApoE homozygous – 39%

(B) Other Factors



JAMA | Original Investigation

Donanemab in Early Symptomatic Alzheimer Disease
The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

John R. Sims, MD; Jennifer A. Zimmer, MD; Cynthia D. Evans, PhD; Ming Lu, MD, MS, MPH; Paul Ardayfio, PhD; JonDavid Sparks, PhD; Alette M. Wessels, PhD; Sergey Shcherbinin, PhD; Hong Wang, PhD; Emel Serap Monkul Nery, MD; Emily C. Collins, PhD; Paul Solomon, PhD; Stephen Salloway, MD; Liana G. Apostolova, MD; Oskar Hansson, MD, PhD; Craig Ritchie, MD, PhD; Dawn A. Brooks, PhD; Mark Mintun, MD; Daniel M. Skovronsky, MD, PhD; for the TRAILBLAZER-ALZ 2 Investigators

Figure 1. Participant Flow in a Trial of Donanemab for Early Symptomatic Alzheimer Disease

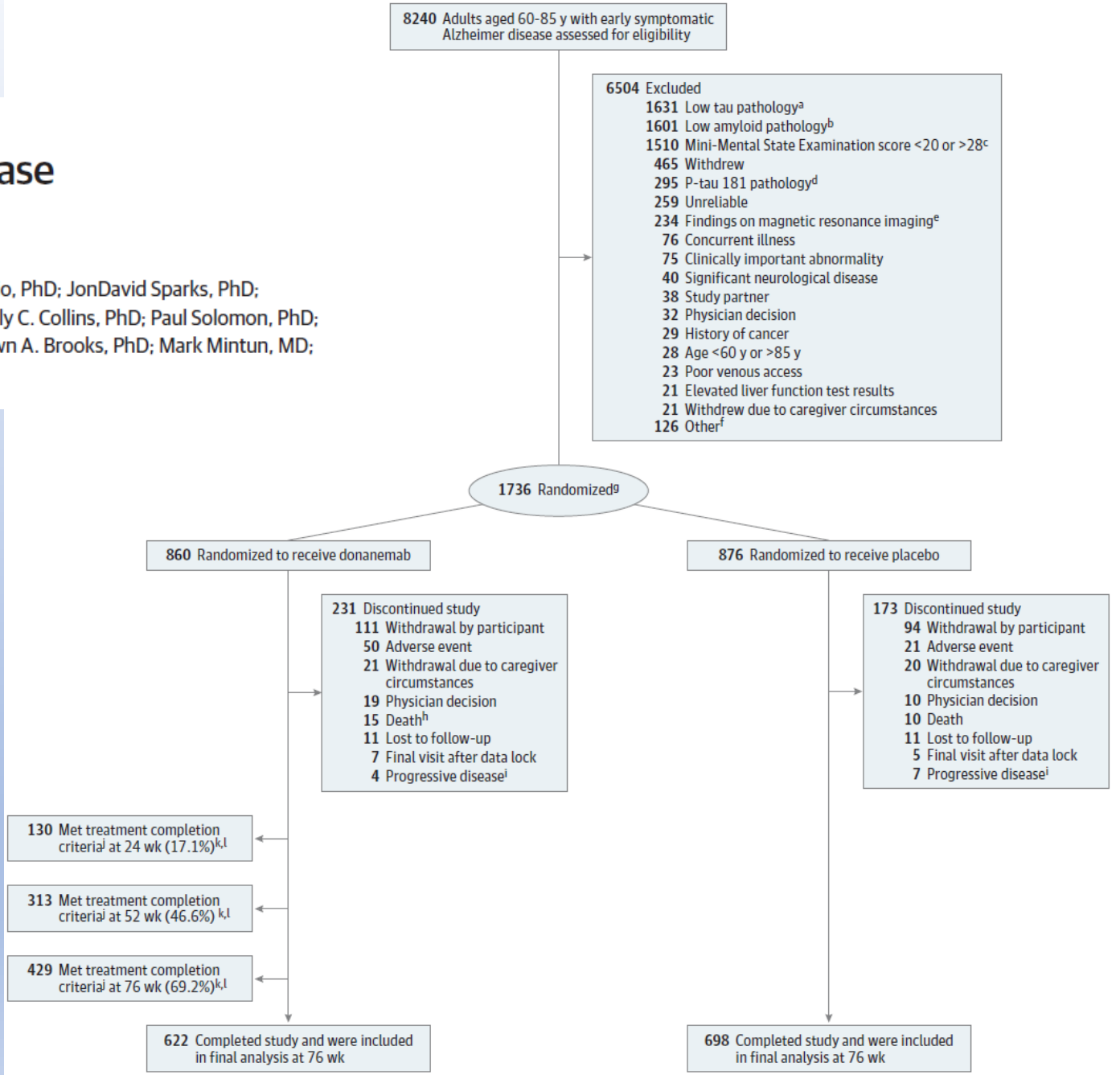
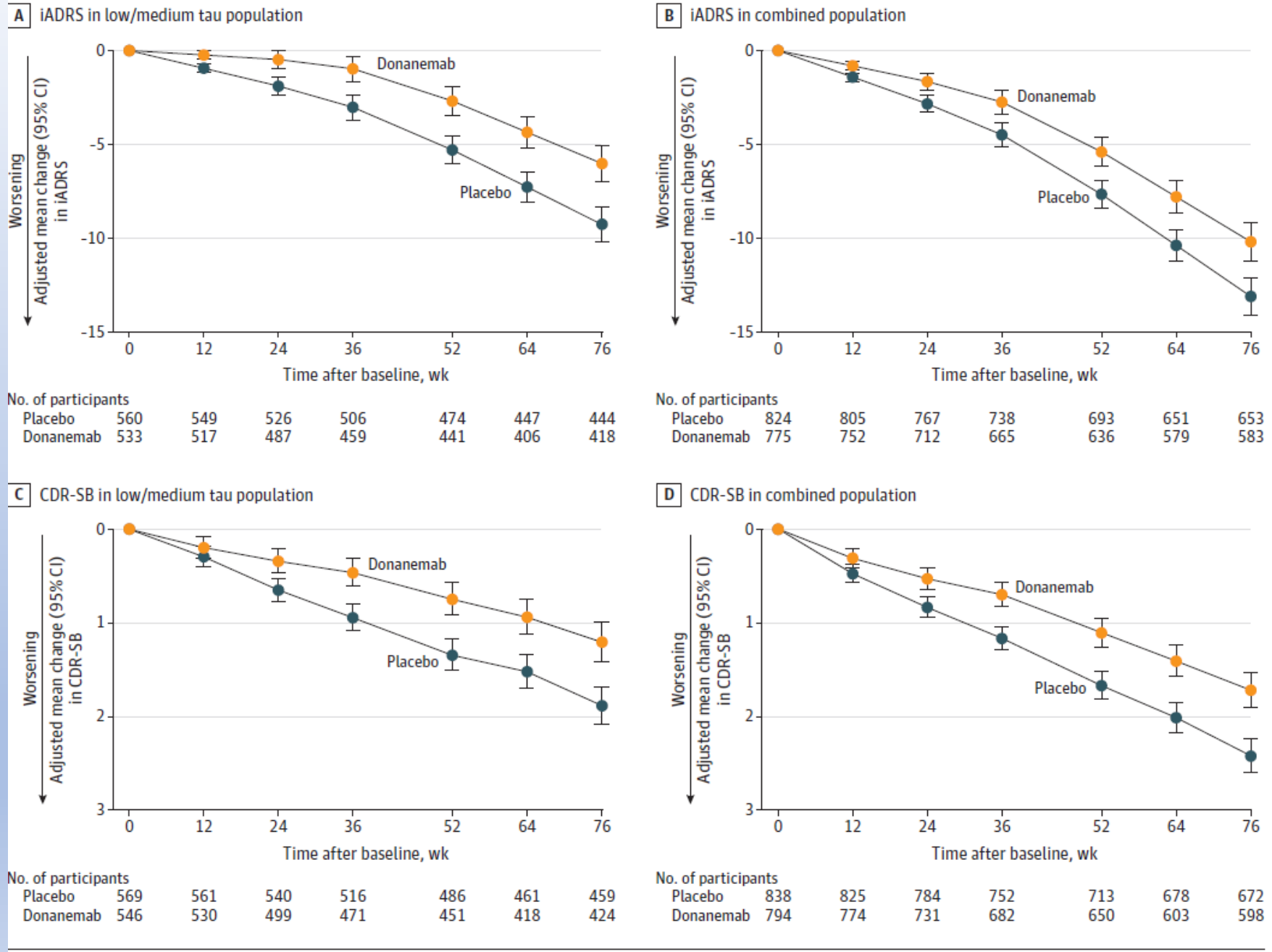


Figure 2. Integrated Alzheimer Disease Rating Scale (iADRS) and Sum of Boxes of the Clinical Dementia Rating Scale (CDR-SB) From Baseline to 76 Weeks



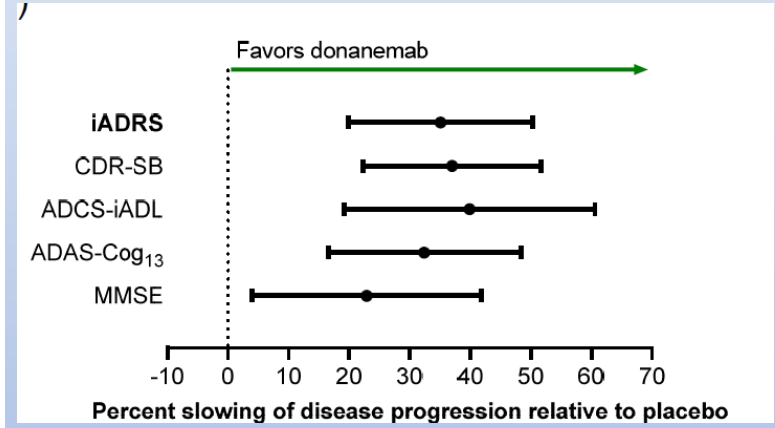
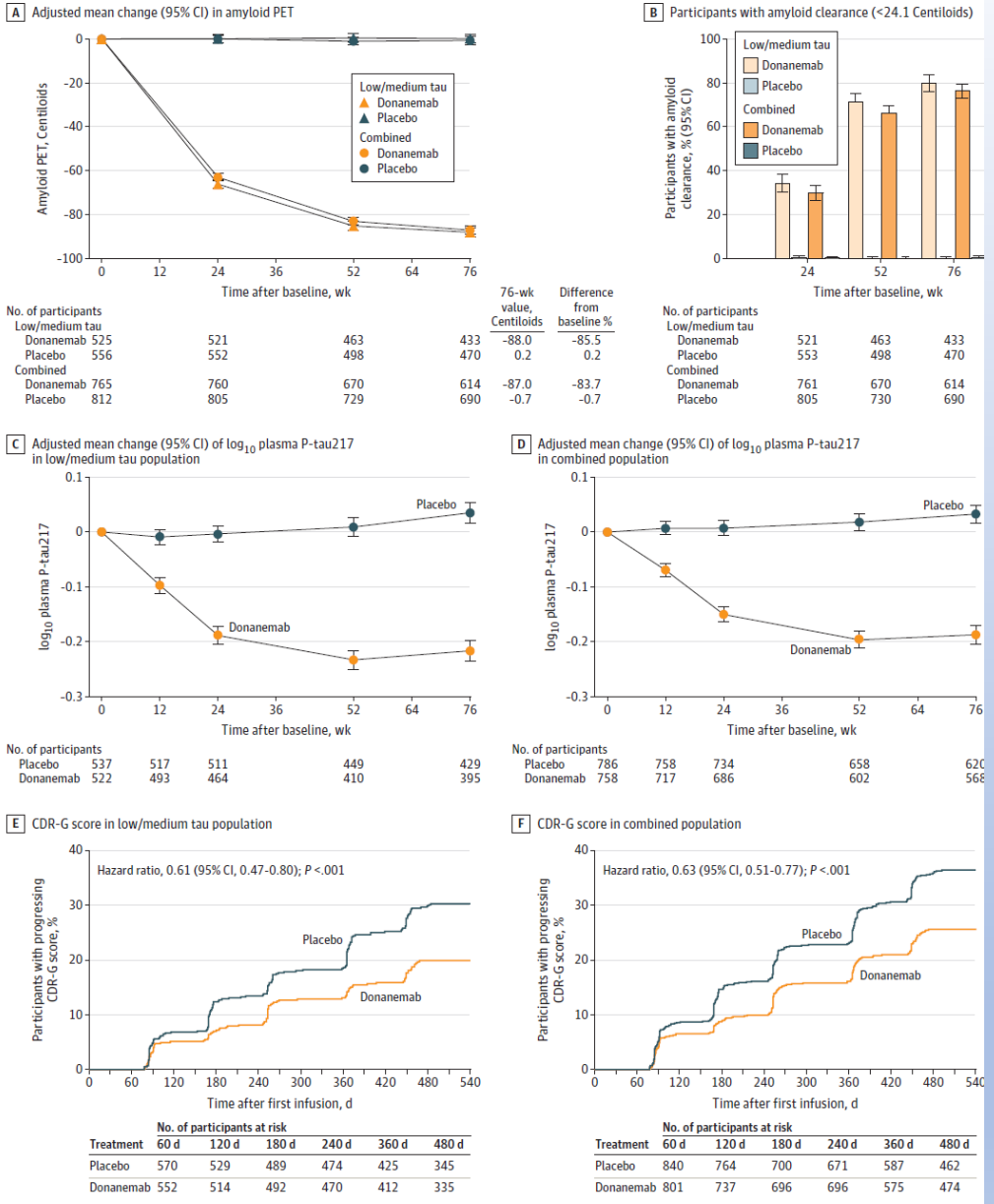


Figure 3. Brain Amyloid, Plasma Phosphorylated Tau 217 (P-tau217), and Hazard Ratios for Risk of Disease Progression



No. of participants					76-wk value, Centiloids	Difference from baseline %
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

No. of participants				
Low/medium tau				
Donanemab	521	463	433	
Placebo	553	498	470	
Combined				
Donanemab	761	670	614	
Placebo	805	730	690	

No. of participants					
Placebo	537	517	511	449	429
Donanemab	522	493	464	410	395

No. of participants					
Placebo	786	758	734	658	620
Donanemab	758	717	686	602	568

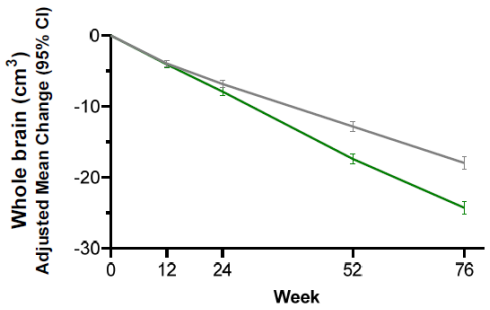
	No. of participants at risk					
Treatment	60 d	120 d	180 d	240 d	360 d	480 d
Placebo	570	529	489	474	425	345
Donanemab	552	514	492	470	412	335

	No. of participants at risk					
Treatment	60 d	120 d	180 d	240 d	360 d	480 d
Placebo	840	764	700	671	587	462
Donanemab	801	737	696	696	575	474

Biomarker data shown were analyzed using mixed models for repeated measures (MMRM). For MMRM analyses, 95% CIs for the least-squares mean changes were calculated with the normal approximation method. $P < .001$ for all time points in panels A-D. B, P value is from Fisher exact test comparing the percent amyloid negative by treatment groups at each visit. E and F, The analysis was conducted using a Cox proportional hazards model. There were 163 events among 573 participants in the placebo group and 100 events among 555 participants in the donanemab group in the low/medium tau population and 288 events among 844 participants in the placebo group and 186 events among 805 participants in the donanemab group in the combined population. CDR-G indicates Clinical Dementia Rating Global Score.

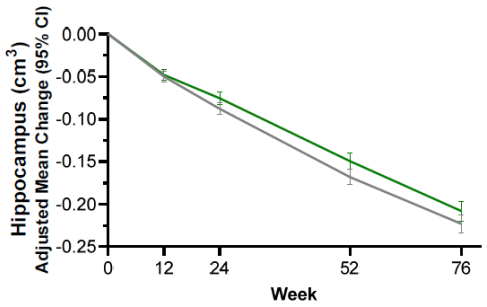
Low/medium-Tau population

A)



Placebo	565	556	525	452	414
Donanemab	535	504	469	419	381

C)



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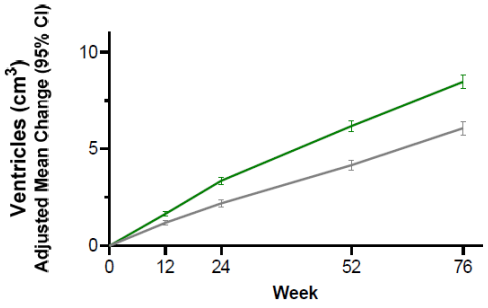
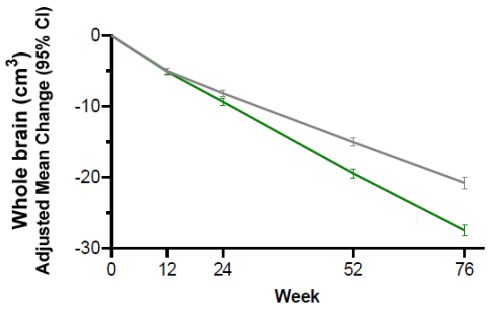
E)



Placebo	565	556	525	452	414
Donanemab	535	504	469	419	381

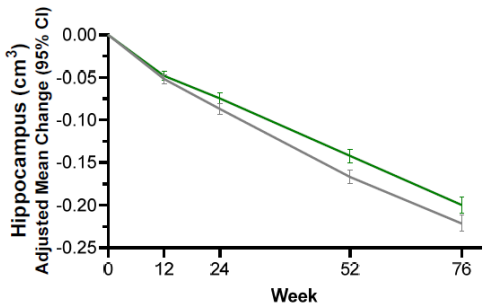
Combined population

B)



Placebo	831	817	760	665	606
Donanemab	786	743	694	611	546

D)



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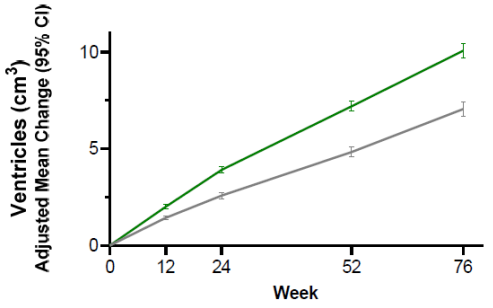
F)



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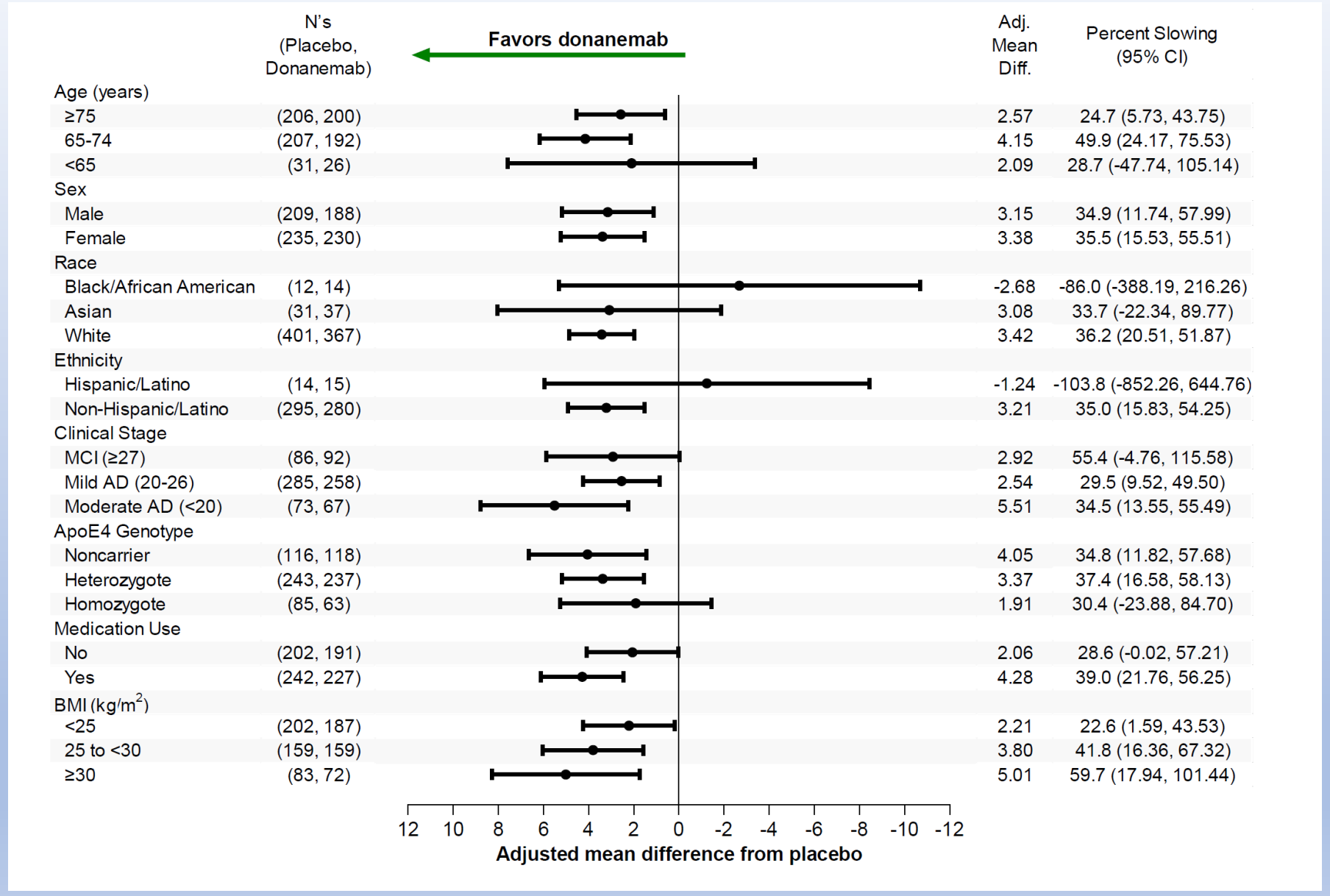
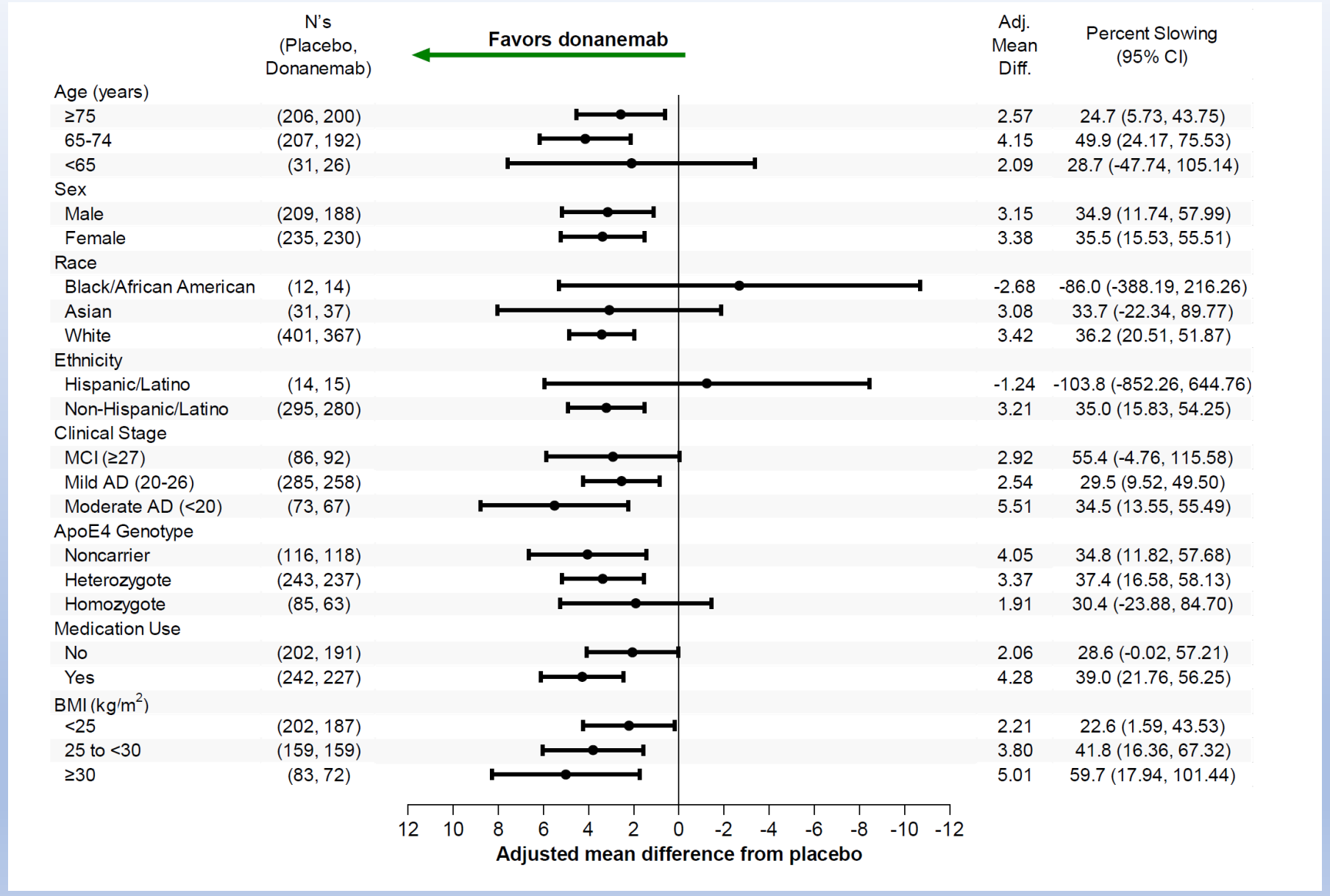

N's (Placebo, Donanemab)
Favors donanemab
Adj. Mean Diff.
Percent Slowing (95% CI)
Age (years)
≥75 (206, 200) 2.57 24.7 (5.73, 43.75)
65-74 (207, 192) 4.15 49.9 (24.17, 75.53)
<65 (31, 26) 2.09 28.7 (-47.74, 105.14)
Sex
Male (209, 188) 3.15 34.9 (11.74, 57.99)
Female (235, 230) 3.38 35.5 (15.53, 55.51)
Race
Black/African American (12, 14) -2.68 -86.0 (-388.19, 216.26)
Asian (31, 37) 3.08 33.7 (-22.34, 89.77)
White (401, 367) 3.42 36.2 (20.51, 51.87)
Ethnicity
Hispanic/Latino (14, 15) -1.24 -103.8 (-852.26, 644.76)
Non-Hispanic/Latino (295, 280) 3.21 35.0 (15.83, 54.25)
Clinical Stage
MCI (≥27) (86, 92) 2.92 55.4 (-4.76, 115.58)
Mild AD (20-26) (285, 258) 2.54 29.5 (9.52, 49.50)
Moderate AD (<20) (73, 67) 5.51 34.5 (13.55, 55.49)
ApoE4 Genotype
Noncarrier (116, 118) 4.05 34.8 (11.82, 57.68)
Heterozygote (243, 237) 3.37 37.4 (16.58, 58.13)
Homozygote (85, 63) 1.91 30.4 (-23.88, 84.70)
Medication Use
No (202, 191) 2.06 28.6 (-0.02, 57.21)
Yes (242, 227) 4.28 39.0 (21.76, 56.25)
BMI (kg/m2)
<25 (202, 187) 2.21 22.6 (1.59, 43.53)
25 to <30 (159, 159) 3.80 41.8 (16.36, 67.32)
≥30 (83, 72) 5.01 59.7 (17.94, 101.44)
12 10 8 6 4 2 0 -2 -4 -6 -8 -10 -12
Adjusted mean difference from placebo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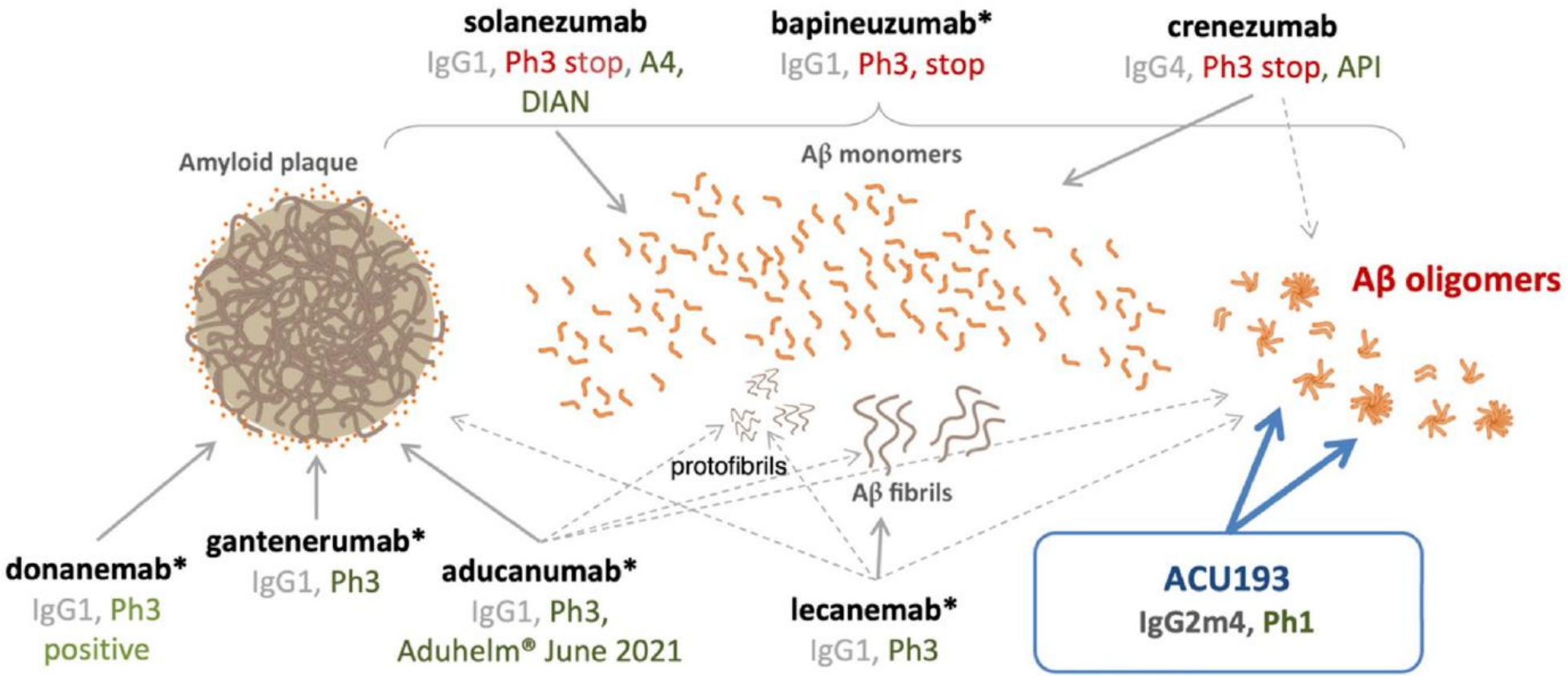
BMI (kg/m2)
<25 (202, 187) 2.21 22.6 (1.59, 43.53)
25 to <30 (159, 159) 3.80 41.8 (16.36, 67.32)
≥30 (83, 72) 5.01 59.7 (17.94, 101.44)
12 10 8 6 4 2 0 -2 -4 -6 -8 -10 -12
Adjusted mean difference from placebo



ACU193 does not significantly bind to Aβ monomers or amyloid plaques

- Non-selective mAbs which bind to Aβ monomers and/ or plaques have reduced ability to bind to toxic AβOs
- Plaque binding mAbs have demonstrated increased inflammatory effects such as ARIA-E in clinical studies

* All IgG1 monoclonal antibodies that bind amyloid plaque have shown high rates of ARIA-E

FIGURE 2 | Summary comparison of ACU193 to amyloid-directed therapeutic antibodies in clinical development.

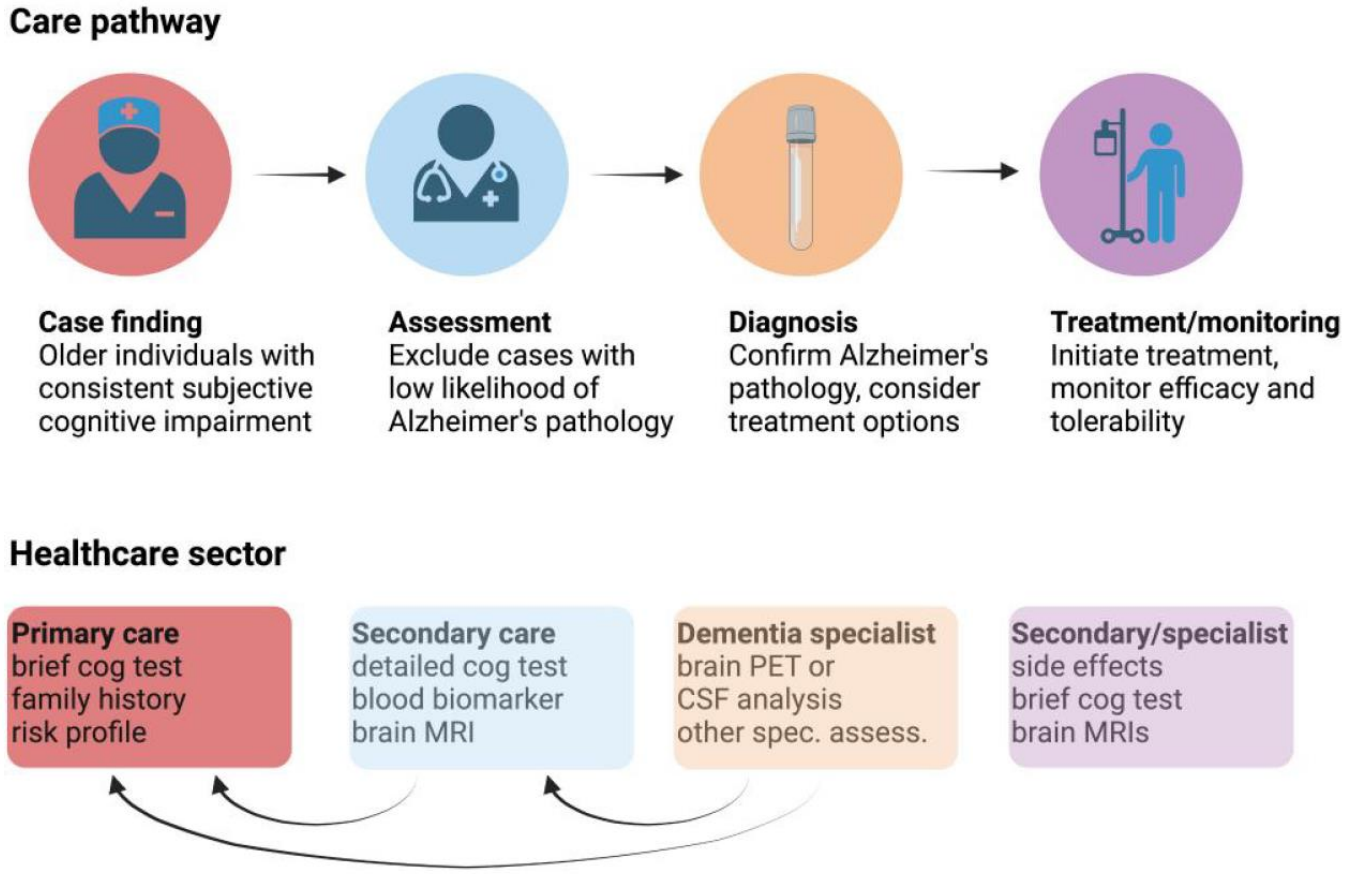


Figure 3 Proposed diagnostic pathway for early Alzheimer's disease case finding, diagnosis and treatment. Proposed model of a care pathway to identify older individuals with minor cognitive complaints/deficits in primary care, followed by an exclusion of subjects with very low likelihood of Alzheimer's disease pathology in secondary care (e.g. by using blood-based biomarkers) and subsequent diagnostic confirmation by a dementia specialist (e.g. by using PET and CSF markers) as well as initiation of DMT treatment after careful evaluation of potential risks and benefits, including monitoring of side effects. Individuals can also move backwards in this model if they do not meet criteria for progression to the next stage (e.g. negative blood-biomarker for Alzheimer's disease).

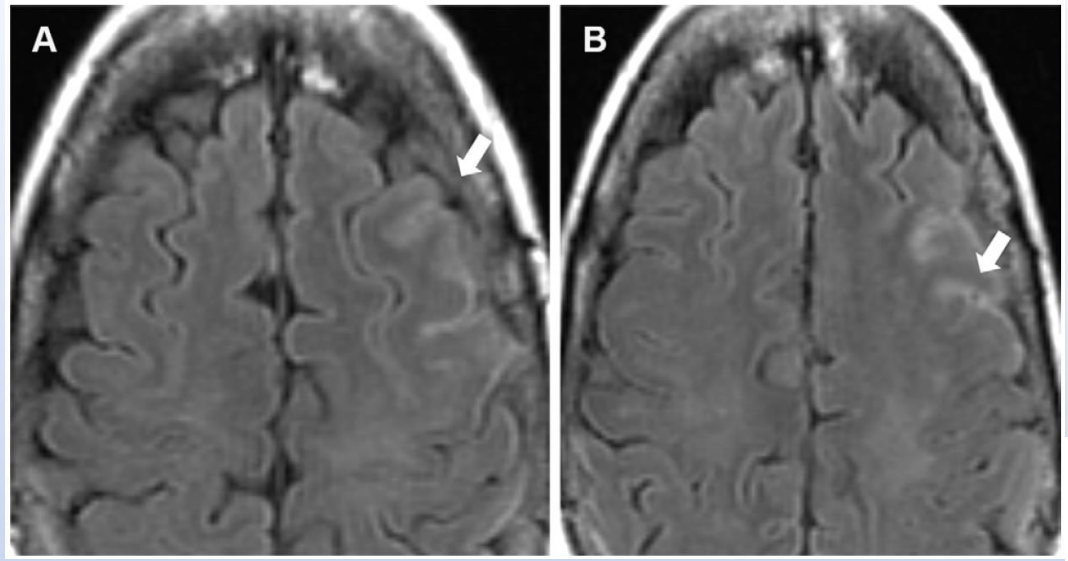
Inclusion and Exclusion Criteria Applied in the Clarity AD Trial of Lecanemab	Appropriate Use Recommendations for Patients Considered for Treatment with Lecanemab
Inclusion Criteria	
Diagnosis of Mild Cognitive Impairment (MCI) or mild AD dementia	Clinical diagnosis of MCI or mild AD dementia as defined in Table 1
Objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler Memory Scale IV-Logical Memory (subscale) II (WMS-IV LMII)	Clinical diagnosis of MCI or mild AD dementia as defined in Table 1
Positive biomarker for brain amyloid pathology	Positive amyloid PET or CSF studies indicative of AD
50-90 years of age	Physician judgement used for patients outside the 50-90 year age range
Mini Mental State Examination (MMSE) score > 22 at Screening and Baseline and < 30 at Screening and Baseline	MMSE 22-30 or other cognitive screening instrument with a score compatible with early AD
Body mass index (BMI) greater than (>)17 and less than (<) 35 at Screening	Physician judgement used for patients at the extremes of BMI
If receiving an acetylcholinesterase inhibitor (donepezil, rivastigmine, galantamine) or memantine or both must be on a stable dose for at least 12 weeks prior to Baseline	Patients may be on cognitive enhancing agents (donepezil, rivastigmine, galantamine, or memantine) for AD; patients may not be on aducanumab
Unless otherwise stated, participants must have been on stable doses of all other (that is, non-AD-related) permitted concomitant medications for at least 4 weeks prior to Baseline	Patients may be on standard of care for other medical illnesses (see below for specifics regarding anticoagulation)
Have an identified study partner	Have a care partner or family member(s) who can ensure that the patient has the support needed to be treated with lecanemab
Provide written informed consent	Patients, care partners, and appropriate family members should understand the requirements for lecanemab therapy and the potential benefit and potential harm of treatment

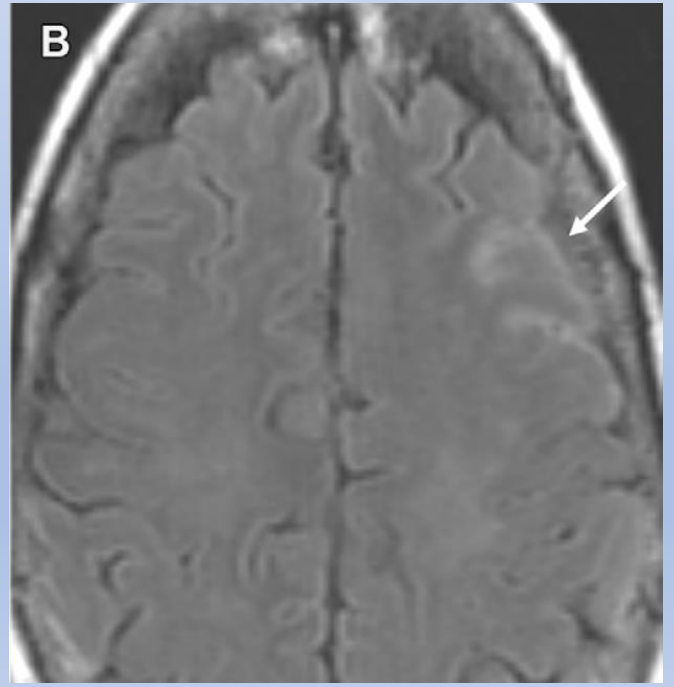
Exclusion Criteria	
Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's AD	Any medical, neurologic, or psychiatric condition that may be contributing to the cognitive impairment or any non-AD MCI or dementia
More than 4 microhemorrhages (defined as 10 millimeter [mm] or less at the greatest diameter); a single macrohemorrhage >10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; multiple lacunar infarcts or stroke involving a major vascular territory; severe small vessel; or other major intracranial pathology	More than 4 microhemorrhages (defined as 10 millimeter [mm] or less at the greatest diameter); a single macrohemorrhage >10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; more than 2 lacunar infarcts or stroke involving a major vascular territory; severe subcortical hyperintensities consistent with a Fazekas score of 3 (60); evidence of amyloid beta-related angiitis (ABRA); cerebral amyloid angiopathy-related inflammation (CAA-ri); or other major intracranial pathology that may cause cognitive impairment
Evidence of other clinically significant lesions on brain MRI at Screening that could indicate a dementia diagnosis other than AD	MRI evidence of a non-AD dementia
History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of Screening	Recent history (within 12 months) of stroke or transient ischemic attacks or any history of seizures
Any psychiatric diagnosis or symptoms (example, hallucinations, major depression, or delusions) that could interfere with study procedures in the participant	Mental illness (e.g, psychosis) that interferes with comprehension of the requirements, potential benefit, and potential harms of treatment and are considered by the physician to render the patient unable to comply with management requirements
Geriatric Depression Scale (GDS) score > 8 at Screening	Major depression that will interfere with comprehension of the requirements, potential benefit, and potential harms of treatment; patients for whom disclosure of a positive biomarker may trigger suicidal ideation. Patients with less severe depression or whose depression resolves may be treatment candidates
Any immunological disease which is not adequately controlled, or which requires treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during the study	Any history of immunologic disease (e.g., lupus erythematosus, rheumatoid arthritis, Crohn's disease) or systemic treatment with immunosuppressants, immunoglobulins, or monoclonal antibodies or their derivatives
Participants with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or international normalized ratio [INR] >1.5 for participants who are not on anticoagulant treatment, example, warfarin)	Patients with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or international normalized ratio [INR] >1.5 for participants who are not on anticoagulant)
Participants who are on anticoagulant therapy should have their anticoagulant status optimized and be on a stable dose for 4 weeks before Screening	Patients on anticoagulants (coumadin, dabigatran, edoxaban, rivaroxaban, apixaban, betrixaban, or heparin) should not receive lecanemab; tPA should not be administered to individuals on lecanemab
Any other medical conditions (example, cardiac, respiratory, gastrointestinal, renal disease) which are not stably and adequately controlled, or which could affect the participant's safety or interfere with the study assessments	Unstable medical conditions that may affect or be affected by lecanemab therapy

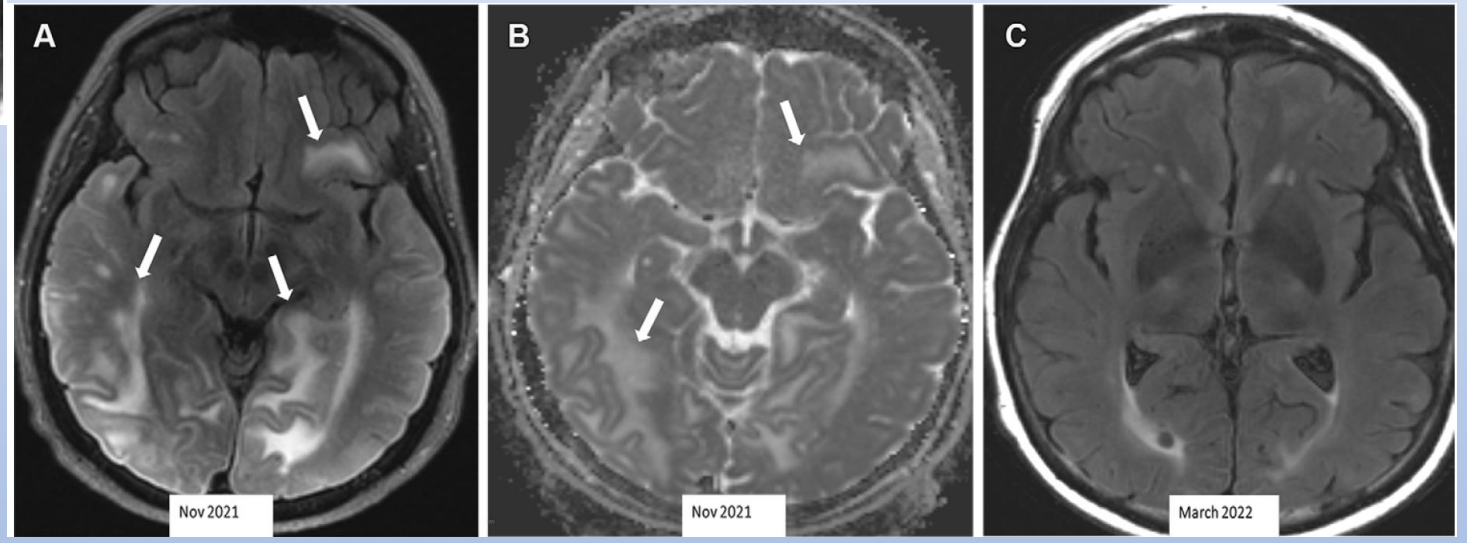
Amyloid Related Imaging Abnormalities

Table 2: ARIA Grading Criteria

ARIA Type	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and cortex/subcortical white matter in one location <5 cm	FLAIR hyperintensity 5–10 cm, or more than one site of involvement each measuring <10 cm	FLAIR hyperintensity >10 cm, often with sulcal involvement, may involve one or more sites
ARIA-H microhemorrhage	Four or more new microhemorrhages	Five to nine new microhemorrhages	10 or more new microhemorrhages
ARIA-H superficial siderosis	One focal area of superficial siderosis	Two focal areas of superficial siderosis	More than two focal areas of superficial siderosis


A
B


B


A
Nov 2021
B
Nov 2021
C
March 2022

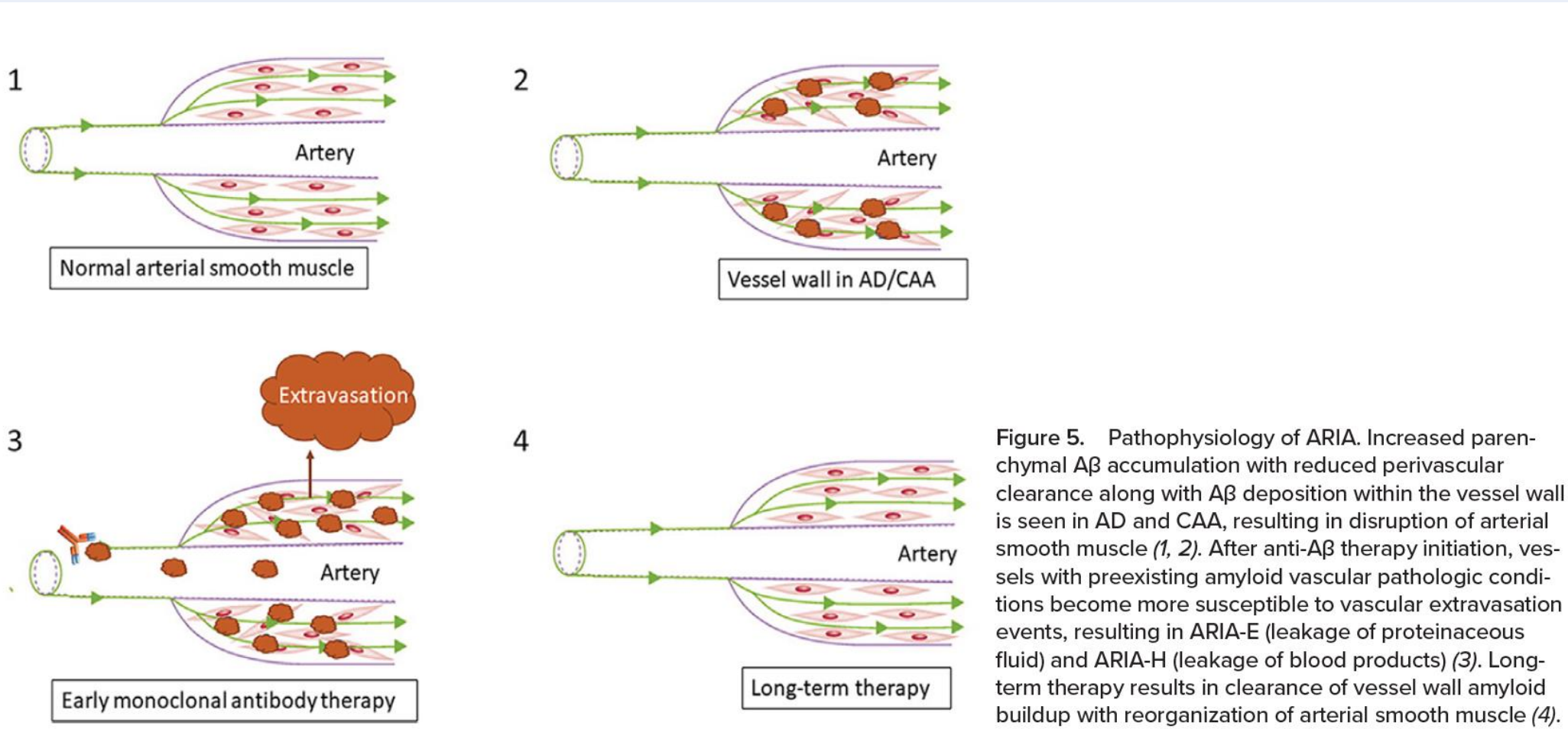
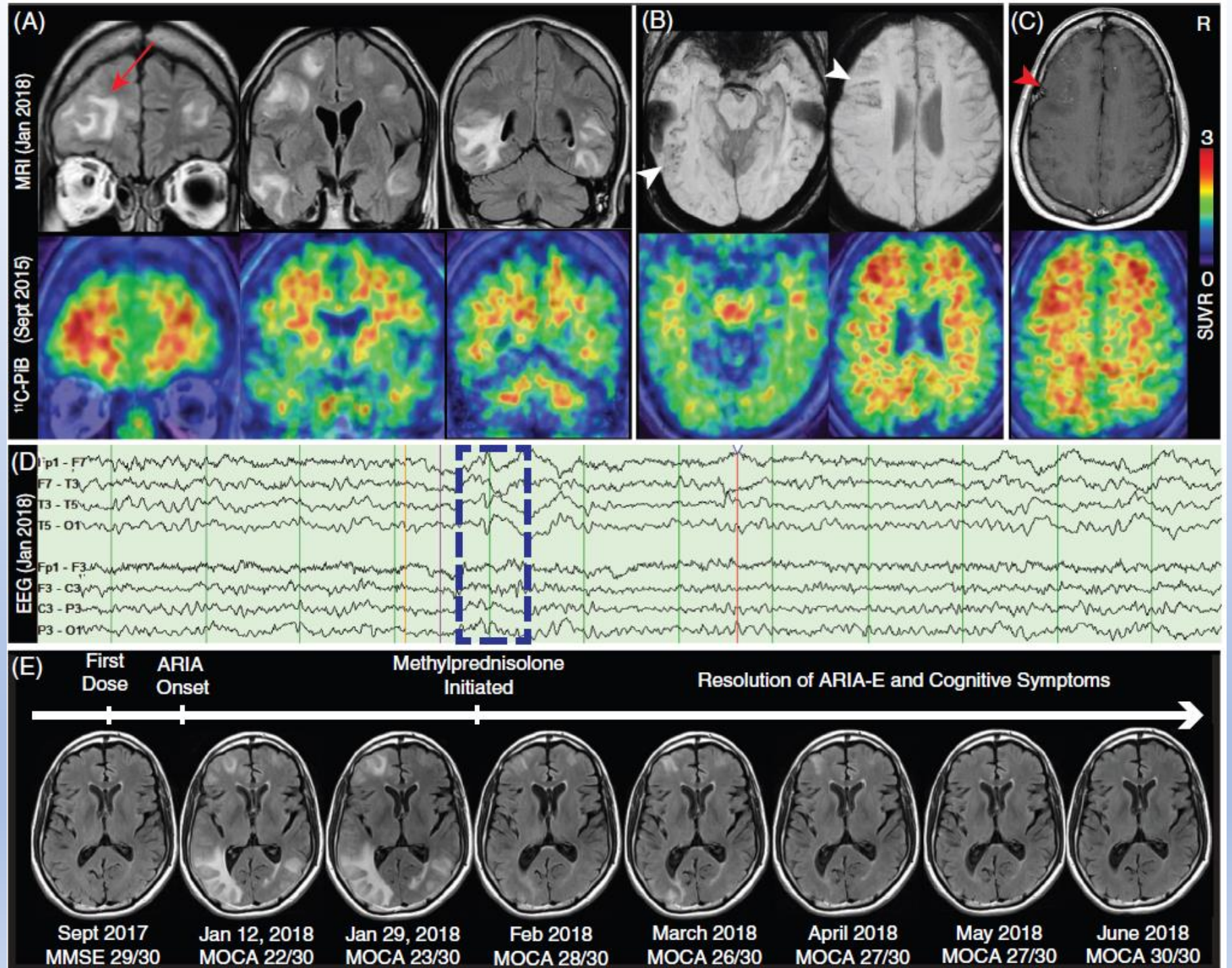


Figure 5. Pathophysiology of ARIA. Increased parenchymal Aβ accumulation with reduced perivascular clearance along with Aβ deposition within the vessel wall is seen in AD and CAA, resulting in disruption of arterial smooth muscle *(1, 2)*. After anti-Aβ therapy initiation, vessels with preexisting amyloid vascular pathologic conditions become more susceptible to vascular extravasation events, resulting in ARIA-E (leakage of proteinaceous fluid) and ARIA-H (leakage of blood products) *(3)*. Long-term therapy results in clearance of vessel wall amyloid buildup with reorganization of arterial smooth muscle *(4)*.


(A)
MRI (Jan 2018)
^{11}C-PiB (Sept 2015)
(B)
(C)
R
3
SUVR 0
(D)
EEG (Jan 2018)
Fp1 - F7
F7 - T3
T3 - T5
T5 - O1
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
(E)
First Dose
ARIA Onset
Methylprednisolone Initiated
Resolution of ARIA-E and Cognitive Symptoms
Sept 2017 MMSE 29/30
Jan 12, 2018 MOCA 22/30
Jan 29, 2018 MOCA 23/30
Feb 2018 MOCA 28/30
March 2018 MOCA 26/30
April 2018 MOCA 27/30
May 2018 MOCA 27/30
June 2018 MOCA 30/30

	Aducanumab		*Donanemab*		*Lecanemab*	
	Most effective dose	Placebo	Most effective dose	Placebo	Most effective dose	Placebo
All ARIA	41.3%	10.3%	38.9%	8%	26.6%	9.4%
ARIA-E	35.2%	2.7%	26.7%	0.8%	12.6%	1.7%
ARIA-H	19.1%	6.6%	30.5%	7.2%	14.0%	7.7%
Discontinuation	6.2%	0.6%	15%	4.8%	6.9%	2.9%
Death	1%	0.9%	0.8%	1.6%	0.7%	0.8%

Table 1. Monoclonal Antibodies Bind Different Epitopes and Conformations of Amyloid-β

					Conformations Recognized			
Antibody	Manufacturer	Origin	Subclass	Epitope	Monomer	Oligomer	Fibril	ARIA-E
Bapineuzumab	Pfizer Inc./Janssen Pharmaceuticals, Inc.	Humanized	IgG1	AA 1–5	Yes	Yes	Yes	High
Solanezumab	Eli Lilly and Company	Humanized	IgG1	AA 16–26	Yes	No	No	Low
Gantenerumab	Hoffman-La Roche	Human	IgG1	AA 3–12, 18–27	Weak	Yes	Yes	High (?)
Crenezumab	Genentech, Inc.	Humanized	IgG4	AA 13–24	Yes	Yes	Yes	Low
Ponezumab	Pfizer Inc.	Humanized	IgG2	AA 30–40	Yes	No	No	None
BAN2401	BioArctic Neuroscience, AB/Eisai Co., Ltd.	Humanized	IgG1	Protofibrils	—	—	—	—
Aducanumab	Biogen, Inc.	Human	IgG1	AA 3–6	No	Yes	Yes	High

Epitope, Conformations Recognized, and ARIA-E are explained further in the text. Dashes indicate absence of information.
AA, amino acid; ARIA-E, amyloid-related imaging abnormalities–edema; Ig, immunoglobulin.

Table 3: Management of ARIA-E

	ARIA-E Severity at MRI		
Clinical Severity of ARIA-E	Mild	Moderate	Severe
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing; once imaging findings resolve, resume dose	Suspend dosing; once imaging findings resolve, resume dose
Mild, moderate, severe, serious ("other medically important event" only)	Suspend dosing; once ARIA-E resolves, same dose treatment can resume	Suspend dosing; once ARIA-E resolves, same dose treatment can resume	Suspend dosing; once ARIA-E resolves, same dose treatment can resume
Serious, except for "other medically important event"	Discontinue dosing	Discontinue dosing	Discontinue dosing

Source.—Reference 48.

Table 4: Management of ARIA-H

	ARIA-H Severity at MRI		
Clinical Severity of ARIA-H	Mild	Moderate	Severe
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing; once imaging findings resolve, resume dose	Discontinue
Mild, moderate, severe, serious ("other medically important event" only)	Suspend dosing; once ARIA-H resolves, same dose treatment can resume	Suspend dosing; once ARIA-H resolves, same dose treatment can resume	Suspend dosing; once ARIA-H resolves, same dose treatment can resume
Serious, except for "other medically important event"	Discontinue dosing	Discontinue dosing	Discontinue dosing

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Questions