Journal Club
Lecanemab in Early Alzheimer’s Disease

2024.01.10

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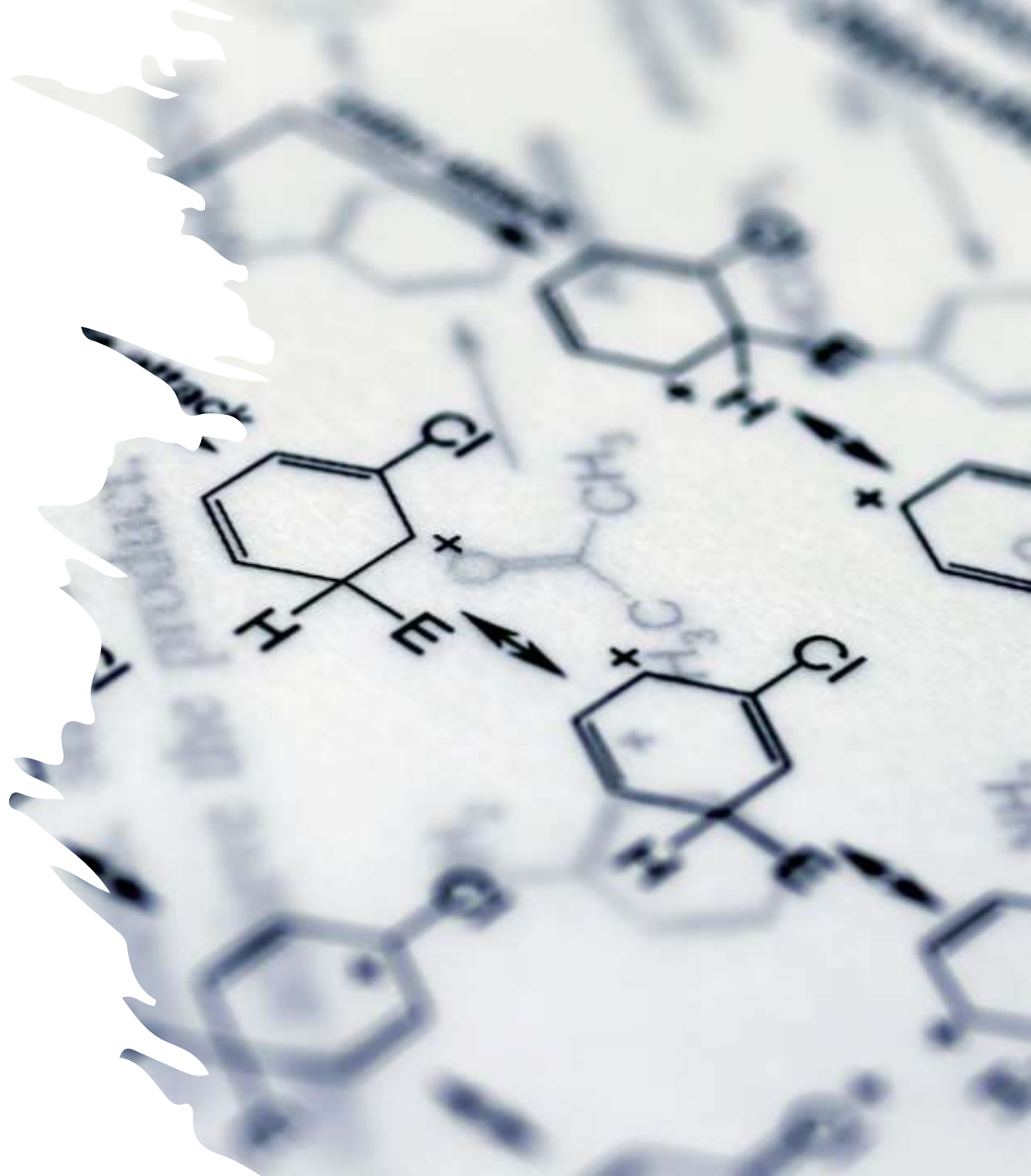

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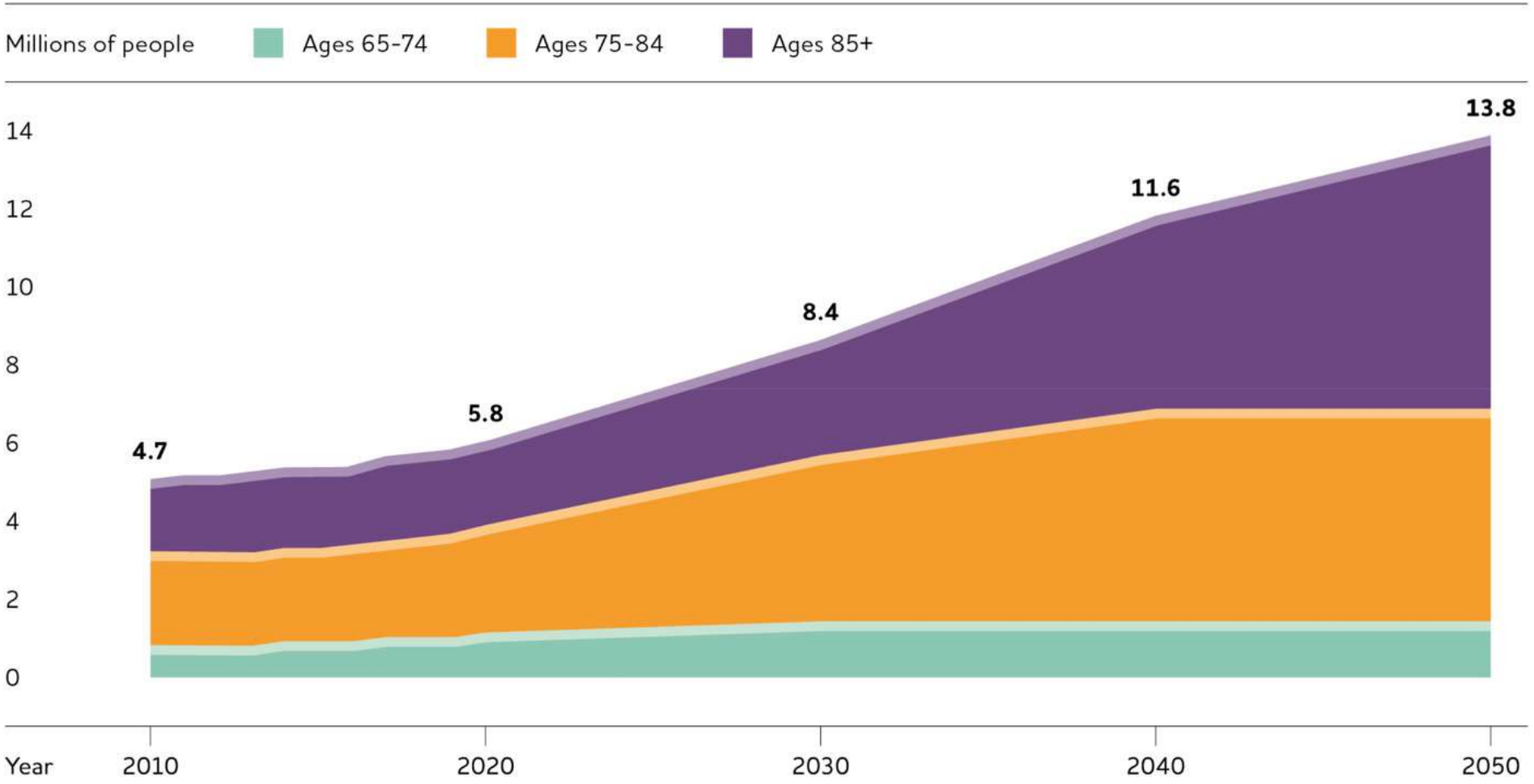
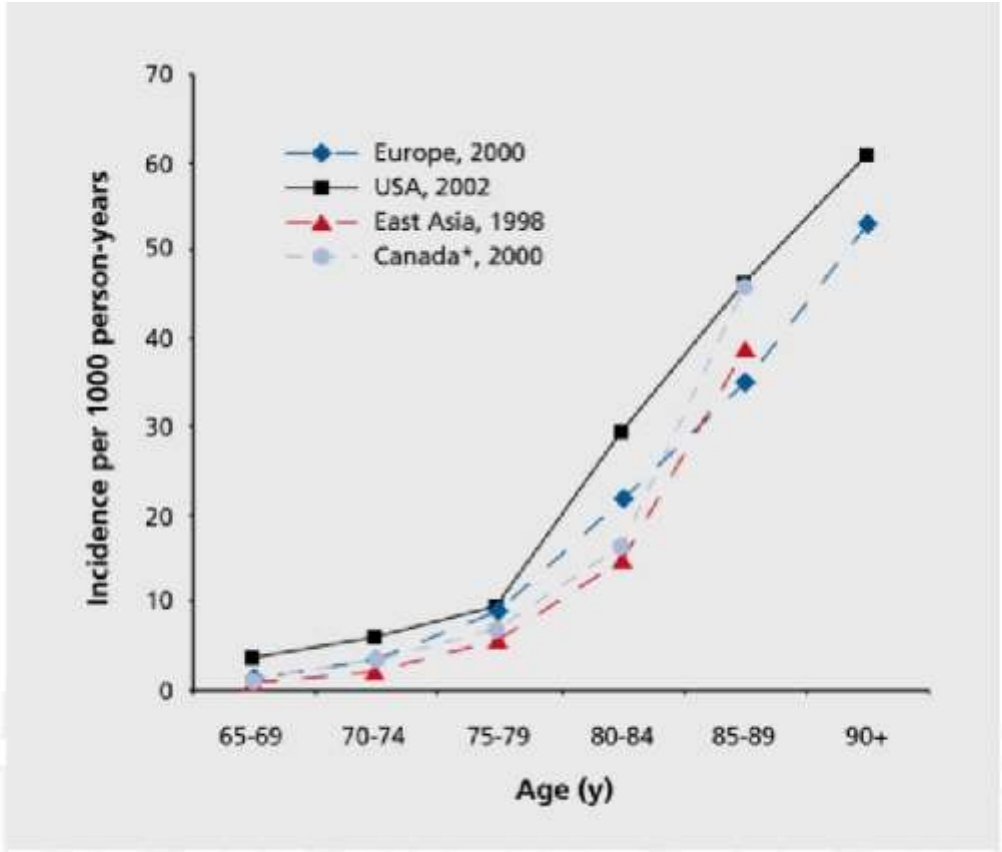
01 Background

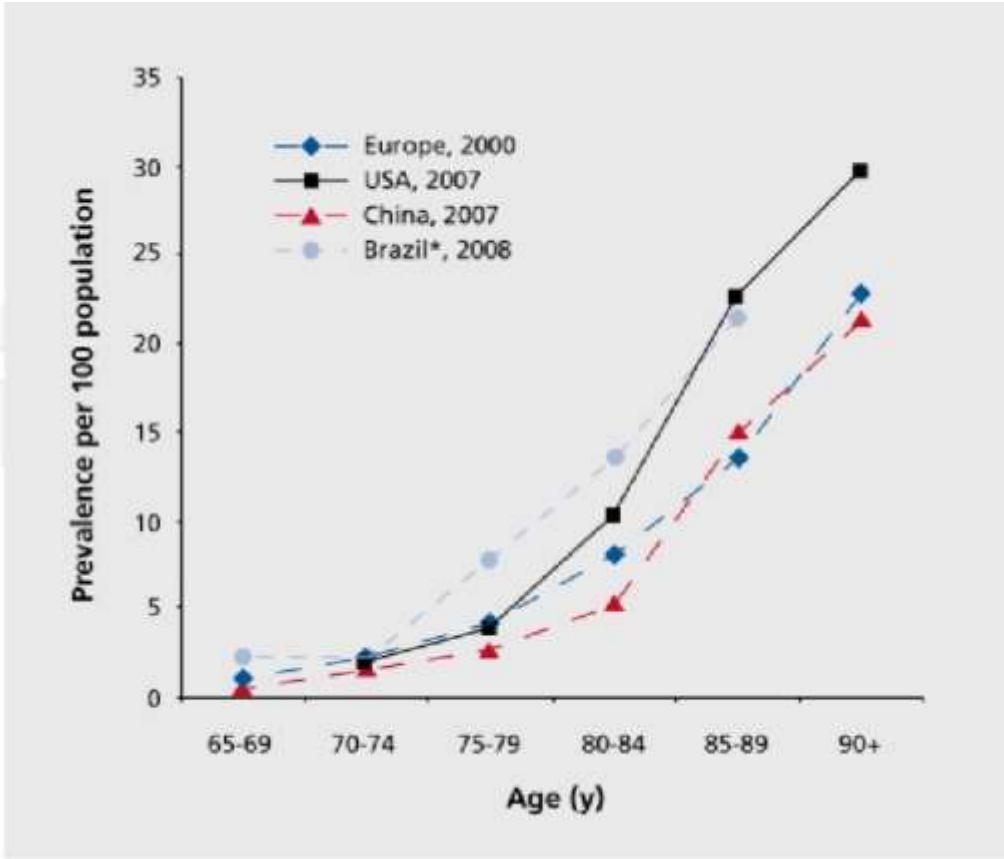
Epidemiology of alzheimer's disease



2020 Alzheimer's disease facts and figures - 2020 - Alzheimer's & Dementia

Epidemiology of alzheimer's disease





Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues Clin Neurosci. 2009 Jun; 11(2): 111–128.

Epidemiology of alzheimer's disease

Table I.

Summary of risk and protective factors for Alzheimer's disease by various etiologic hypotheses.

Etiologic hupothesis	Contents: risk ans protective factors	Epidemiologic evidence
Genetic susceptibility	Risk factors: APOE ε4 allele and familial aggregation	Strong
Vascular pathway hypothesis	Risk factors: midlife high blood pressure and high BMI, diabet, cerebrovascular disease, and smoking; Protective factors: light-to-moderate alchohol consumption, and antihypertensive therapy	Moderate or sufficient
Psychosocial hypothesis	Protecive factors: high educational attainment, mentaly stimulating activities, social activity and enriched social network, and physical activity	Moderate or sufficient
Nutritional and dietary hypothesis	Risk factor deficiency in folate, vitamin B12, and antioxidants (vitamins A, E, and C); Protective factors: Fish (omege-3 fatty acids) and vegetable consumption.	Insufficient or limited/mixed
Others (eg, toxic or inflammatory factors)	Risk factors: traumatic head injuries, occupational exposure to toxins and electromagnetic fields, depression, and hormone replacement therapy; Protective factors: nosteroidal anti-inflammatory drugs	Insufficient or limited/mixed

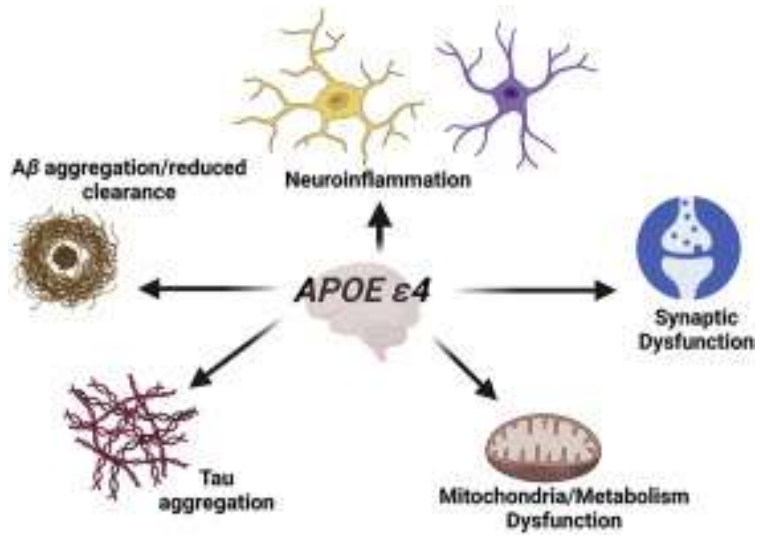
Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues Clin Neurosci. 2009 Jun; 11(2): 111–128.

Risk factors: APOE ε4 allele and familial aggregation

Alzheimer's Disease Genetic Risk Factor APOE-ε4 Also Affects Normal Brain Function

Amanda M. DiBattista,[a] Nicolette M. Heinsinger,[a] and G. William Rebeck*,[a]

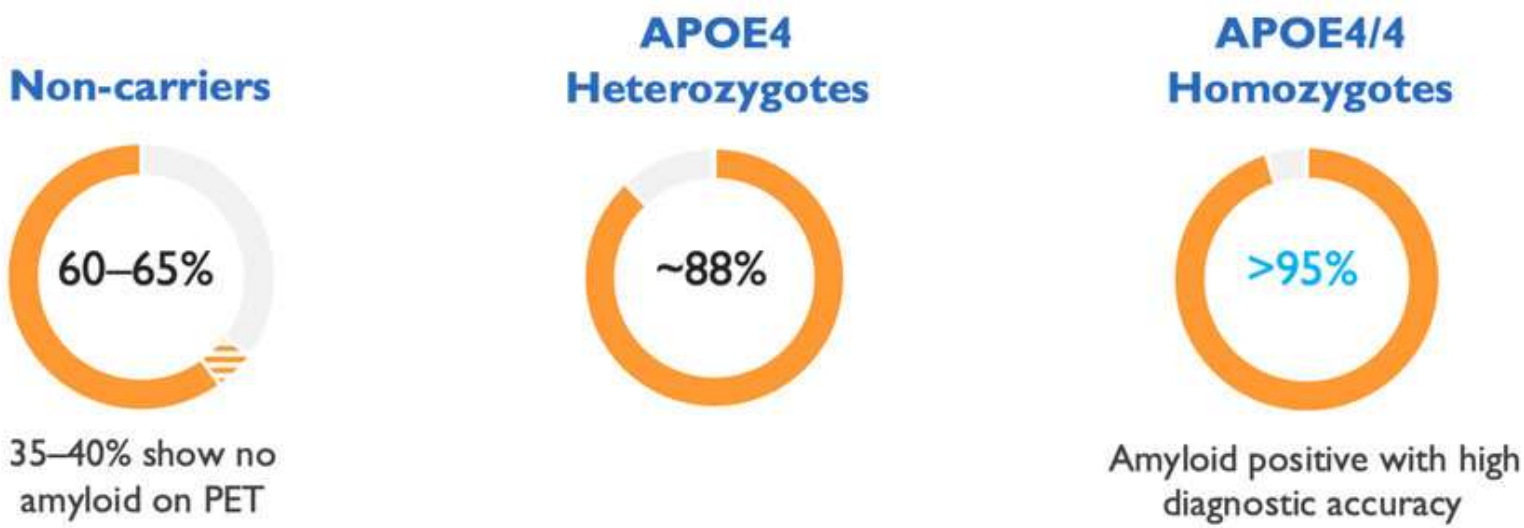
APOE genotype is recognized as the strongest genetic risk factor of AD [122; 123]. The recent studies outlined here support the hypothesis that APOE genotype is also associated with differences in normal brain function early in life before brain amyloid accumulates. Animal studies have demonstrated that while APOE4 TR mice lack classical AD pathological changes, they have impairments in behaviors dependent on the hippocampus, and show gross changes to neuronal morphology and brain biochemistry. Human studies have shown that the brain develops differently in APOE-ε4 carriers from birth, such that brain activation may be increased in select brain areas in young APOE-ε4 carriers. As APOE-ε4 carriers reach ages of amyloid accumulation, decreases in glucose utilization, brain activity and gray matter occur. These brain differences associated with APOE genotype may arise from effects on apoE levels, apoE lipidation, brain inflammation, or hippocampal hyperexcitability prior to the development of AD pathological changes. Whether these early effects of APOE are related to the later development of AD is unknown, but, importantly, several of them have been shown to be altered by diet or drugs. Studies of APOE-ε4 positive individuals early in life could lead to the identification of new biomarkers of AD risk not associated with AD pathological changes, and these biomarkers would allow very early preventative therapies to be tested in APOE-ε4 positive individuals.



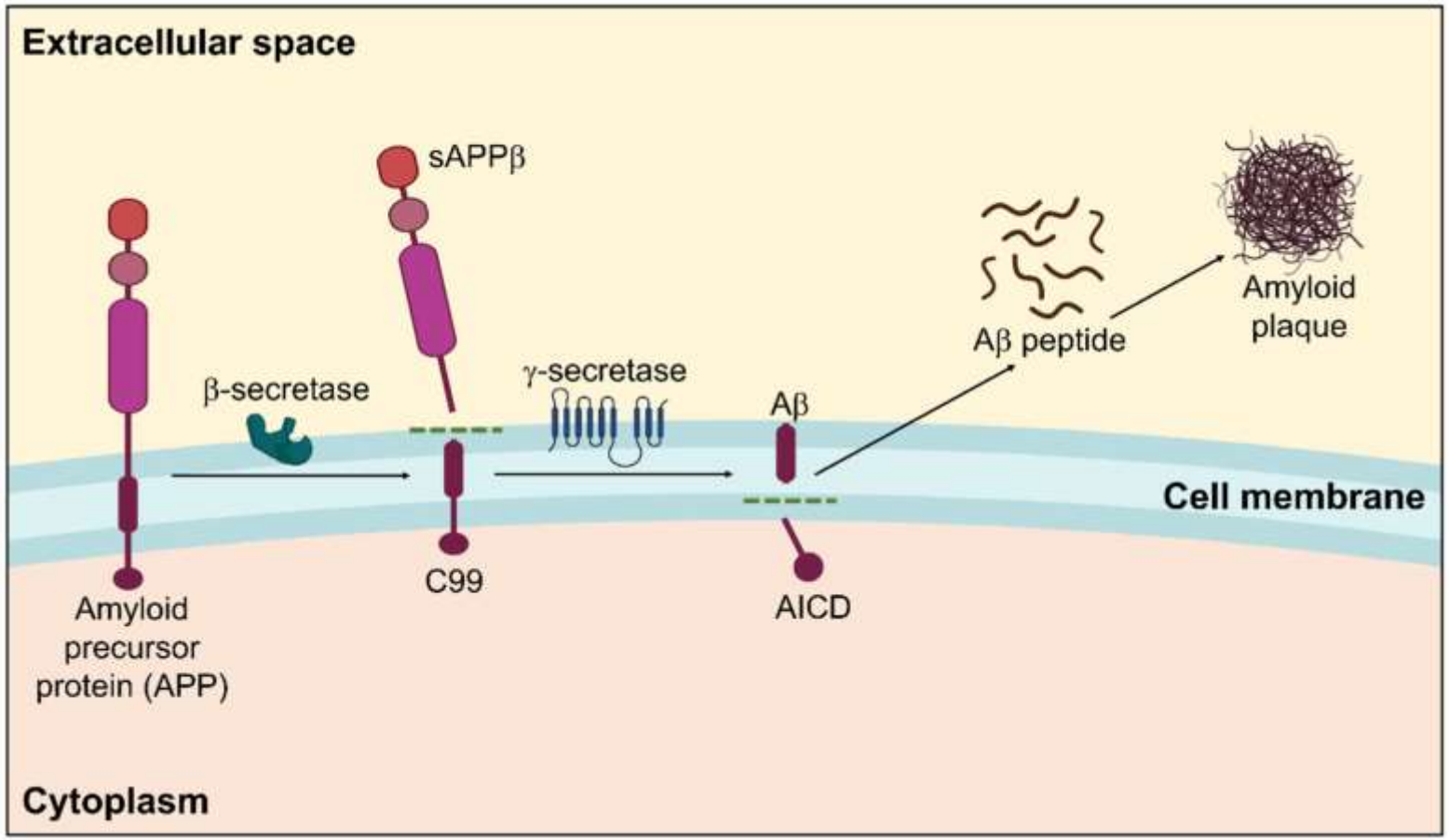
BEHAVIORAL AND NEUROCOGNITIVE DEFICITS IN APOE e4

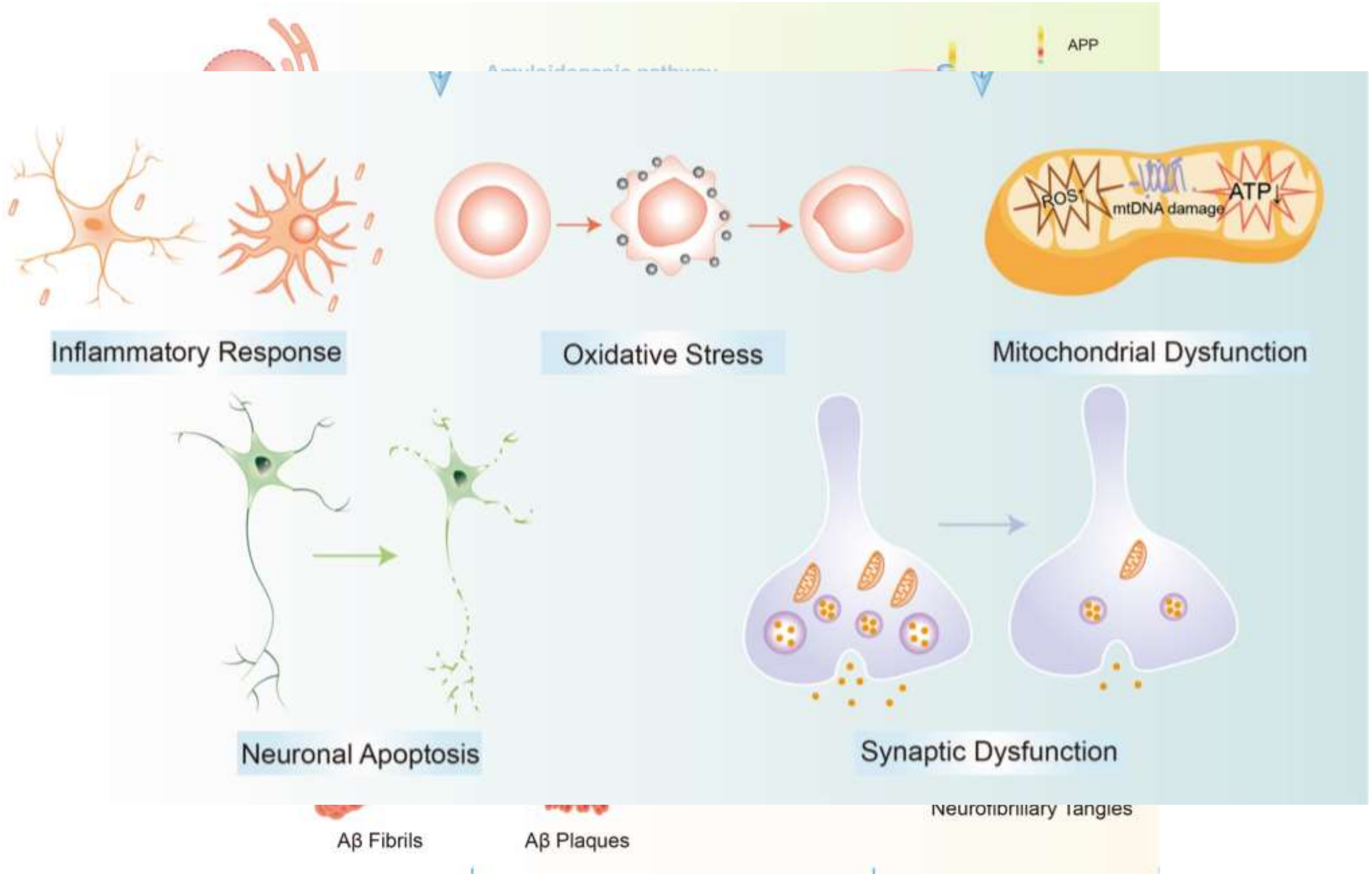
Go to:

In comparison with APOE e4 heterozygotes or noncarriers, cognitively intact e4 homozygous carriers have profoundly more deficits in episodic recall tasks (Nilsson et al. 2006), higher rates of cognitive domain decline before the diagnosis of MCI or AD (Caselli et al. 2004, 2007), and show age-related memory decline earlier in life (Caselli et al. 1999).



Amyloid-β plaques

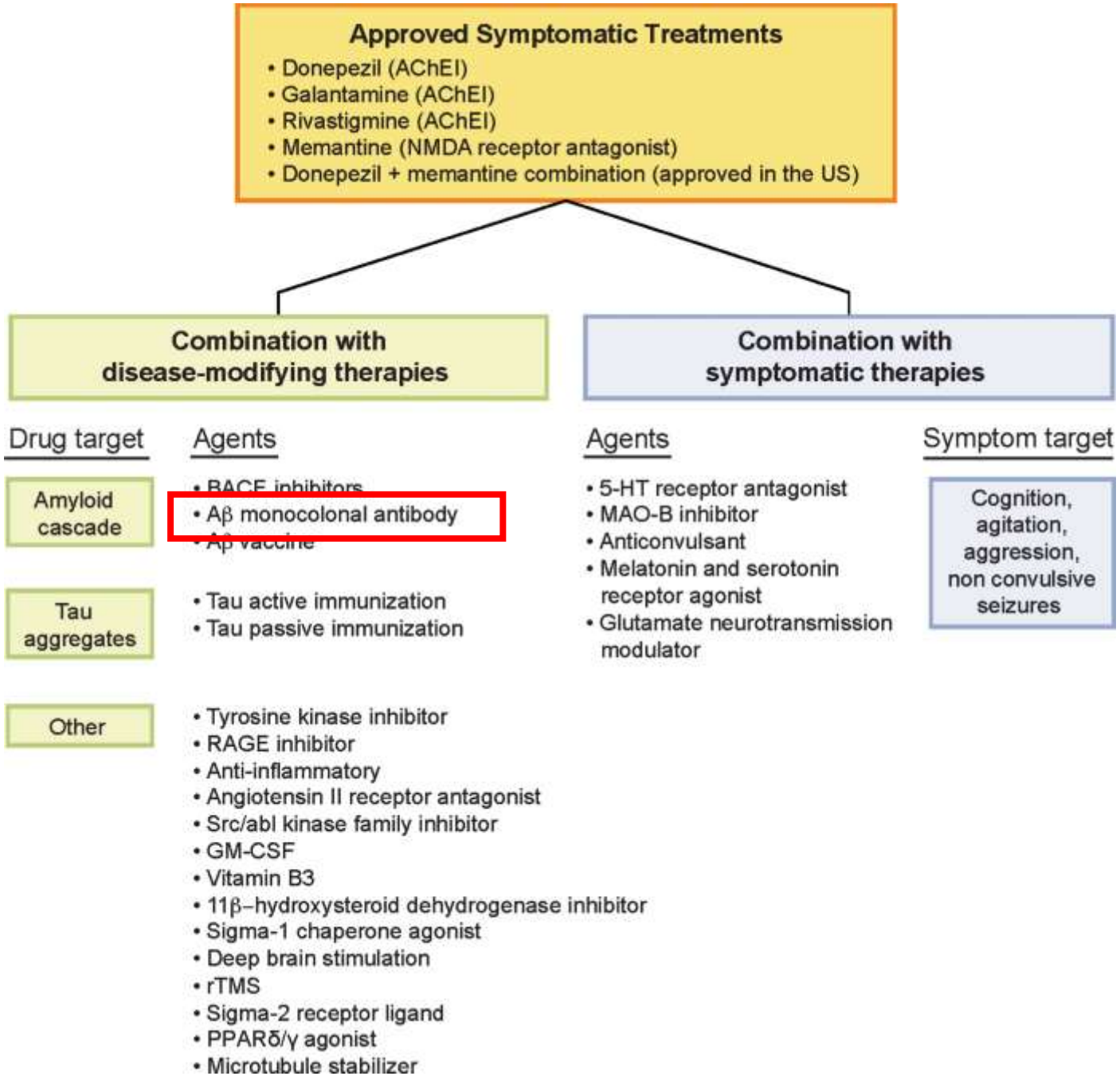




https://www.nature.com/articles/s41392-023-01484-7

Treatment of Alzheimer's Disease

Agent	Tacrine (Cognex®)	Donepezil (Aricept®)	Rivastigmine (Exelon®)	Galantamine (Razadyne® Razadyne ER®)	Memantine (Namenda™)
Manufacturer/ Distributor	West-Ward Horizon	Eisai Pfizer	Novartis	Janssen Shire	Merz Forest
Mechanism(s)	AChEI, BuChEI	AChEI	AChEI, BuChEI	AChEI, NRM	NMDA antagonist
Dose Forms (mg)	10, 20, 30, 40	5, 10	1.5, 3, 4.5, 6	4, 8, 12[d] 4mg/ml[d] 8, 16, 24[e]	5, 10
Dose Frequency	4x /day	1x /day	2x /day	2x /day[d] 1x /day[e]	2x /day
Serum $T_{1/2}$ (hrs.)	1.3 – 2	70	2 – 8 [a]	6 – 8	60 – 80
Dose Range	40 – 160 mg/d	5 – 10 mg/d	3 – 12 mg/d	8 – 24 mg/d	5 – 20 mg/d
Target Dose	80 – 160 mg/d	5 – 10 mg/d	6 – 12 mg/d	16 – 24 mg/d	10 – 20 mg/d
Dose Titration	6 wks.	4 – 6 wks.	2 – 4 wks.	4 wks.	1 wk.
Metabolism [b]	CYP1A2	CYP2D6, 3A4	Non-hepatic	CYP2D6,3A4	Non-hepatic
Protein-binding	75%	96%	40%	18-19%	45%
Taken with food?	Yes	Not necessary	Yes	Yes	Not necessary
Hepatotoxicity?	Yes [c]	No	No	No	No


Approved Symptomatic Treatments
• Donepezil (AChEI)
• Galantamine (AChEI)
• Rivastigmine (AChEI)
• Memantine (NMDA receptor antagonist)
• Donepezil + memantine combination (approved in the US)
Combination with disease-modifying therapies
Combination with symptomatic therapies
Drug target
Agents
Agents
Symptom target
Amyloid cascade
• BACE inhibitors
• Aβ monocolonal antibody
• Aβ vaccine
Tau aggregates
• Tau active immunization
• Tau passive immunization
Other
• Tyrosine kinase inhibitor
• RAGE inhibitor
• Anti-inflammatory
• Angiotensin II receptor antagonist
• Src/abl kinase family inhibitor
• GM-CSF
• Vitamin B3
• 11β–hydroxysteroid dehydrogenase inhibitor
• Sigma-1 chaperone agonist
• Deep brain stimulation
• rTMS
• Sigma-2 receptor ligand
• PPARδ/γ agonist
• Microtubule stabilizer
• 5-HT receptor antagonist
• MAO-B inhibitor
• Anticonvulsant
• Melatonin and serotonin receptor agonist
• Glutamate neurotransmission modulator
Cognition, agitation, aggression, non convulsive seizures

Aducanumab

Brand Name	Aduhlem 100mg/ml
Mechanism	IgG1 monoclonal antibody that selectively binding amyloid aggregates
Indications	Alzheimer's Disease
Dosage	10mg/kg infused intravenously over approximately 1 hour , Q4W
Dosage Adjustment	ARIA-E/H : Mild (Severity on MRI): Dosing may be continued Moderate or Severe (Severity on MRI): Dosing should be suspended
Adverse Event	Amyloid-related imaging abnormalities-edema (ARIA-E) (35%) Headache (21%) ARIA-H microhemorrhage (19%) ARIA-H superficial siderosis (15%) Falls (15%)

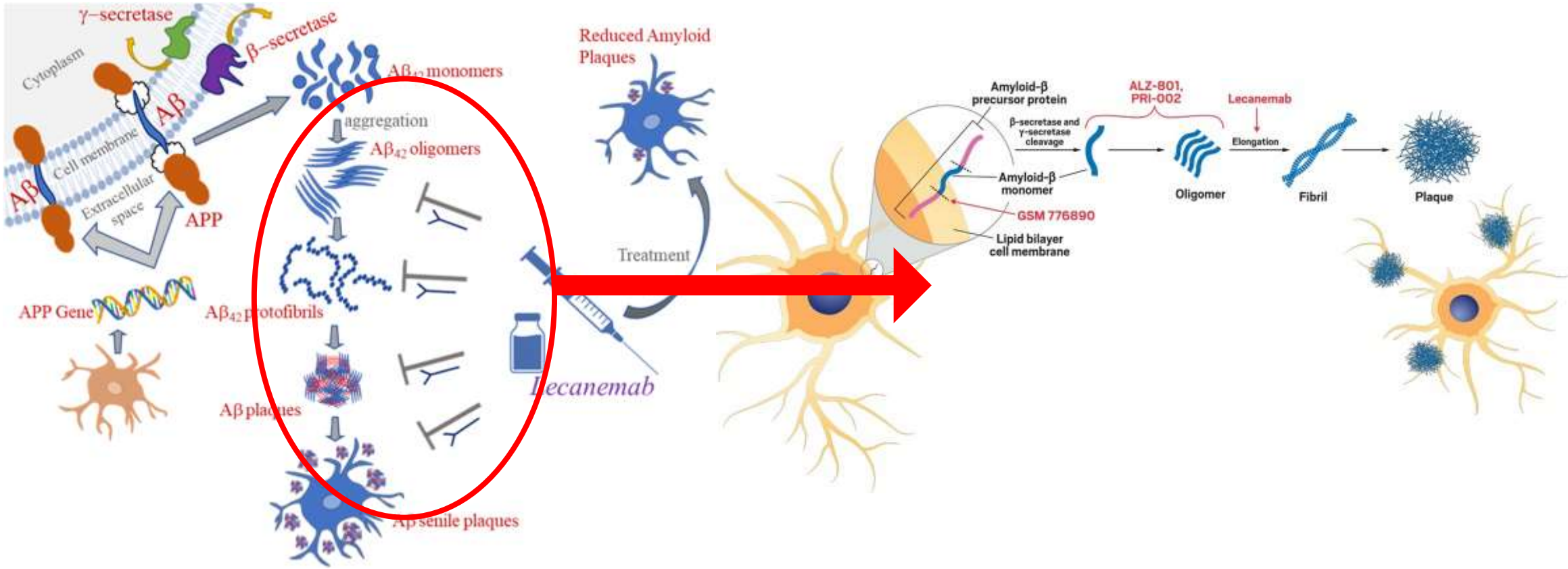
https://reference.medscape.com/drug/aduhelm-aducanumab-4000138#4

Lecanemab

Brand Name	Leqembi 200mg/2mL
Mechanism	IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils
Indications	Early Alzheimer's Disease
Dosage	10mg/kg infused intravenously over approximately 1 hour , Q2W
Dosage Adjustment	ARIA-E/H : Mild (Severity on MRI): Dosing may be continued Moderate or Severe (Severity on MRI): Dosing should be suspended
Adverse Event	Infusion-related reactions (20-26%) ARIA-H (14%) Headache (11-14%) AREA-E (10-13%) Cough (9%) Diarrhea (8%) Superficial siderosis of CNS (6%) Rash (6%)

https://www.drugs.com/dosage/lecanemab.html

Mechanism


γ–secretase
β–secretase
Cytoplasm
Aβ
Cell membrane
Extracellular space
APP
APP Gene
Aβ monomers
aggregation
Aβ oligomers
Aβ protofibrils
Aβ plaques
Aβ senile plaques
Reduced Amyloid Plaques
Treatment
Lecanemab
Amyloid-β precursor protein
β-secretase and γ-secretase cleavage
Amyloid-β monomer
GSM 776890
Lipid bilayer cell membrane
ALZ-801, PRI-002
Oligomer
Lecanemab
Elongation
Fibril
Plaque

Lecanemab

Brand Name	Leqembi 200mg/2mL
Mechanism	IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils
Indications	Early Alzheimer's Disease
Dosage	10mg/kg infused intravenously over approximately 1 hour , Q2W
Dosage Adjustment	ARIA-E/H : Mild (Severity on MRI): Dosing may be continued Moderate or Severe (Severity on MRI): Dosing should be suspended
Adverse Event	Infusion-related reactions (20-26%) ARIA-H (14%) Headache (11-14%) AREA-E (10-13%) Cough (9%) Diarrhea (8%) Superficial siderosis of CNS (6%) Rash (6%)

https://www.drugs.com/dosage/lecanemab.html

Donanemab

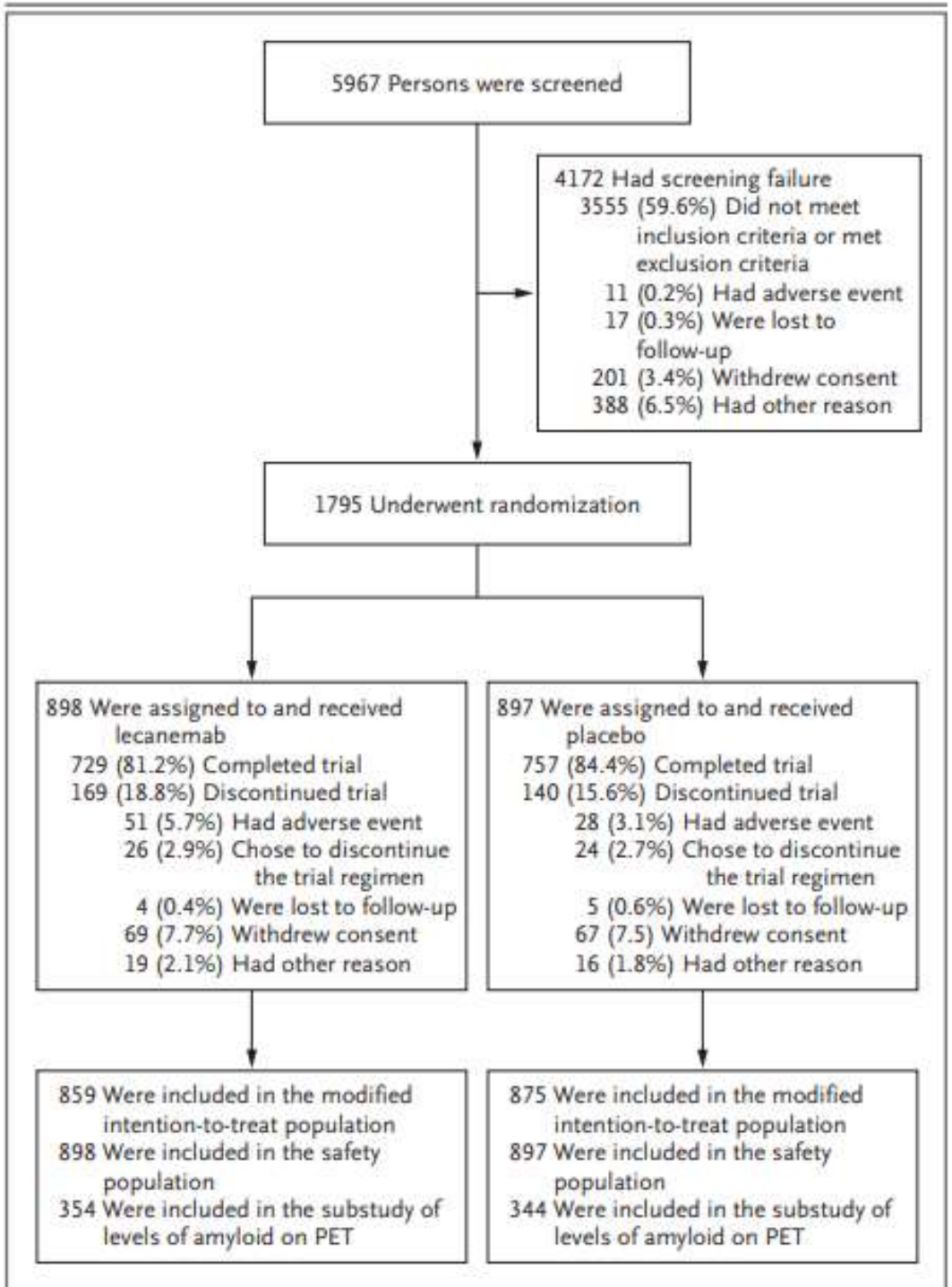
Brand Name	X
Mechanism	humanized IgG1 monoclonal antibody targeted against an epitope at the N-terminal of a specific type of amyloid beta (Aβ)
Indications	Early Alzheimer’s Disease
Dosage	700 mg for the first 3 doses Q4W, then 1400 mg for up to 72 weeks
Adverse Event	Infusion-related reactions (20-26%) ARIA-H (26.1%) Headache (11-14%) AREA-E (21.7%)

https://www.drugs.com/dosage/lecanemab.html

02 **Methods**

Clarity AD

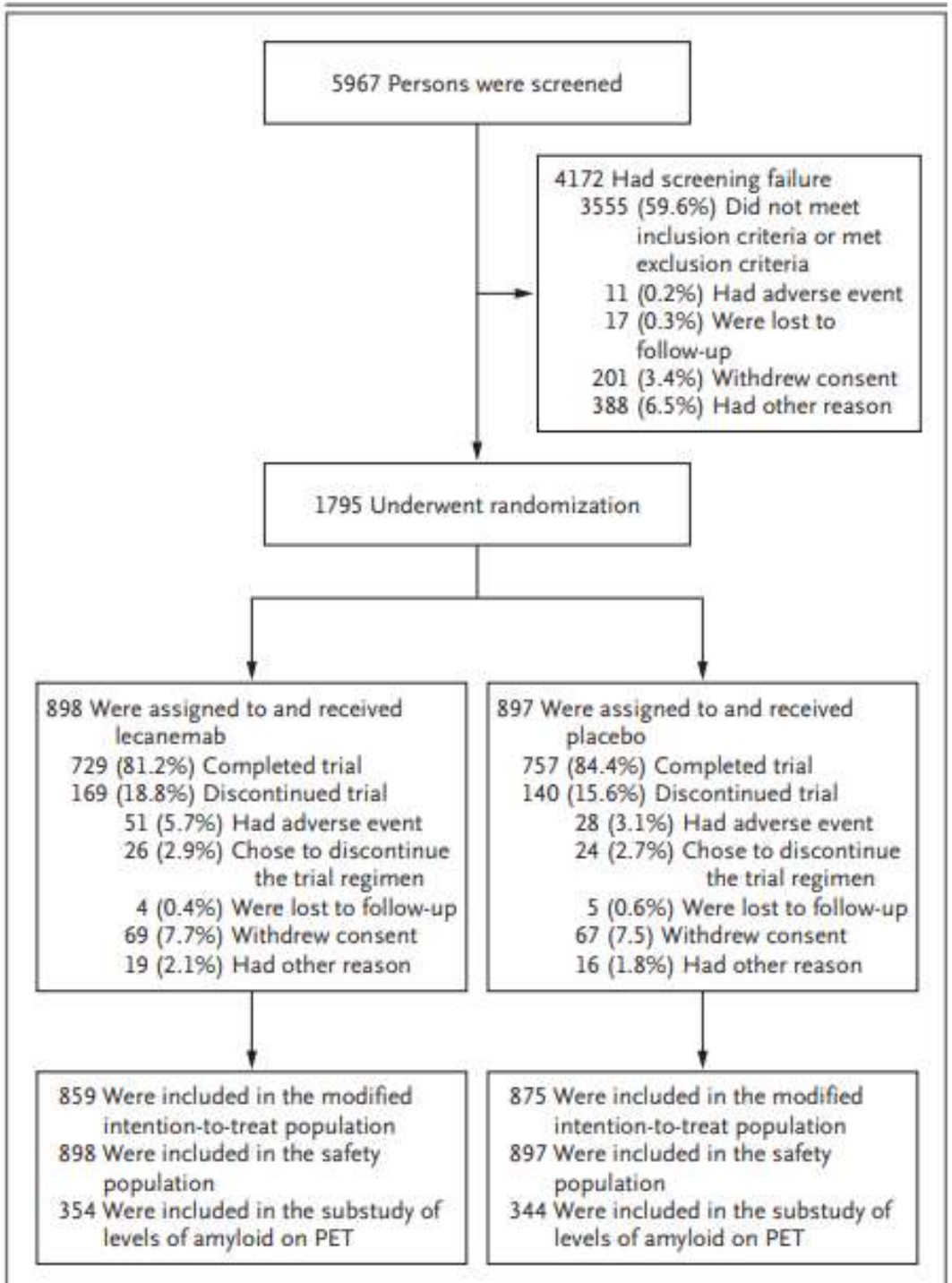
International, **double-blind**, Placebo-controlled, **phase 3** trial



Inclusion Criteria:

- ✓ 50 to 90 years of age
- ✓ with either mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease– related dementia on the basis of National Institute on Aging–Alzheimer's Association criteria.
- ✓ Amyloid positivity was determined by PET or CSF measurement of Aβ
- ✓ at least 1 standard deviation below the age-adjusted mean in the Wechsler Memory Scale IV–Logical Memory II.

Clarity AD



Exclusion Criteria:

- ✕ **Females who are breastfeeding or pregnant at Screening**
- ✕ **History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of Screening.**
- ✕ **Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that couldinterfere with study procedures in the subject.**
- ✕ **Evidence of other clinically significant lesions on brain MRI at Screening that could indicate a dementia diagnosis other than AD.**

Primary Endpoint:

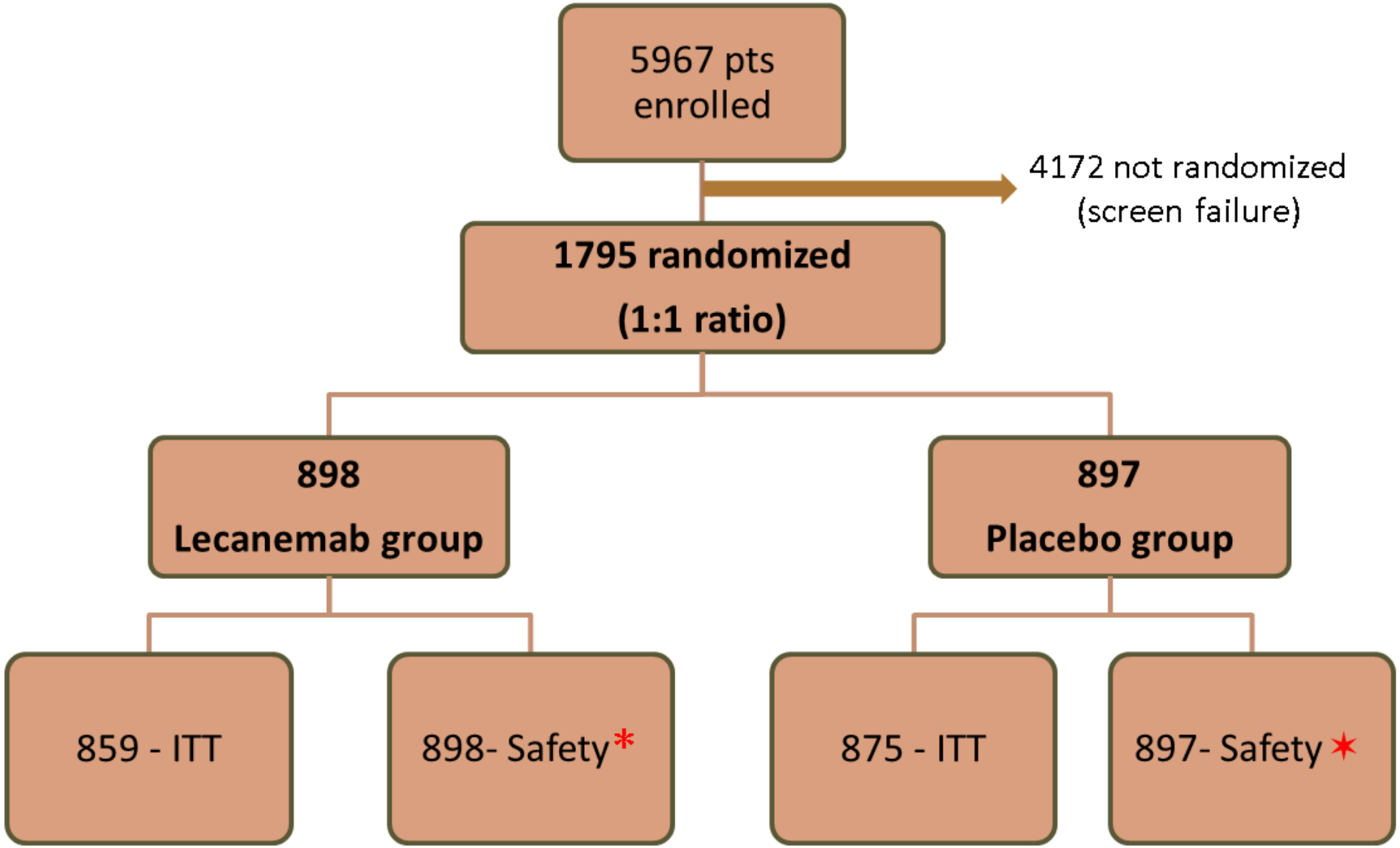
- the change in the score on the Clinical Dementia Rating (CDR)–Sum of Boxes (CDR-SB)18 from baseline at 18 months.

Secondary end points

The change from baseline at 18 months in the following:

1. amyloid burden on PET as measured in centiloids
2. the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale(ADAS-cog14)
3. the Alzheimer's Disease Composite Score
4. the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL)

03 Result


5967 pts enrolled
4172 not randomized (screen failure)
1795 randomized (1:1 ratio)
898 Lecanemab group
897 Placebo group
859 - ITT
898- Safety*
875 - ITT
897- Safety*

Baseline characteristics

Table 1. Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Lecanemab (N=859)	Placebo (N=875)
Age — yr	71.4±7.9	71.0±7.8
Sex — no. (%)		
Female	443 (51.6)	464 (53.0)
Male	416 (48.4)	411 (47.0)
Race — no. (%)†		
White	655 (76.3)	677 (77.4)
Black	20 (2.3)	24 (2.7)
Asian	147 (17.1)	148 (16.9)
Other or missing	37 (4.3)	26 (3.0)
Hispanic ethnic group — no. (%)†	107 (12.5)	108 (12.3)
Time since diagnosis — yr	1.41±1.51	1.34±1.54
Time since onset of symptoms — yr	4.13±2.35	4.15±2.53
Global CDR score — no. (%)‡		
0.5	694 (80.8)	706 (80.7)
1	165 (19.2)	169 (19.3)
Clinical subgroup — no. (%)		
Mild dementia due to Alzheimer's disease	331 (38.5)	331 (37.8)
Mild cognitive impairment due to Alzheimer's disease	528 (61.5)	544 (62.2)
ApoE ε4 status — no. (%)		
Noncarrier	267 (31.1)	275 (31.4)
Carrier	592 (68.9)	600 (68.6)
Heterozygotes	456 (53.1)	468 (53.5)
Homozygotes	136 (15.8)	132 (15.1)
Current use of medication for symptoms of Alzheimer's disease — no. (%)	447 (52.0)	468 (53.5)

Table 1. (Continued.)

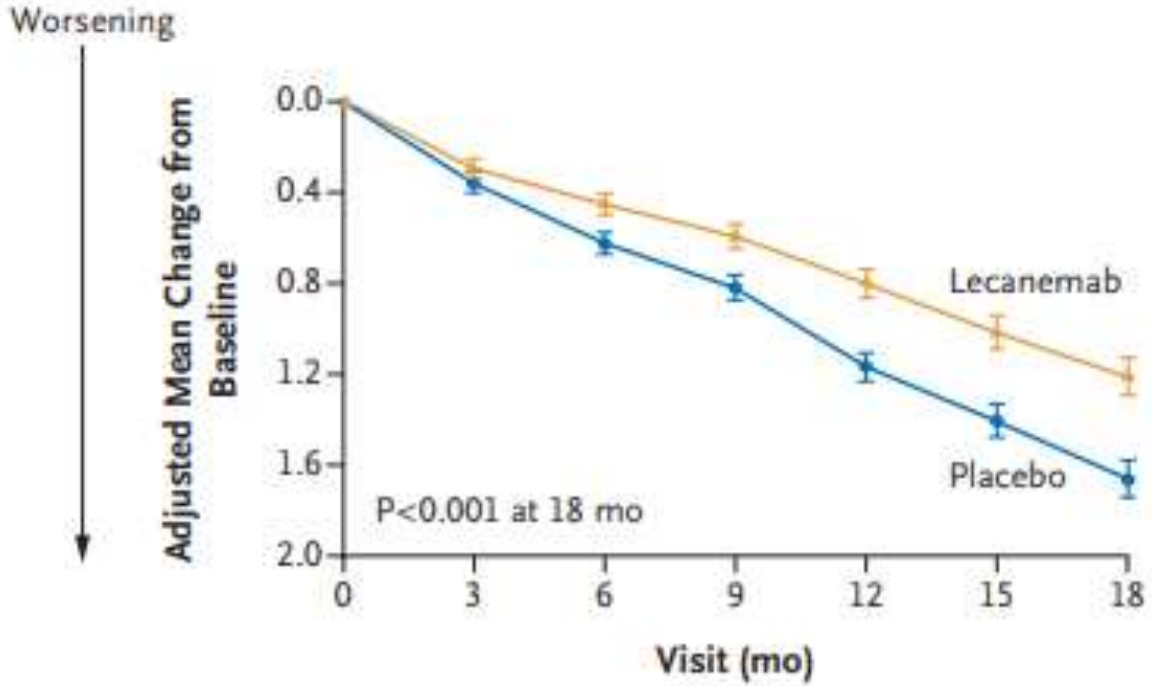
Characteristic	Lecanemab (N=859)	Placebo (N=875)
ADCS-MCI-ADL score††		
Mean	41.2±6.6	40.9±6.9
Range	13 to 53	12 to 53
MMSE score‡‡		
Mean	25.5±2.2	25.6±2.2
Range	22 to 30	22 to 30
CDR-SB score§		
Mean	3.17±1.34	3.22±1.34
Range	0.5 to 8.0	0.5 to 8.5
Amyloid burden on PET — centiloids¶		
Mean	77.92±44.84	75.03±41.82
Range	−16.6 to 213.2	−17.0 to 179.6
ADAS-cog14 score‖		
Mean	24.45±7.08	24.37±7.56
Range	4.7 to 47.7	5.0 to 60.7
ADCOMS**		
Mean	0.398±0.147	0.400±0.147
Range	0.08 to 0.94	0.07 to 0.91

Primary Endpoint

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	

A CDR-SB Score



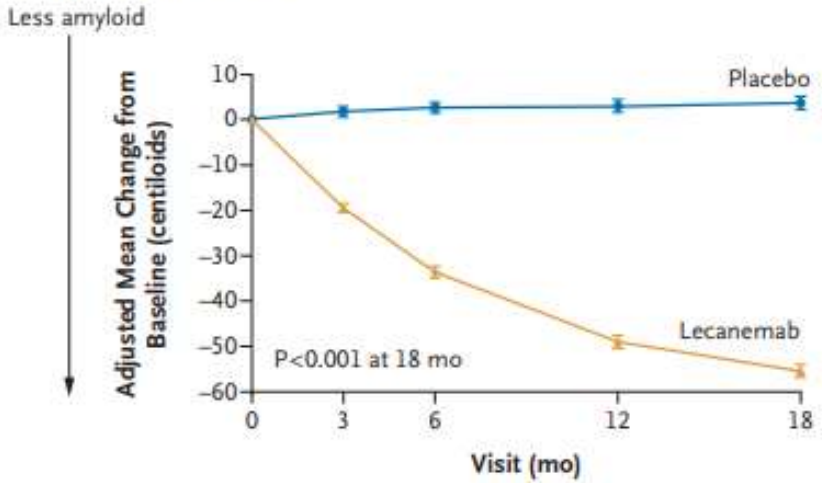
No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

Secondary end points

End Point	Lecanemab (N=859)	Placebo (N=875)
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	

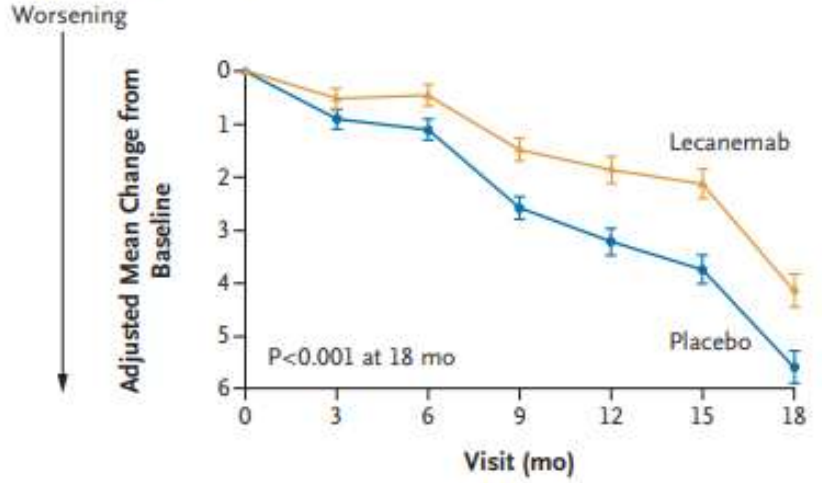
B Amyloid Burden on PET



No. of Participants

Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

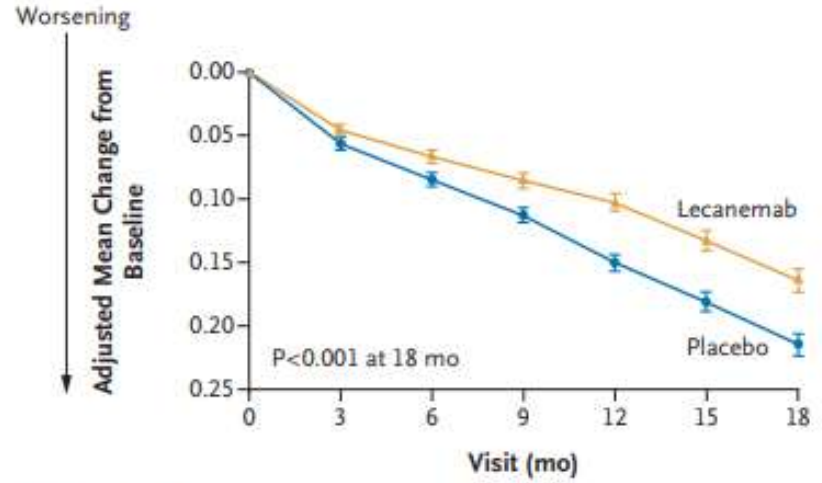
C ADAS-Cog14 Score



No. of Participants

Lecanemab	854	819	793	771	753	730	703
Placebo	872	844	823	807	770	762	738

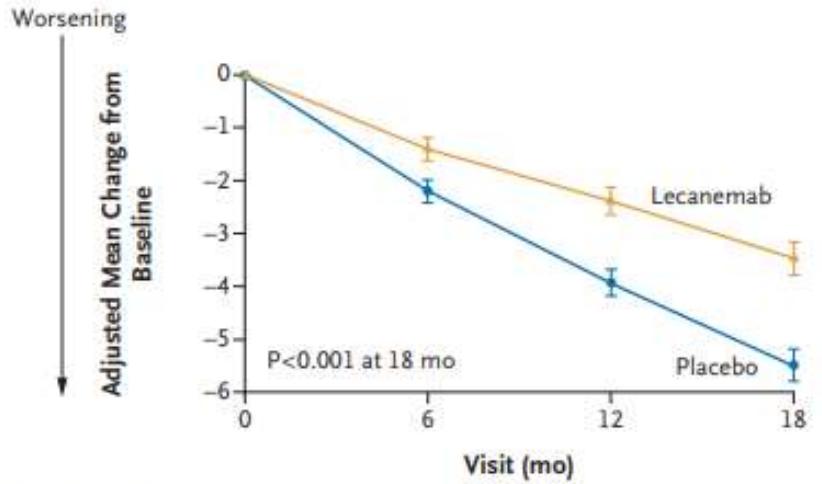
D ADCOMS



No. of Participants

Lecanemab	857	820	796	774	757	733	708
Placebo	875	847	822	808	775	764	749

E ADCS-MCI-ADL Score



No. of Participants

Lecanemab	783	756	716	676
Placebo	796	783	739	707

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)

Summary

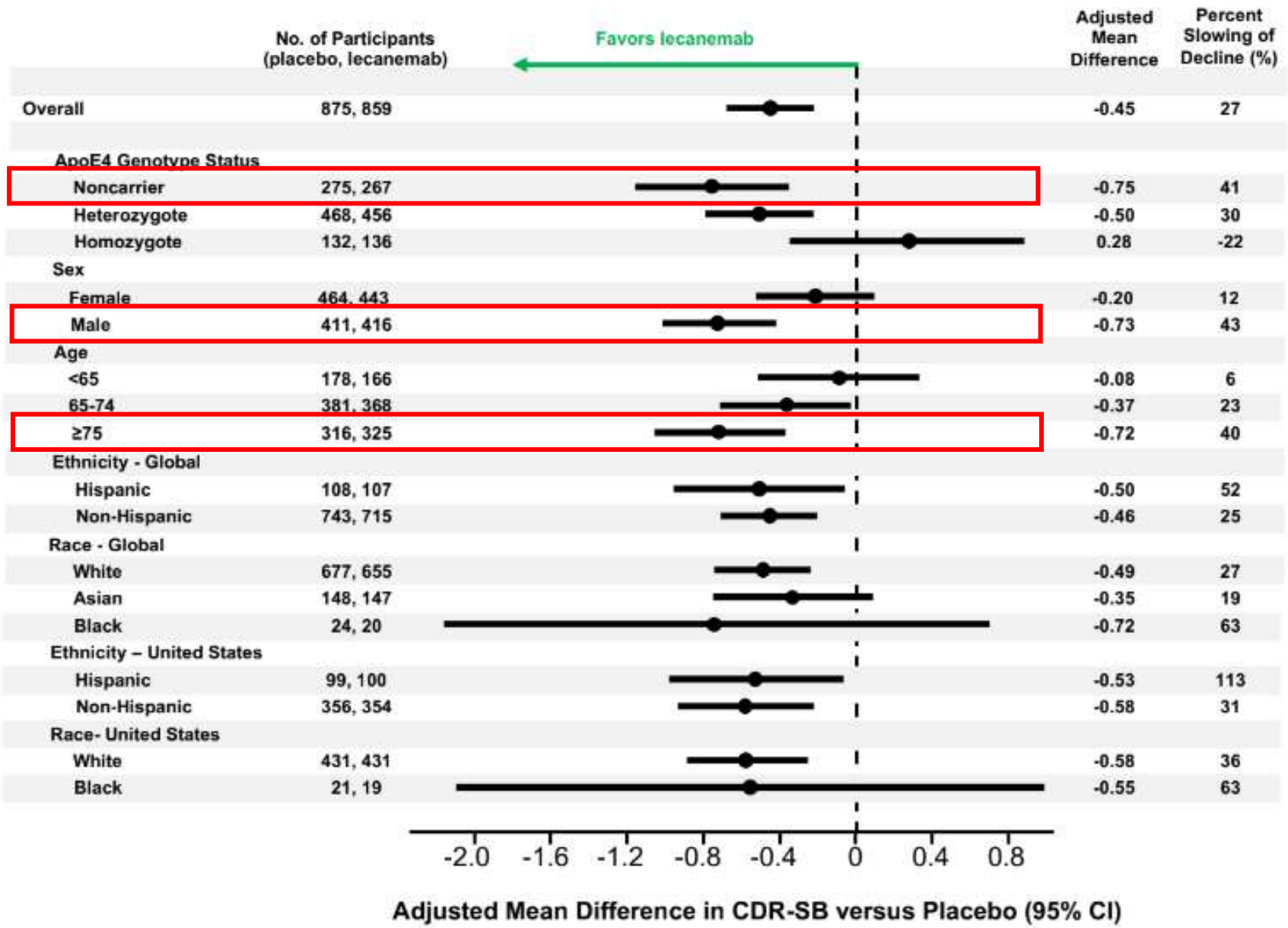
- Efficacy

At 18 months, mean CDR-SB scores had worsened in both groups. The mean change in CDR-SB score was smaller (indicating less cognitive and functional decline) in the lecanemab group. Results for secondary clinical end points were in the same direction as those for the primary end point.

- Safety

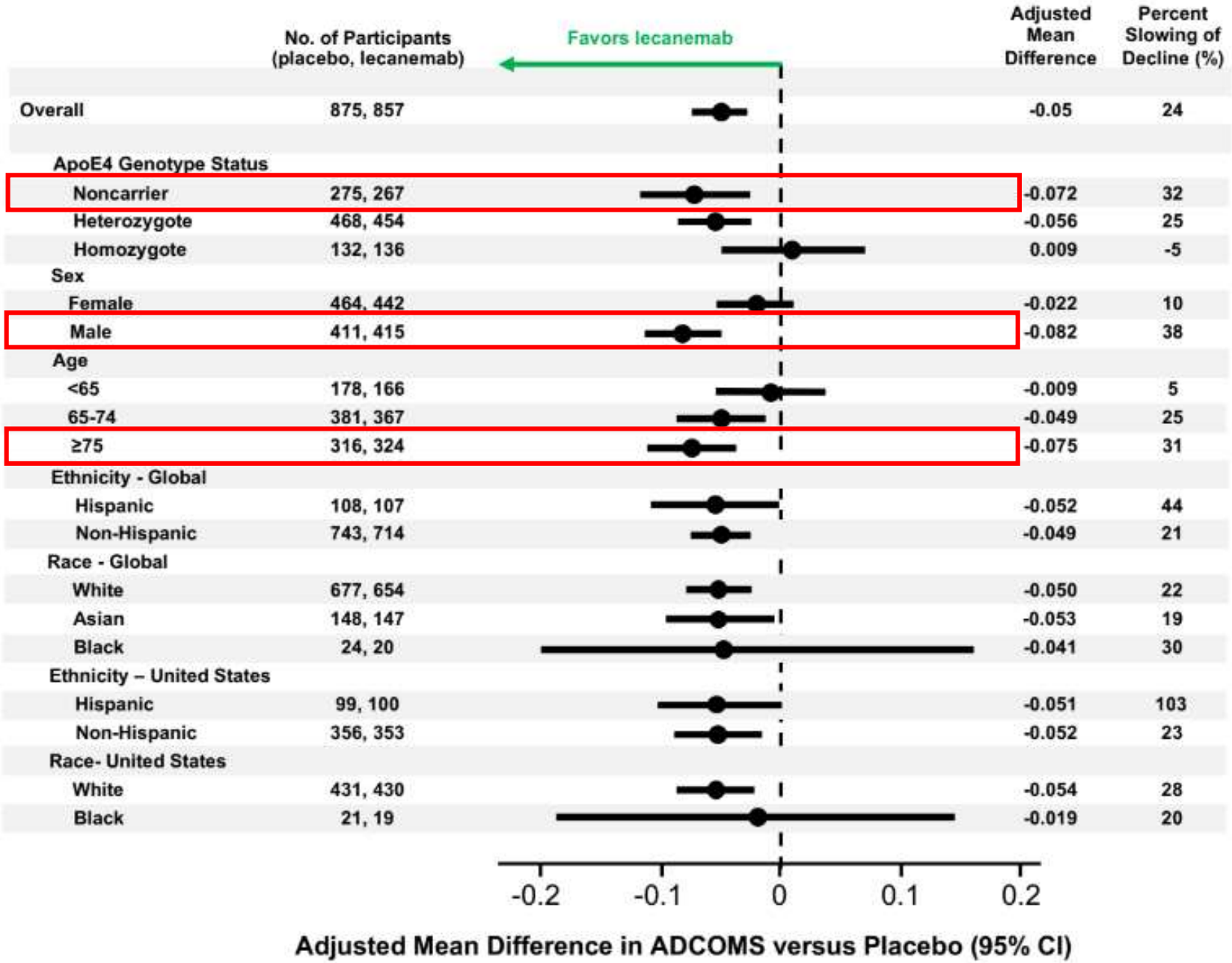
Overall incidences of adverse events were similar in the two groups. The most common adverse events in the lecanemab group included infusion-related reactions and amyloid-related imaging abnormalities with edema or effusions.

04 Discussion



CDR-SB in subgroup analysis
(Relative superior)

1. ApoE4 Noncarrier
2. Male
3. Age>75



ADCOMS in subgroup analysis
(Relative superior)

1. ApoE4 Noncarrier
2. Male
3. Age>75

Limitation

- Longer-term follow-up is needed; an open-label extension study is ongoing.
- The trial was conducted during the Covid-19 pandemic and, as a result, faced challenges including missing data, missed doses, delayed assessments, and intercurrent illnesses.
- Occurrences of amyloid-related imaging abnormalities may have led to unblinding of participants and investigators.

	Aducanumab	**Lecanemab**	Donanemab
Reduce the change of CDR-SB score (%)	23%	27%	36%
frequency	Q4W	Q2W	Q4W
Adverse event (ARIA)	35%	14%	36.8%
Cost (USD/year)	28200	26500	39000

Conclusion

- Efficacy

In this phase 3 trial, the change from baseline at 18 months in the CDR-SB score (primary end point) was less with lecanemab than with placebo, favoring lecanemab. Results for secondary clinical end points were in the same direction as those for the primary end point.

- Safety

1. Infusion-related reaction : Higher in Lecanemab group , most grade 1 or 2.

2.ARIA : Higher in Lecanemab group , mostly mild to moderate (91%).

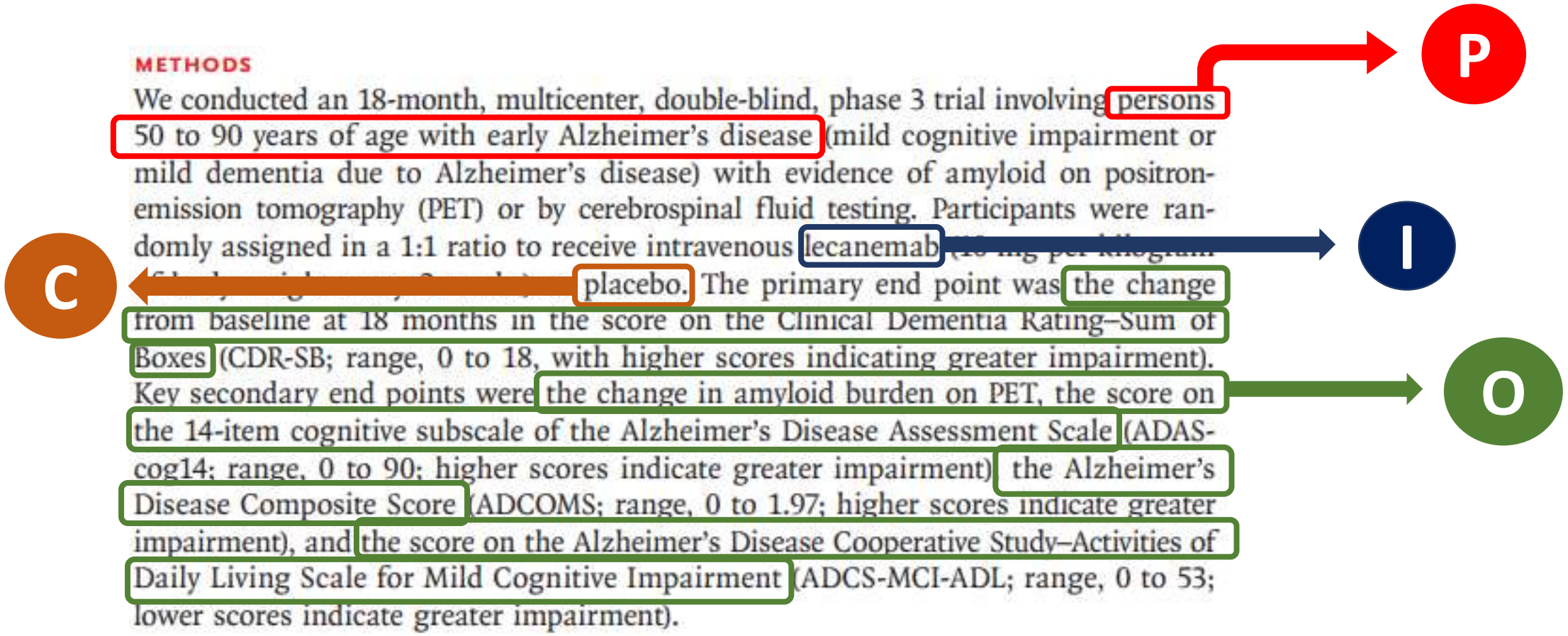
3. Other AEs: Lecanemab group was similar with placebo group.

Conclusion

1. The efficacy of Lecanemab in delaying early dementia is about 27%, which is great progress in improving dementia.
2. Lecanemab only treats patients with mild Alzheimer's disease and has not been usea in patients with moderate to severe Alzheimer's disease.
3. Amyloid-beta peptides accumulation occurs before patients develop dementia. How to identify potential patients and administer medication early is a problem.
4. Two cases died in the Lecanemab clinical trial. They were treated with anticoagulants due to stroke and heart disease. Lecanemab may led to bleeding due toremoved amyloid peptides that usually accumulate in blood vessels.

05 Appraisal

Section A:
1. Did the study address a clearly focused research question?



METHODS

We conducted an 18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years of age with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) with evidence of amyloid on positron-emission tomography (PET) or by cerebrospinal fluid testing. Participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab placebo. The primary end point was the change from baseline at 18 months in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment). Key secondary end points were the change in amyloid burden on PET, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90; higher scores indicate greater impairment), the Alzheimer's Disease Composite Score (ADCOMS; range, 0 to 1.97; higher scores indicate greater impairment), and the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL; range, 0 to 53; lower scores indicate greater impairment).

Yes Can't tell No

Section A:
2. Was the assignment of participants to interventions randomised?

METHODS

We conducted an 18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years of age with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) with evidence of amyloid on positron-emission tomography (PET) or by cerebrospinal fluid testing. Participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. The primary end point was the change from baseline at 18 months in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment). Key secondary end points were the change in amyloid burden on PET, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90; higher scores indicate greater impairment), the Alzheimer's Disease Composite Score (ADCOMS; range, 0 to 1.97; higher scores indicate greater impairment), and the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL; range, 0 to 53; lower scores indicate greater impairment).

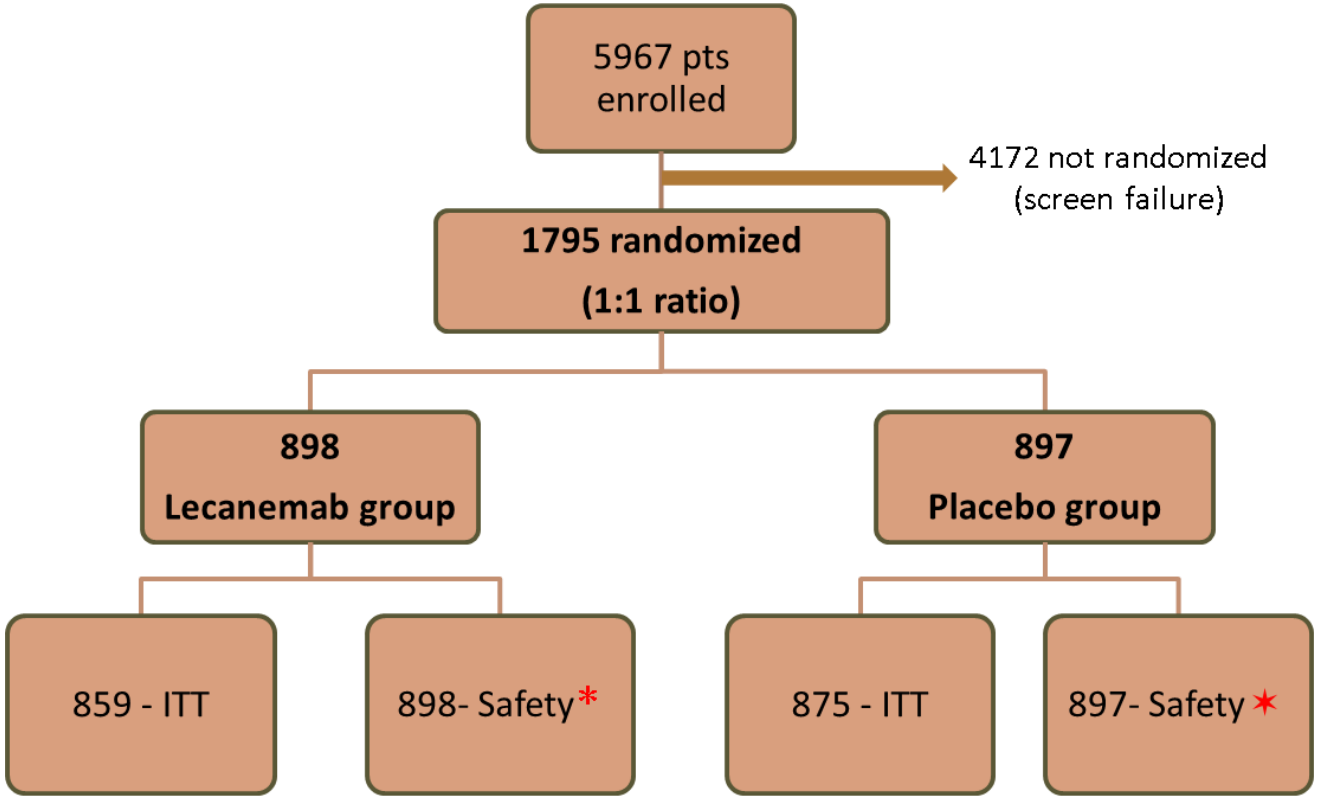

Yes


Can't tell


No

Section A:

3. Were all participants who entered the study accounted for at its conclusion?



Yes Can't tell No

Section B:

4. (a) Were the participants ‘blind’ to intervention they were given?

4. (b) Were the investigators ‘blind’ to the intervention they were giving to participants?

METHODS

We conducted an 18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years of age with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) with evidence of amyloid on positron-emission tomography (PET) or by cerebrospinal fluid testing. Participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. The primary end point was the change from baseline at 18 months in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment). Key secondary end points were the change in amyloid burden on PET, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90; higher scores indicate greater impairment), the Alzheimer's Disease Composite Score (ADCOMS; range, 0 to 1.97; higher scores indicate greater impairment), and the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL; range, 0 to 53; lower scores indicate greater impairment).

METHODS

TRIAL DESIGN AND OVERSIGHT

Clarity AD was an 18-month, multicenter, double-blind, placebo-controlled, parallel-group trial involving persons with early Alzheimer's disease. Eligible participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab (10 mg per kilogram every 2 weeks) or placebo. The randomization was stratified according to clinical subgroup (mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease–related dementia on the basis of the criteria noted below), the presence or absence of concomitant approved medication for symptoms of Alzheimer's disease at baseline (e.g., acetylcholinesterase inhibitors, memantine, or both), apolipoprotein E (ApoE) ε4 carriers or noncarriers, and geographic region. During the trial, participants underwent serial blood testing for plasma biomarkers and could participate in three optional

Yes

Can’t tell

No

Section B:
4. (c) Were the people assessing/analysing outcomes ‘blinded’?

An independent data and safety monitoring board consisting of experts in Alzheimer's disease and statistics reviewed unblinded safety data during the trial. An independent medical monitoring team, whose members were unaware of the trial-group assignments, reviewed ARIA, infusion-related reactions, and hypersensitivity reactions. Clinical assessment raters were unaware of the safety assessments and the trial-group assignments. All the authors vouch for the completeness and accuracy of the data, the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org), and the full reporting of adverse events.


Yes


Can’t tell


No

Section B:

5. Were the study groups similar at the start of the randomized controlled trial?

Table 1. Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Lecanemab (N=859)	Placebo (N=875)
Age — yr	71.4±7.9	71.0±7.8
Sex — no. (%)		
Female	443 (51.6)	464 (53.0)
Male	416 (48.4)	411 (47.0)
Race — no. (%)†		
White	655 (76.3)	677 (77.4)
Black	20 (2.3)	24 (2.7)
Asian	147 (17.1)	148 (16.9)
Other or missing	37 (4.3)	26 (3.0)
Hispanic ethnic group — no. (%)†	107 (12.5)	108 (12.3)
Time since diagnosis — yr	1.41±1.51	1.34±1.54
Time since onset of symptoms — yr	4.13±2.35	4.15±2.53
Global CDR score — no. (%)‡		
0.5	694 (80.8)	706 (80.7)
1	165 (19.2)	169 (19.3)
Clinical subgroup — no. (%)		
Mild dementia due to Alzheimer's disease	331 (38.5)	331 (37.8)
Mild cognitive impairment due to Alzheimer's disease	528 (61.5)	544 (62.2)
ApoE ε4 status — no. (%)		
Noncarrier	267 (31.1)	275 (31.4)
Carrier	592 (68.9)	600 (68.6)
Heterozygotes	456 (53.1)	468 (53.5)
Homozygotes	136 (15.8)	132 (15.1)
Current use of medication for symptoms of Alzheimer's disease — no. (%)	447 (52.0)	468 (53.5)

Section B:

5. Were the study groups similar at the start of the randomized controlled trial?

Table 1. (Continued.)

Characteristic	Lecanemab (N=859)	Placebo (N=875)
ADCS-MCI-ADL score††		
Mean	41.2±6.6	40.9±6.9
Range	13 to 53	12 to 53
MMSE score‡‡		
Mean	25.5±2.2	25.6±2.2
Range	22 to 30	22 to 30
CDR-SB score§		
Mean	3.17±1.34	3.22±1.34
Range	0.5 to 8.0	0.5 to 8.5
Amyloid burden on PET — centiloids¶		
Mean	77.92±44.84	75.03±41.82
Range	−16.6 to 213.2	−17.0 to 179.6
ADAS-cog14 score‖		
Mean	24.45±7.08	24.37±7.56
Range	4.7 to 47.7	5.0 to 60.7
ADCOMS**		
Mean	0.398±0.147	0.400±0.147
Range	0.08 to 0.94	0.07 to 0.91

Section B:

6. Apart from the experimental intervention, did each study group receive the same level of care(that is, were they treated equally)?

Subjects who enroll at sites able to participate in the longitudinal tau PET substudy (based on the site's geographical location or proximity to the tau PET ligand manufacturing sites), have an amyloid positive study-specific PET scan, and who have consented to participate in the amyloid PET substudy will be offered participation in the tau PET substudy. There must be at least 48 hours between each procedure (CSF collection, amyloid PET scan, and tau PET scan) and randomization, and should be completed in the stated order. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and undergo scanning procedures. For subjects who discontinue early from the study, the medical monitor must be consulted before a tau PET scan is performed. Clinical assessments (MMSE, CDR-SB, and ADAS-cog14) will be conducted every 3 months, and HRQoL assessments (EQ-5D-5L, QOL-AD, ADCS MCI-ADL, and Zarit Burden Interview) will be conducted every 6 months. Safety MRIs will be conducted at 9 and 13 weeks of treatment and every 3 months for the first 6 months of treatment. Safety MRIs will be conducted every 6 months thereafter until completion of the Core study. Volumetric MRI sequences will be taken from all subjects at each of the safety MRI assessments or at the Early Termination/Follow-up safety assessments, while analyses will be conducted for these measures at 6, 12, and 18 months of treatment. In some cases, unscheduled visits may be needed to follow up on regularly scheduled safety or safety MRI findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reasons for the unscheduled visit as determined by the investigator. Amyloid PET will be collected in the amyloid PET substudy at 3, 6, 12, and 18 months of treatment for those subjects who consent. CSF will be collected in the CSF substudy at 12 and 18 months of treatment for those subjects who consent. Physical examinations, safety assessments, blood for standard clinical laboratory assessments, blood for biomarker and anti-drug antibody (ADA) assessments, and blood for PK will be collected throughout the 18 months of treatment. Vital signs will be assessed when study drug is administered both predose and after infusion.

Concomitant Drug/Therapy

Immunoglobulin therapy and therapy with biologic drugs are not permitted for a period of 6 months before the Baseline until the Follow-up visit. Subjects who are on anticoagulants at Screening are required to have their anticoagulation status optimized and stable for at least 4 weeks before Screening.

Subjects who are on approved AD treatments, such as AChEIs or memantine are required to be on a stable dose for 12 weeks prior to Baseline and to keep the dose stable during the study. Subjects who enter the study and are not taking these medications should not initiate these medications while on study unless medically necessary. Subjects who initiate approved AD treatment, such as AChEIs or memantine, during the treatment period or change their dose of AD medication during the treatment period will continue on the study per the protocol and per the Schedule of Assessments.

Subjects who initiate non-AD drugs (with the exception of prohibited drugs) during the treatment period, which are approved in their country for treatment of cognitive impairment, will continue on the study per protocol and per the Schedule of Assessments.

Section C:
7. Were the effects of intervention reported comprehensively?

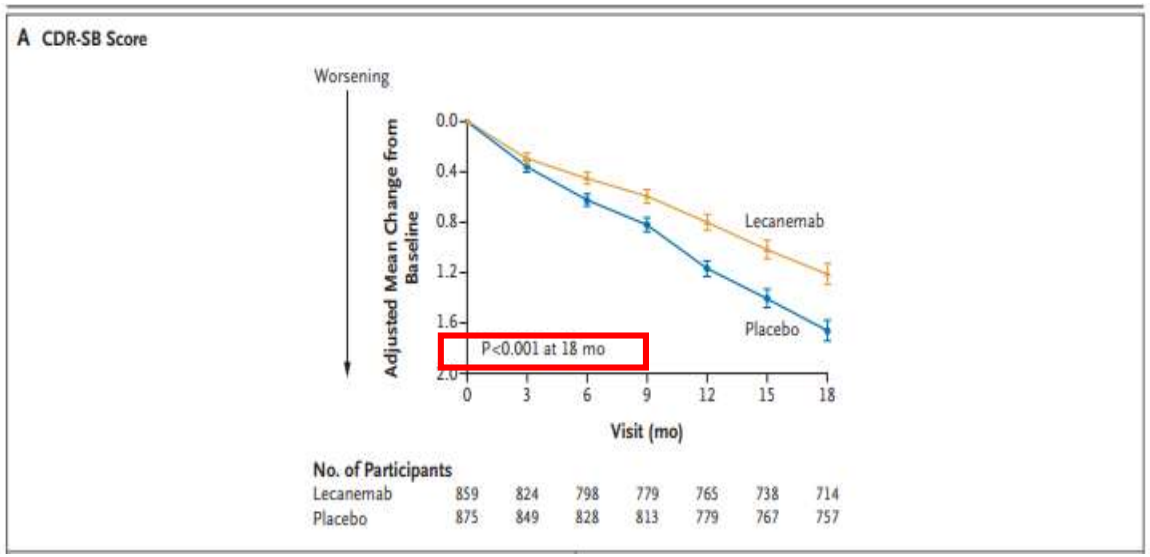
End Point	Lecanemab (N=859)	Placebo (N=875)
Primary efficacy end point		
Change from baseline to 18 mo in the CDR-SB score		
No. of participants evaluated	859	875
Adjusted mean change	1.21	1.66
Adjusted mean difference vs. placebo (95% CI)	−0.45 (−0.67 to −0.23)	
P value vs. placebo	<0.001	
Secondary 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	

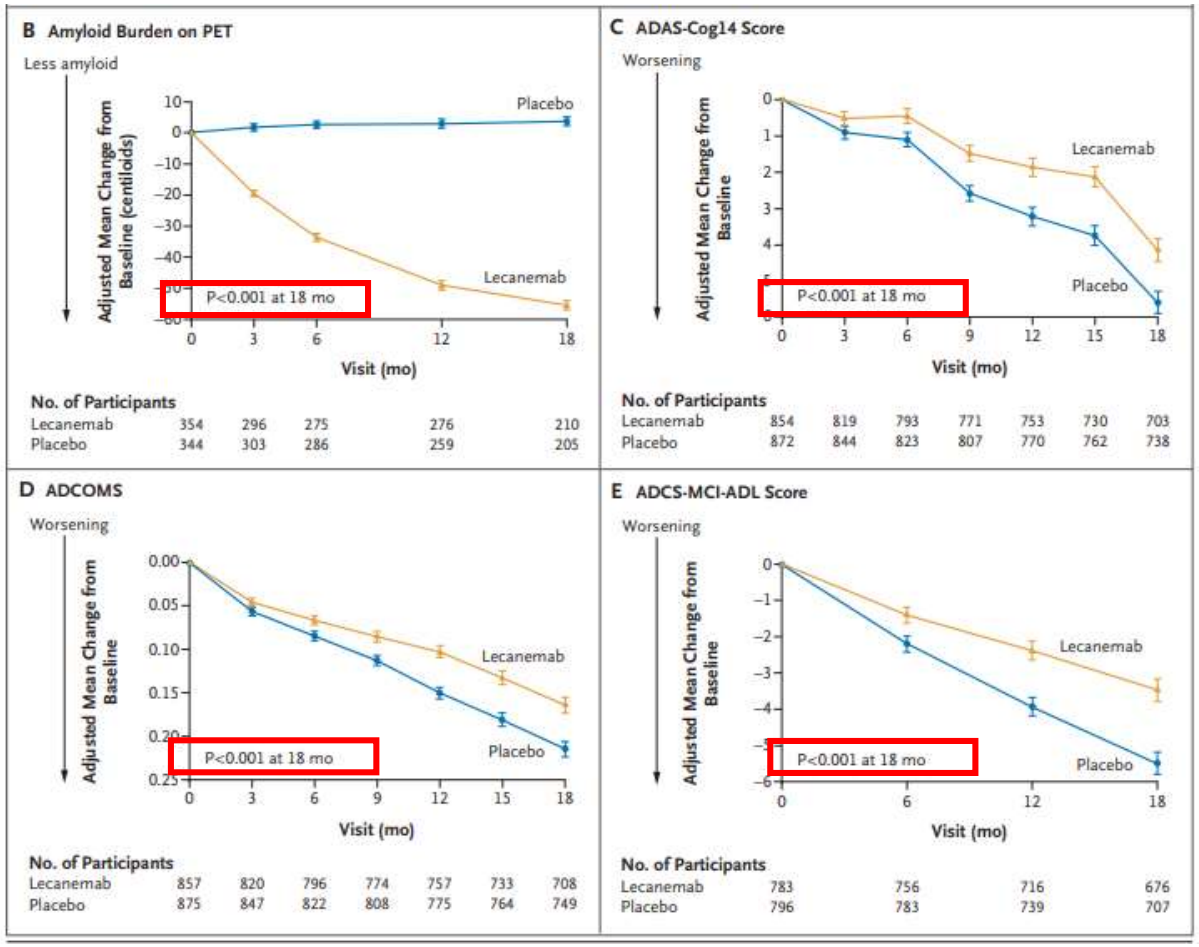

Yes


Can’t tell


No

Section C:
8. Was the precision of the estimate of the intervention or treatment effect reported?





Yes Can't tell No

Section C:

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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	

Yes

Can't tell

No

Section C:
9. Do the benefits of the experimental intervention outweigh the harms and costs?

- **Efficacy**

In this phase 3 trial, the change from baseline at 18 months in the CDR-SB score (primary end point) was less with lecanemab than with placebo, favoring lecanemab. Results for secondary clinical end points were in the same direction as those for the primary end point.

- **Safety**

1. Infusion-related reaction : Higher in Lecanemab group , most grade 1 or 2.

2.ARIA : Higher in Lecanemab group , mostly mild to moderate (91%).

3. Other AEs: Lecanemab group was similar with placebo group.

 **Yes**

 **Can't tell**

 **No**

Section D:
10. Can the results be applied to your local population?

Race — no. (%)†		
White	655 (76.3)	677 (77.4)
Black	20 (2.3)	24 (2.7)
Asian	147 (17.1)	148 (16.9)
Other or missing	37 (4.3)	26 (3.0)


Yes


Can’t tell


No

Section D:
11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?

Agent	Tacrine (Cognex®)	Donepezil (Aricept®)	Rivastigmine (Exelon®)	Galantamine (Razadyne® Razadyne ER®)	Memantine (Namenda™)
Manufacturer/ Distributor	West-Ward Horizon	Eisai Pfizer	Novartis	Janssen Shire	Merz Forest
Mechanism(s)	AChEI, BuChEI	AChEI	AChEI, BuChEI	AChEI, NRM	NMDA antagonist
Dose Forms (mg)	10, 20, 30, 40	5, 10	1.5, 3, 4.5, 6	4, 8, 12[d] 4mg/ml[d] 8, 16, 24[e]	5, 10
Dose Frequency	4x /day	1x /day	2x /day	2x /day[d] 1x /day[e]	2x /day
Serum $T_{1/2}$ (hrs.)	1.3 – 2	70	2 – 8 [a]	6 – 8	60 – 80
Dose Range	40 – 160 mg/d	5 – 10 mg/d	3 – 12 mg/d	8 – 24 mg/d	5 – 20 mg/d
Target Dose	80 – 160 mg/d	5 – 10 mg/d	6 – 12 mg/d	16 – 24 mg/d	10 – 20 mg/d
Dose Titration	6 wks.	4 – 6 wks.	2 – 4 wks.	4 wks.	1 wk.
Metabolism [b]	CYP1A2	CYP2D6, 3A4	Non-hepatic	CYP2D6,3A4	Non-hepatic
Protein-binding	75%	96%	40%	18-19%	45%
Taken with food?	Yes	Not necessary	Yes	Yes	Not necessary
Hepatotoxicity?	Yes [c]	No	No	No	No

Thanks for listening