

# LA NUOVA ERA DELLE TERAPIE ANTI-AMILOIDE: LA COLLABORAZIONE TRA NEUROLOGO E GERIATRA

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# Disclosures

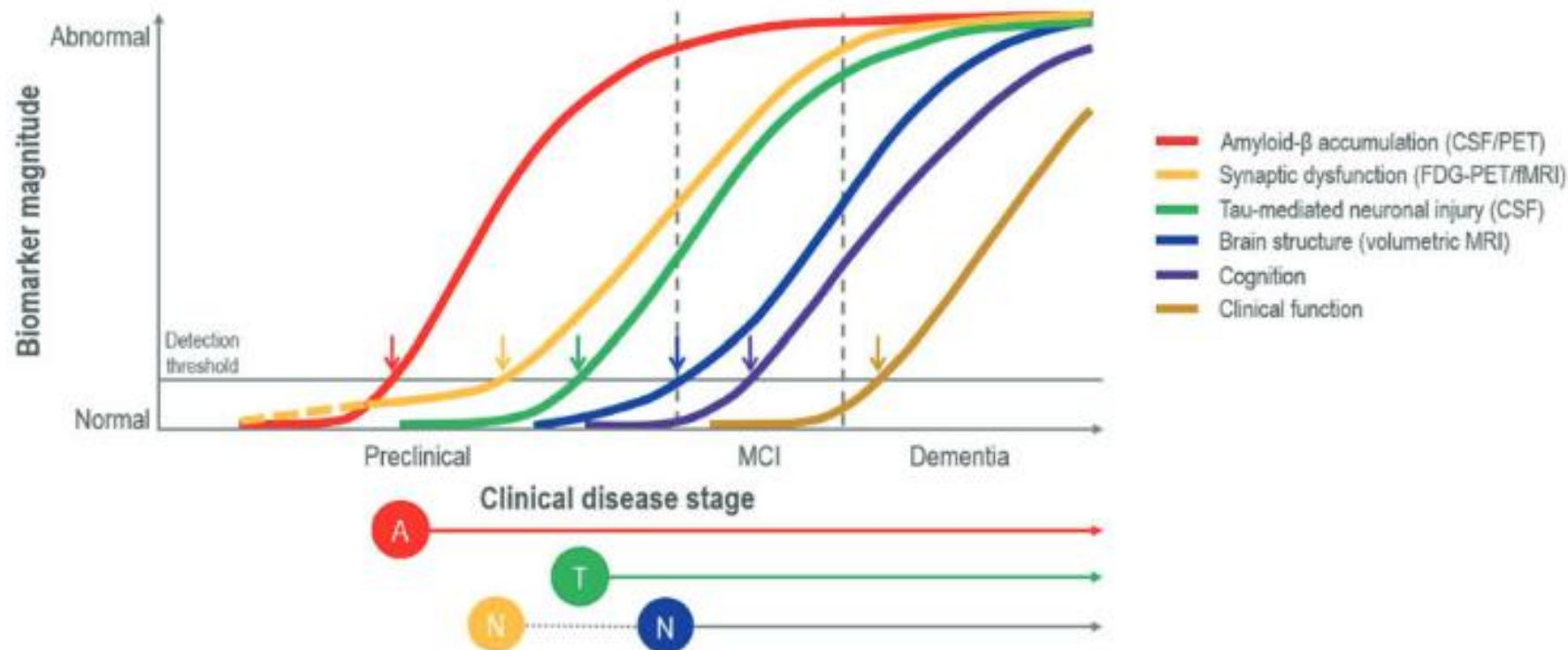
- I have received speaker's honoraria, travel fees or reimbursements from: AbbVie, Allergan, Bial, Lundbeck, Sanofi, UCB pharma, Zambon.
- I have been a member of scientific advisory boards for UCB Pharma, Bial, Sanofi, AbbVie, Lilly, Zambon.
- I have served as Associate Editor for the European journal of Neurology. I am currently on the Editorial board of European journal of Neurology and Parkinsonisms and related disorders journal
- I am currently the Co\_chair of Scientific Panel of Movement Disorders for the European Academy of Neurology

## **DISCLAIMER**

**Vi ricordiamo che, nel corso di questo meeting, gli argomenti trattati saranno esclusivamente nell'ambito delle indicazioni previste dal riassunto delle caratteristiche di prodotto, in accordo con quanto previsto dal Decreto Legislativo 24 aprile 2006, n.219.**

**Vi anticipiamo che qualsiasi eventuale domanda inerente aspetti che siano al di fuori delle indicazioni previste dal riassunto delle caratteristiche di prodotto potrà essere eventualmente affrontata in incontri 1:1 con i relatori, in separata sede e alla fine del meeting, ma non potrà essere oggetto di discussione durante la sessione plenaria.**

# Alzheimer Disease clinical biological continuum

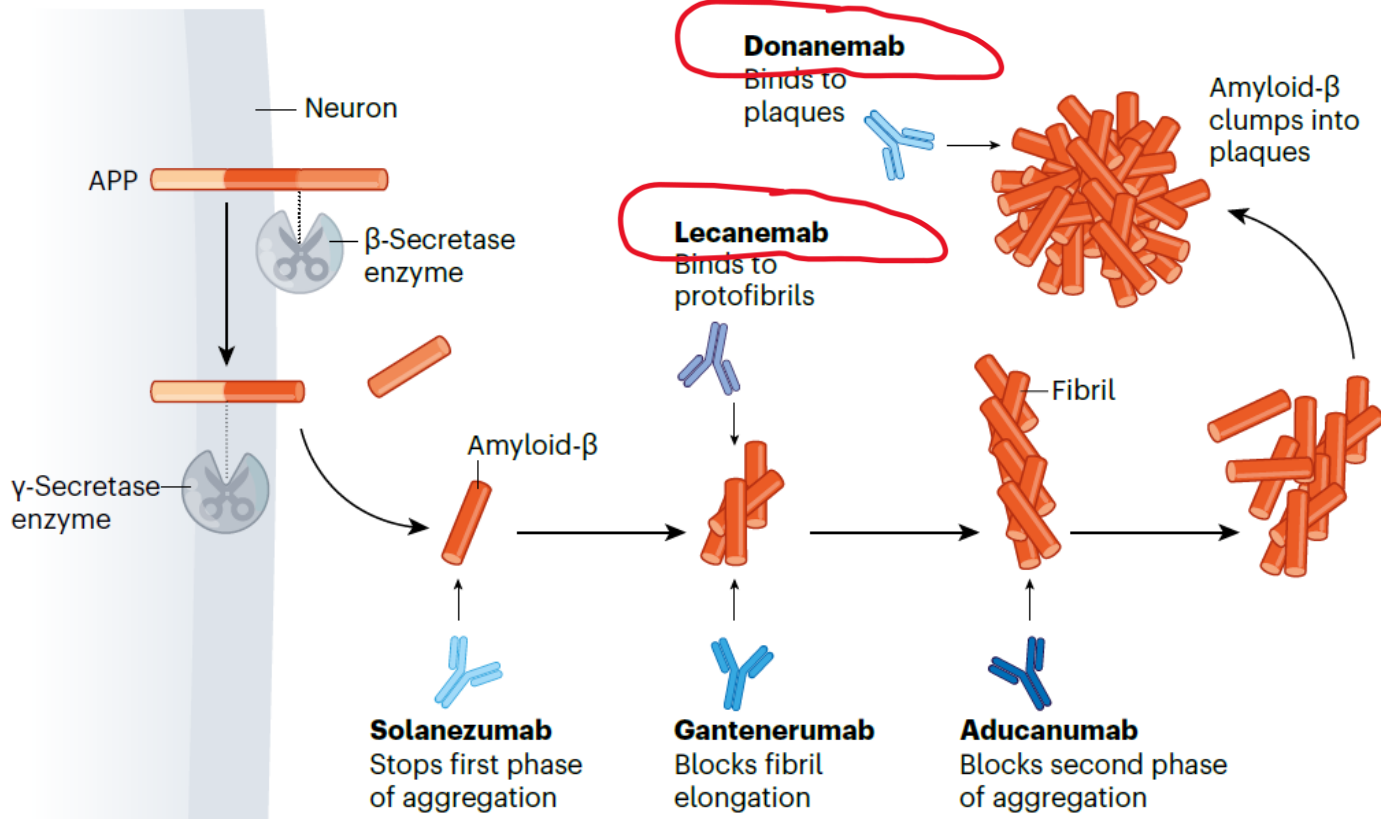


Positivity in the 'A' dimension (purple and red) is essential to place an individual on the AD continuum, as it reflects AD-related brain pathophysiological changes in the earliest phases. Additional positivity in the 'T' (light blue) and 'N' (dark blue) dimensions represents the presence of the full pathophysiological manifestations of AD as it is currently defined.

# Immunotherapy and Alzheimer disease

## ANTIBODIES AGAINST AMYLOID

Several clinical trials are testing whether drugs called monoclonal antibodies can stem the symptoms of Alzheimer's by preventing the toxic clumping of amyloid- $\beta$  proteins. This process starts when enzymes cleave the amyloid precursor protein (APP). Amyloid- $\beta$  proteins elongate into fibrils and then nucleate into plaques. All of the drugs bind to amyloid- $\beta$ , but their primary targets in the process are different.



**3 anti-amyloid monoclonal antibodies approved for *the treatment of early AD*:**

- Aducanumab (dismissed)
- Lecanemab
- Donanemab

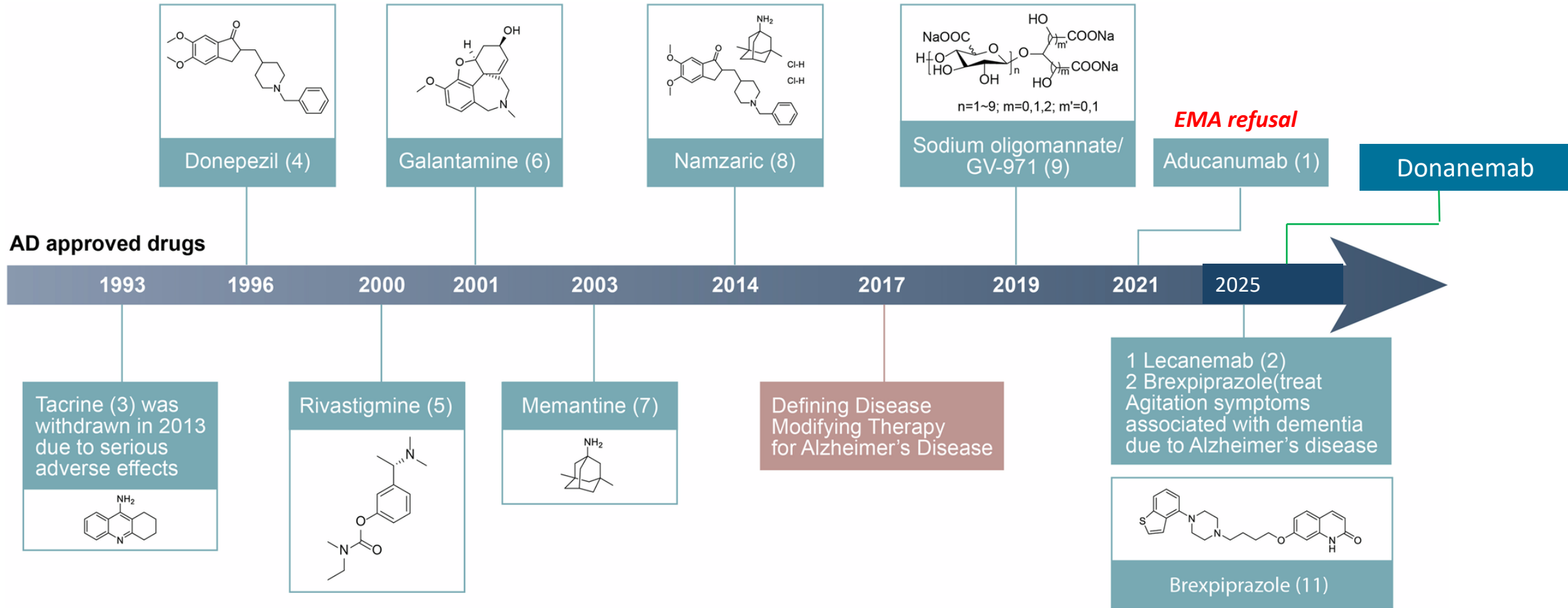
# Immunotherapy and Alzheimer disease

**Table.** Clinical Phase 3 Trials of Anti-A $\beta$  Antibody Therapies for Patients with Alzheimer's Disease.

Monoclonal antibody	Target	Participants	Primary endpoint	Clinical efficacy
Lecanemab	Protofibril, oligomer and fibril	MCI, mild AD	CDR-SB	Yes
Donanemab	Plaque(N3pG)	MCI, mild AD	iADRS	Yes
Aducanumab	Oligomer ~ fibril	MCI, mild AD	CDR-SB	Partially
Gantenerumab	Monomer ~ fibril	MCI, mild AD	CDR-SB	No
Solanezumab	Monomer	mild AD	ADAS-cog14	No
Bapineuzumab	Monomer~oligomer	mild to moderate AD	ADAS-cog11	No

AD: Alzheimer's disease, ADAS-cog: cognitive subscale of the Alzheimer's Disease Assessment Scale, CDR-SB: clinical dementia rating-sum of boxes, iADRS: integrated Alzheimer's Disease Rating Scale, MCI: mild cognitive impairment, N3pG: N-truncated pyroglutamate amyloid-peptide at position 3

# Evolution of Alzheimer disease therapies





Donanemab is indicated for the treatment of adult patients with a clinical diagnosis of **mild cognitive impairment and mild dementia due to Alzheimer's disease** (Early symptomatic Alzheimer's disease) who are apolipoprotein E  $\epsilon$ 4 (ApoE  $\epsilon$ 4) heterozygotes or non-carriers with confirmed amyloid pathology



Donanemab **should be administered every 4 weeks**. The recommended dose of donanemab is 350 mg for the first dose, 700 mg for the second dose, 1 050 mg for the third dose, followed by 1 400 mg every 4 weeks. Treatment should be maintained until amyloid plaques are cleared (e.g. at 6 or 12 months) as confirmed using a validated method. **The maximum treatment duration is 18 months** which should not be exceeded even if plaque clearance is not confirmed.



- **conditions that do not allow MRI assessment**

- MRI: prior intracerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis or vasogenic oedema (ARIA-E), or other findings, which are suggestive of cerebral amyloid angiopathy (CAA)

- severe white matter disease

- **patients with bleeding disorders** that are not under adequate control.

- initiation in patients receiving **ongoing anticoagulant therapy**

- patients with **poorly controlled hypertension**.

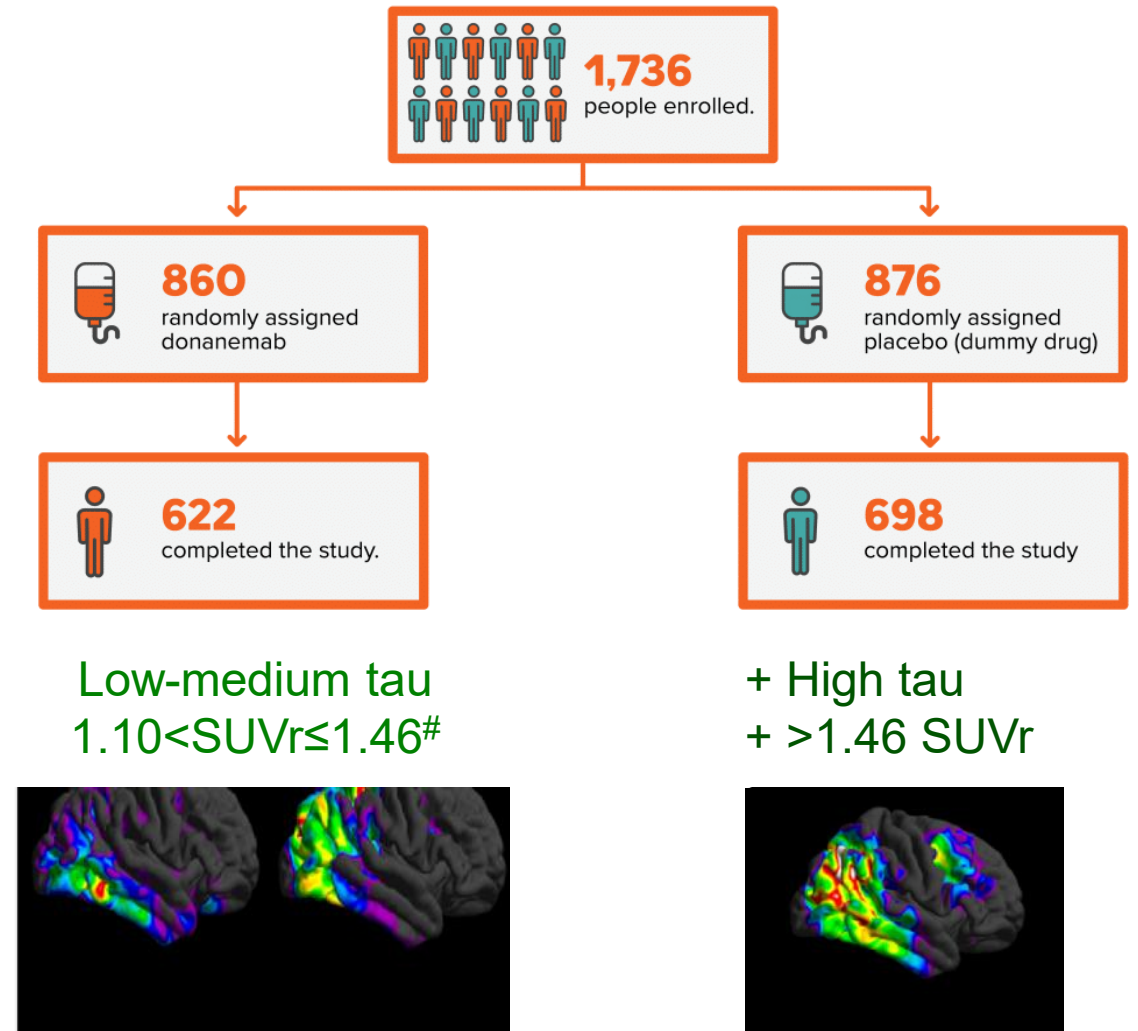


# TRAILBLAZER-ALZ 2 - Study Design

- TRAILBLAZER-ALZ 2 was a 76-week Phase 3, randomized, double-blind, parallel, multicenter, placebo-controlled trial
- The objective was to assess efficacy and adverse events of donanemab, an IgG1 monoclonal antibody designed to clear brain amyloid plaque

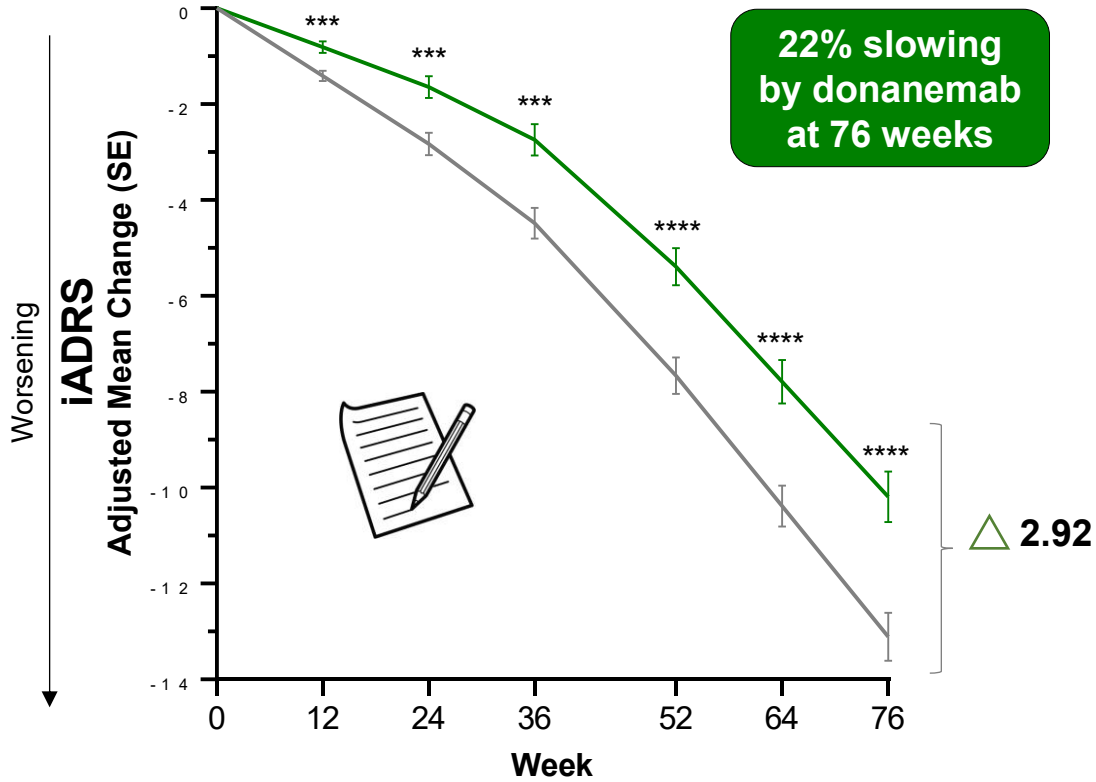
1,736 Eligible participants were randomly assigned to receive DON or PBO in a 1:1 ratio, **with stratification by baseline tau categorization (low-medium vs high tau)**

- Participants received either:
  - DON 700 mg IV Q4W for the first 3 doses, and 1400 mg Q4W thereafter
  - PBO IV Q4W, for up to 72 weeks
- If amyloid plaque level (assessed at 24 weeks and 52 weeks) was  $<11$  CL on any 1 PET scan or  $<25$  but  $\geq 11$  CL on 2 consecutive PET scans (TRAILBLAZER-ALZ cut-offs), DON was switched to PBO in a blinded procedure



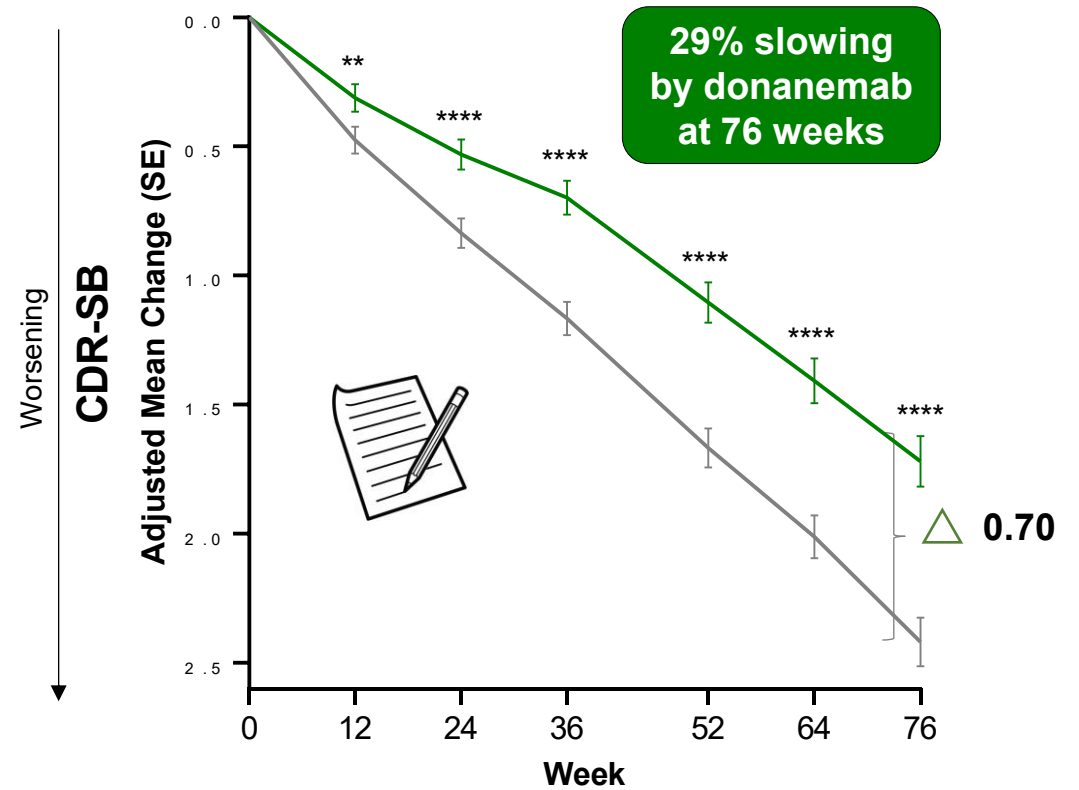
# Primary and Secondary outcomes : Combined Tau Population

**iADRS: Overall Population<sup>1</sup>**



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

**CDR-SB: Overall Population<sup>1</sup>**



— Placebo	838	825	784	752	713	678	672
— Donanemab	794	774	731	682	650	603	598

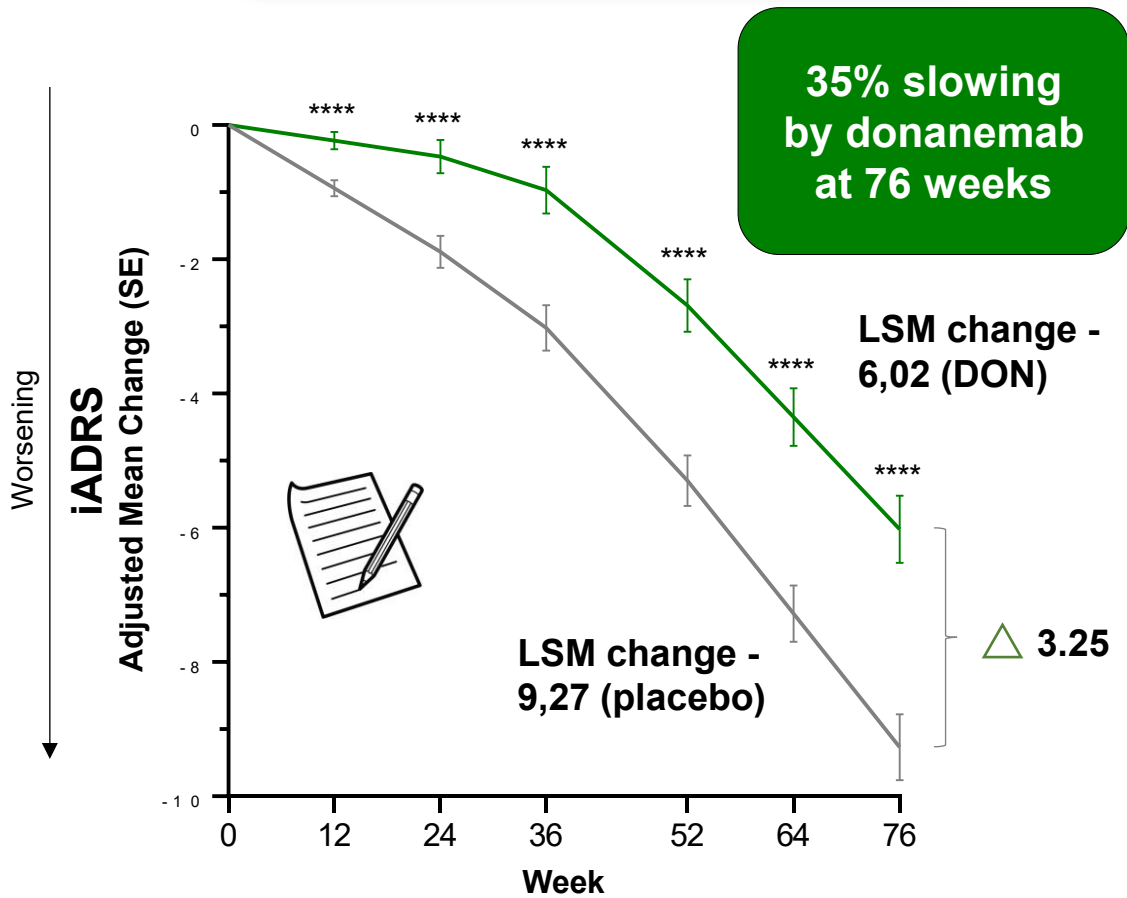
\*\*\*\* P<0.001

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

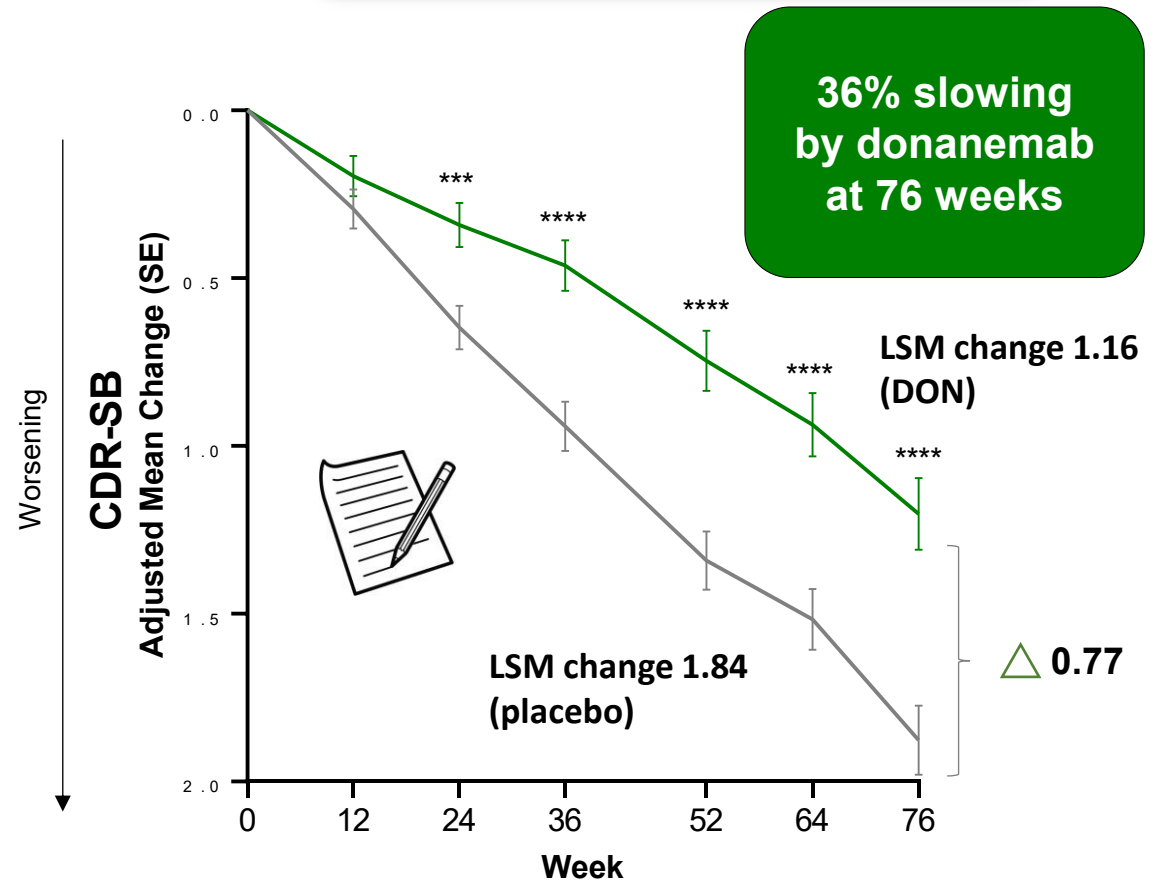
**Disclaimer:** Il trattamento con *donanemab* in Europa è approvato in pazienti MCI o early AD non-carrier o eterozigoti per APOE ε4 per un massimo di 18 mesi.

# Primary Outcome: in Low-medium Tau Population

iADRS: Low-medium Tau Population



CDR-SB: Low-Medium Tau Population



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

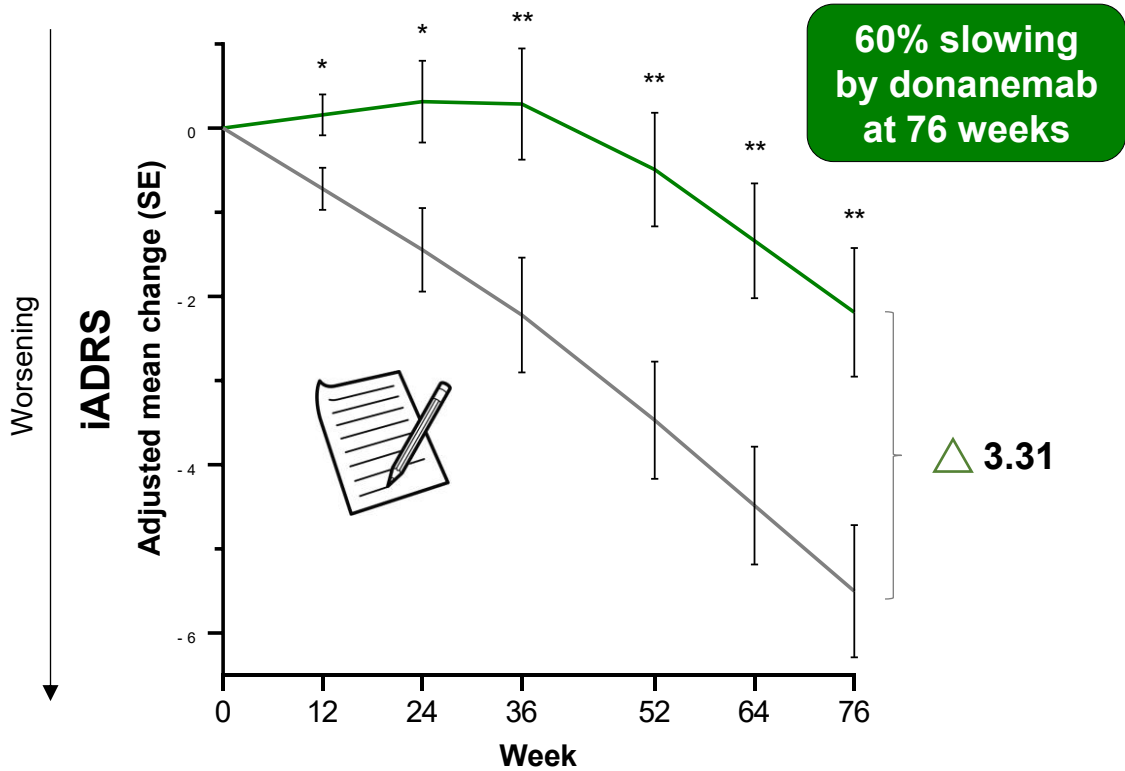
Placebo	569	561	540	516	486	461	459
Donanemab	546	530	499	471	451	418	424

\*\*\*\* P<0.001; LSM: least-squares mean

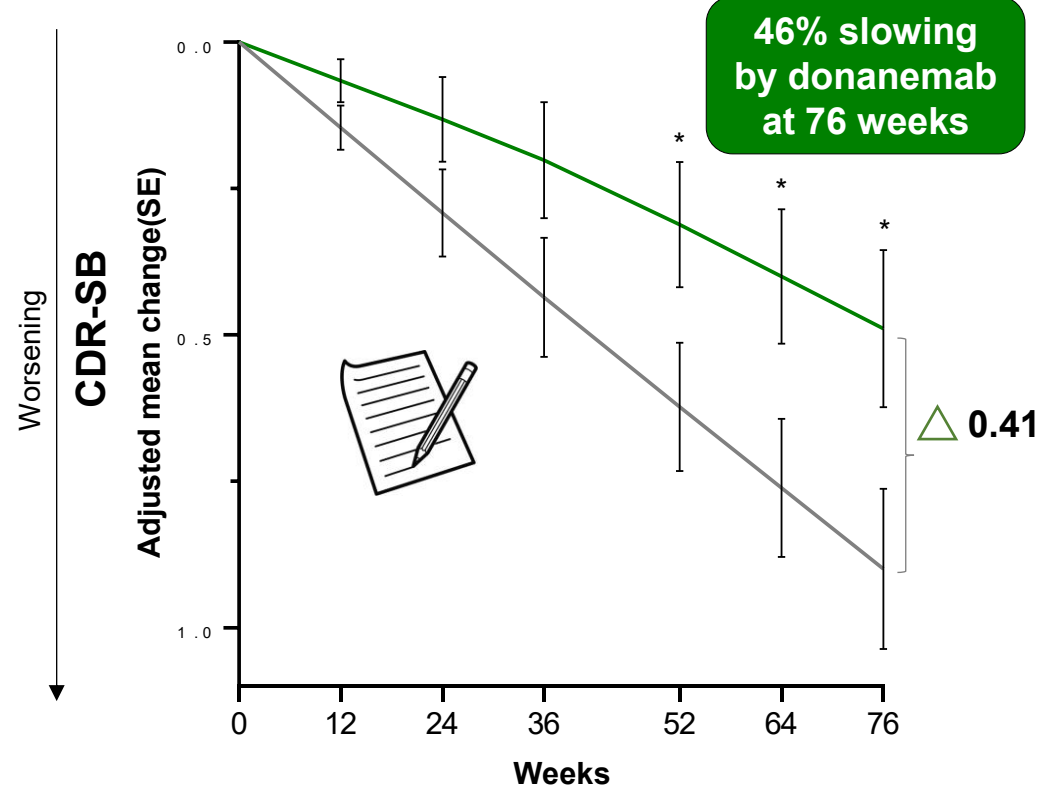
\*\*\*\* P<0.001; LSM: least-squares mean

# Pre-specified subpopulation: MCI (Low-medium Tau Population)

**iADRS: Low-medium Tau Population**



**CDR-SB: Low-Medium Tau Population**



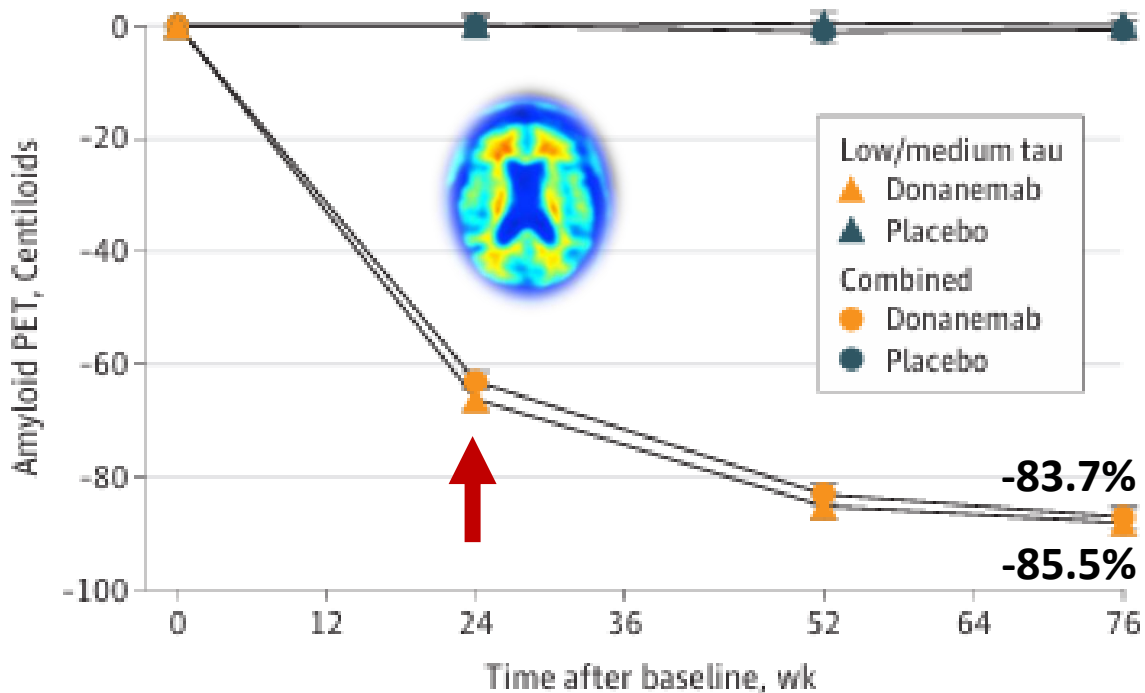
—	Placebo	102	100	98	99	93	89	86
—	Donanemab	112	110	103	101	96	91	92

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

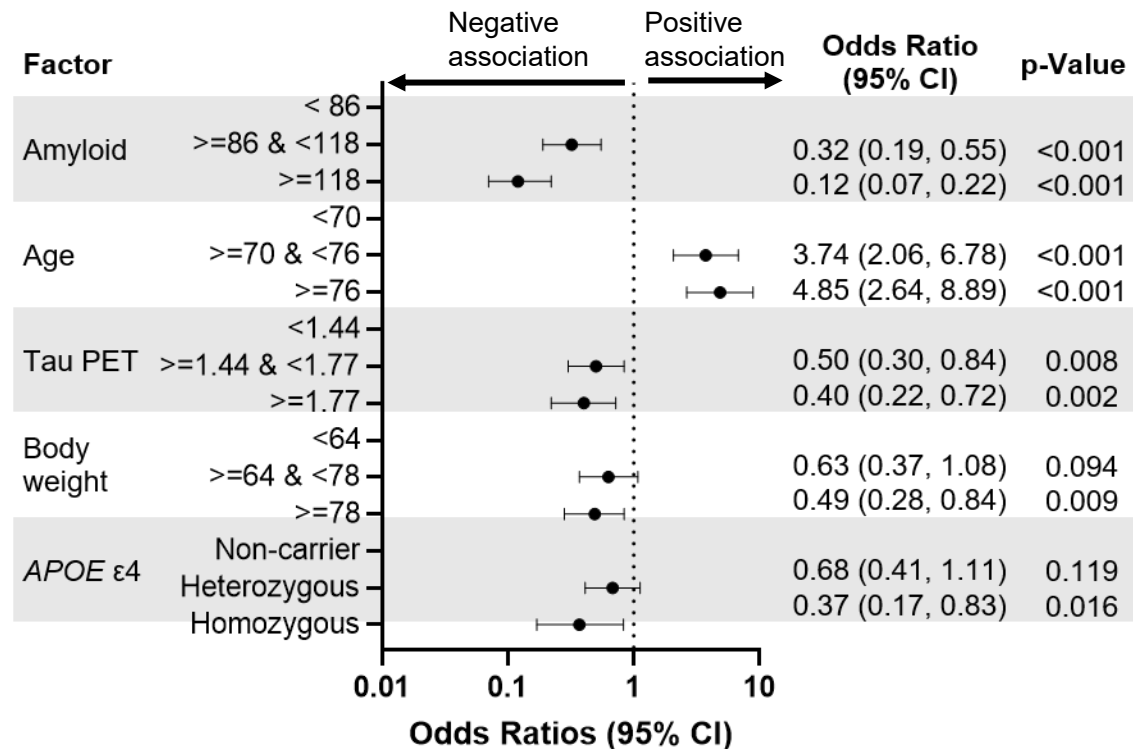
Donanemab showed greater clinical impact in participants at earlier disease stage

# Secondary outcomes: change in Amyloid PET

## Amyloid clearance



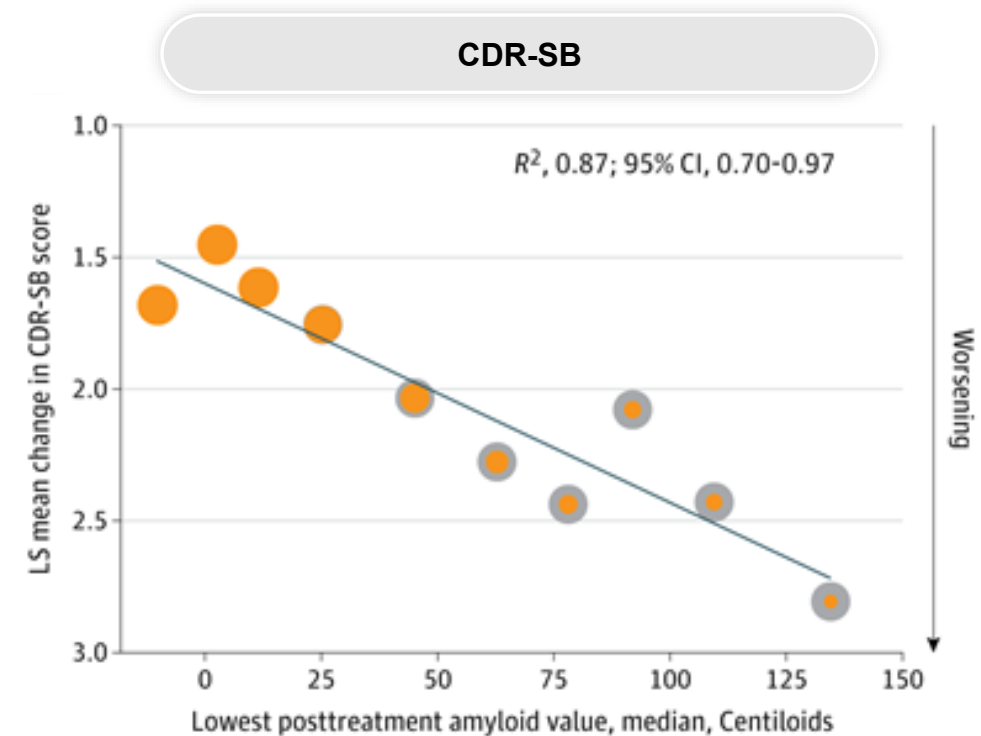
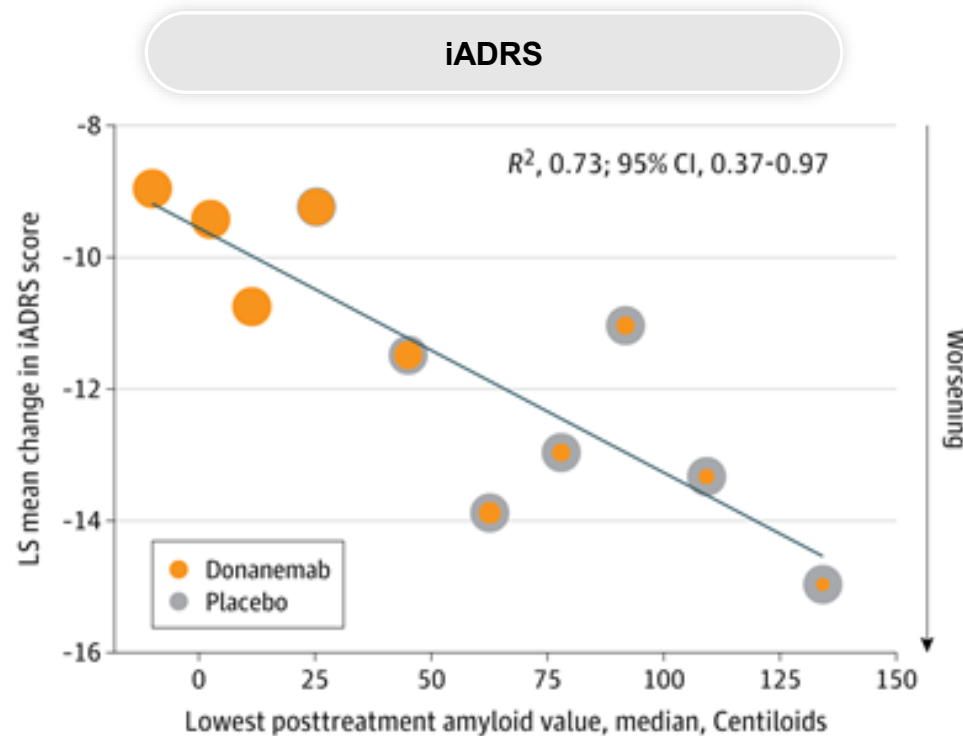
## 5 key common predictors at week 24



modified from Sims JR, et al. *JAMA*. 2023

# Secondary outcomes: change in Amyloid PET

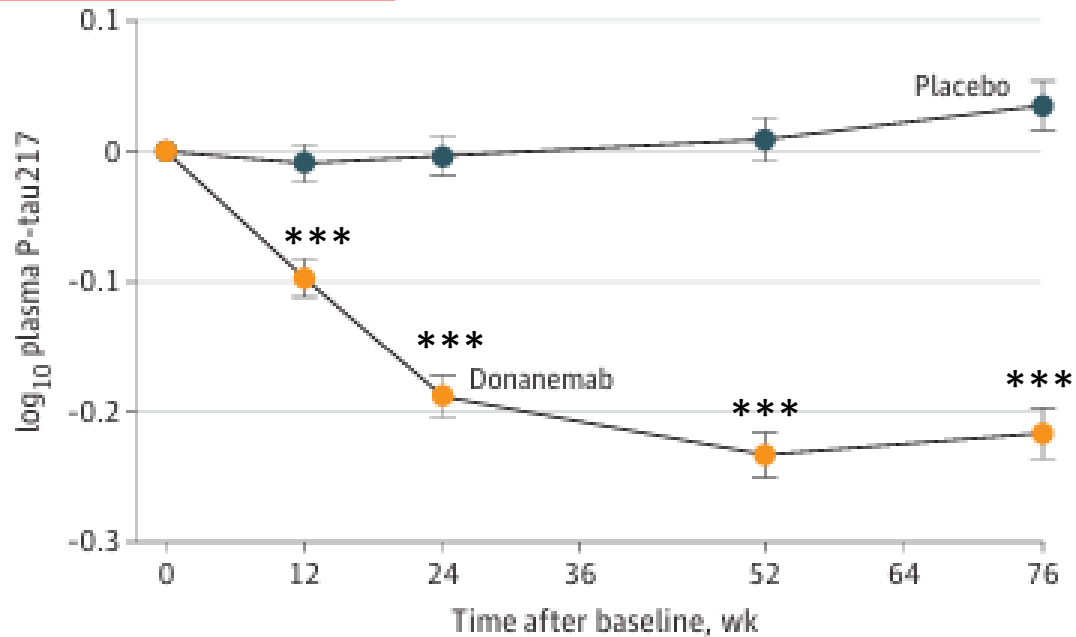
## Correlation of Post-treatment Amyloid value with changes in Clinical Progression



Ming Lu, et al. JAMA Neurol 2025

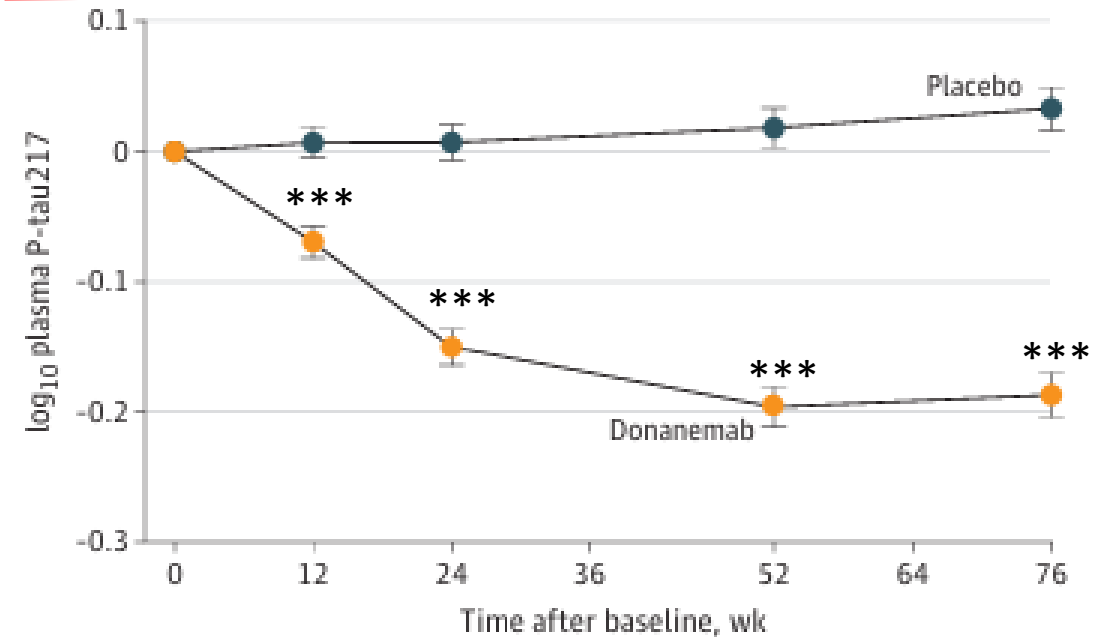
# Exploratory Outcomes: Change of Plasma P-tau217

**C** Adjusted mean change (95% CI) of  $\log_{10}$  plasma P-tau217 in low/medium tau population



No. of participants	0	12	24	52	76
Placebo	537	517	511	449	429
Donanemab	522	493	464	410	395

**D** Adjusted mean change (95% CI) of  $\log_{10}$  plasma P-tau217 in combined population



No. of participants	0	12	24	52	76
Placebo	786	758	734	658	620
Donanemab	758	717	686	602	568

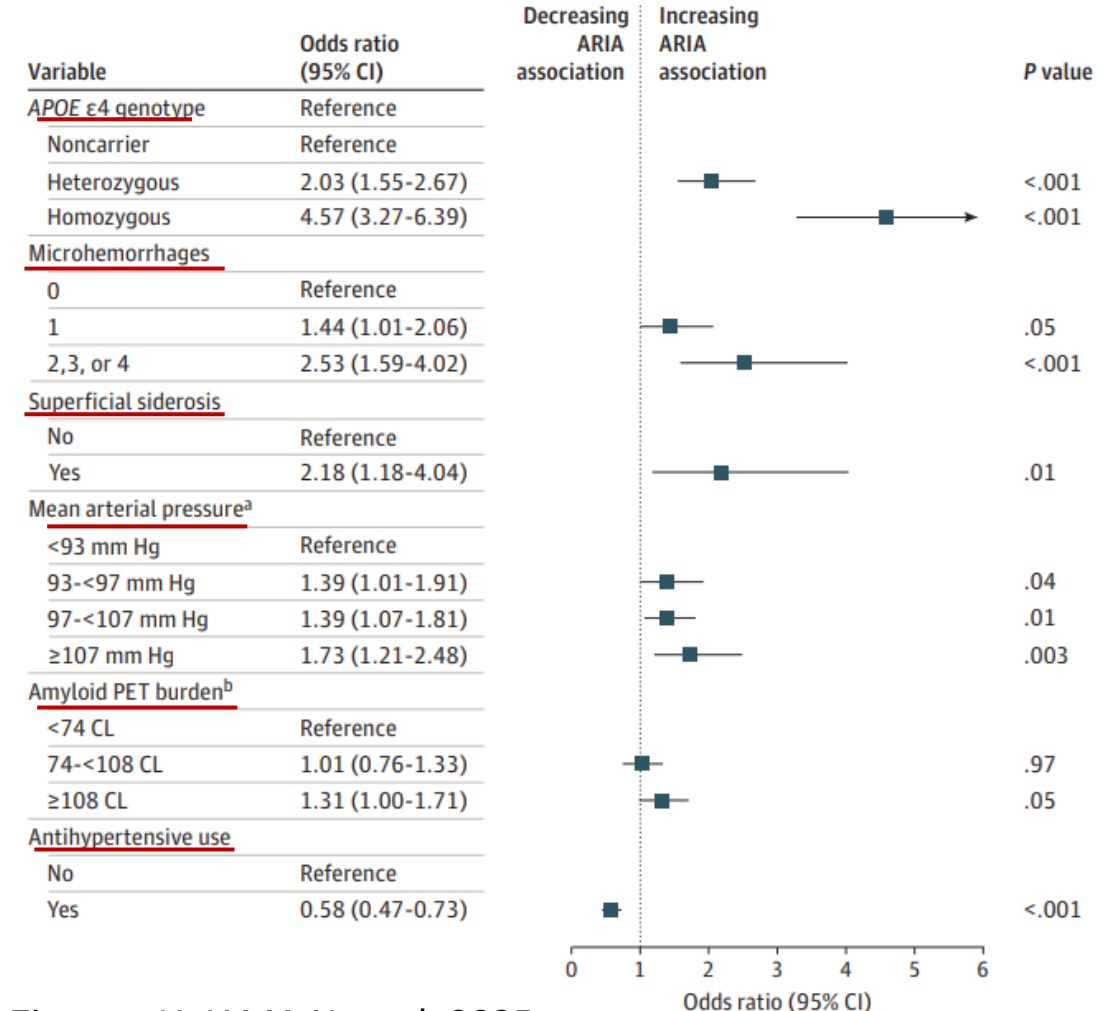
Sims JR, et al. *JAMA*. 2023;330(6):512-527.

**Disclaimer:** Il trattamento con *donanemab* in Europa è approvato in pazienti MCI o early AD non-carrier o eterozigoti per APOE ε4 per un massimo di 18 mesi.

# Amyloid-Related Imaging Abnormalities With Donanemab in Early Symptomatic Alzheimer Disease

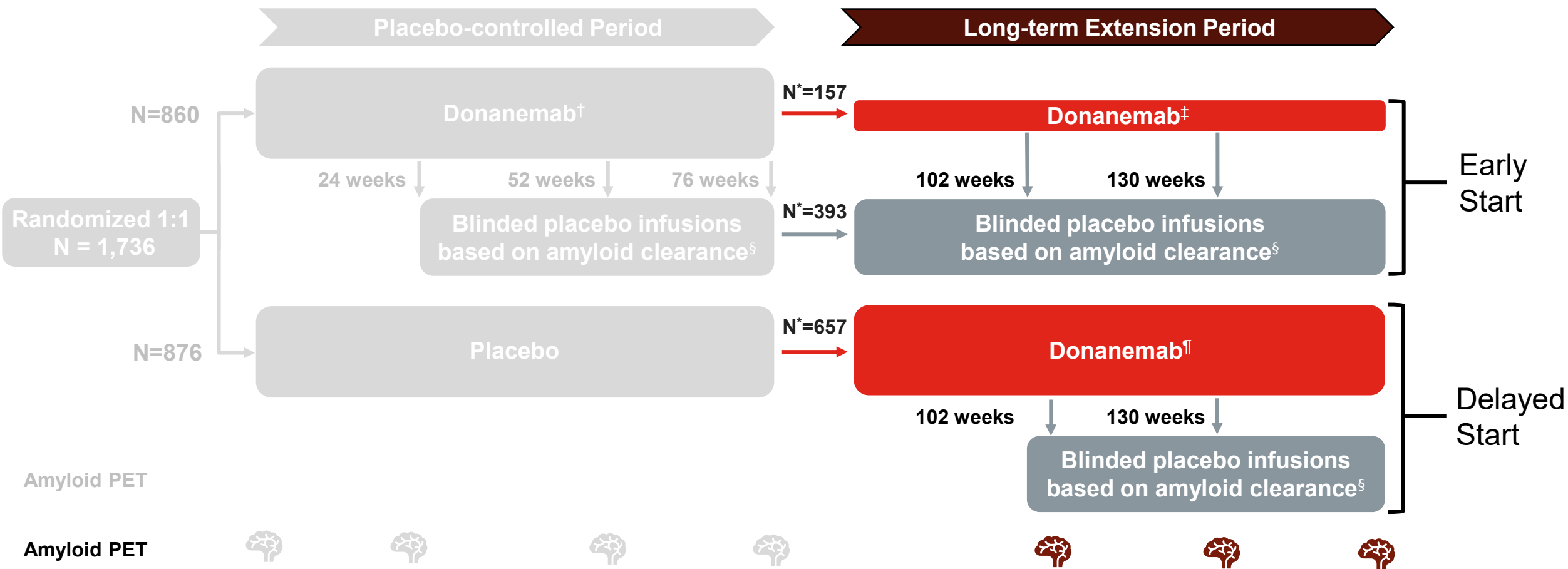
Event	No. (%)		
	Placebo-controlled trials <sup>a</sup>		Open-label addendum, donanemab-treated participants (n = 1047)
	Placebo (n = 999)	Donanemab (n = 984)	
Any ARIA (E or H) <sup>b</sup>	142 (14.2)	364 (37.0)	335 (32.0)
Serious adverse events <sup>c</sup>	0	16 (1.6)	9 (0.9)
Treatment discontinuation <sup>c</sup>	8 (0.8)	52 (5.3)	27 (2.6)
<u>ARIA-E<sup>b</sup></u>	19 (1.9)	240 (24.4)	207 (19.8)
<u>APOE ε4 carrier status, No./total No. (%)</u>			
Noncarrier	2/282 (0.7)	43/291 (14.8)	43/391 (11.0)
Heterozygote	10/538 (1.9)	126/522 (24.1)	115/535 (21.5)
Homozygote	6/174 (3.4)	70/168 (41.7)	48/114 (42.1)
<u>Symptomatic<sup>d</sup></u>	1 (0.1)	57 (5.8)	42 (4.0)
<u>APOE ε4 carrier status, No./total No. (%)</u>			
Noncarrier	0/282	12/291 (4.1)	10/391 (2.6)
Heterozygote	0/538	32/522 (6.1)	24/535 (4.5)
Homozygote	1/174 (0.6)	13/168 (7.7)	7/114 (6.1)
Serious adverse events <sup>c</sup>	0	15 (1.5)	7 (0.7)
Treatment discontinuation <sup>c</sup>	4 (0.4)	28 (2.8)	14 (1.3)
<u>ARIA-H<sup>b</sup></u>	130 (13.0)	308 (31.3)	285 (27.2)
<u>APOE ε4 carrier status, No./total No. (%)</u>			
Noncarrier	30/282 (10.6)	55/291 (18.9)	71/391 (18.2)
Heterozygote	66/538 (12.3)	162/522 (31.0)	156/535 (29.2)
Homozygote	34/174 (19.5)	90/168 (53.6)	57/114 (50.0)
<u>Symptomatic</u>	3 (0.3)	10 (1.0)	2 (0.2)
Serious adverse events <sup>c</sup>	0	4 (0.4)	3 (0.3)
Treatment discontinuation <sup>c</sup>	4 (0.4)	24 (2.4)	13 (1.2)

## Association of Baseline Risk Factors With ARIA



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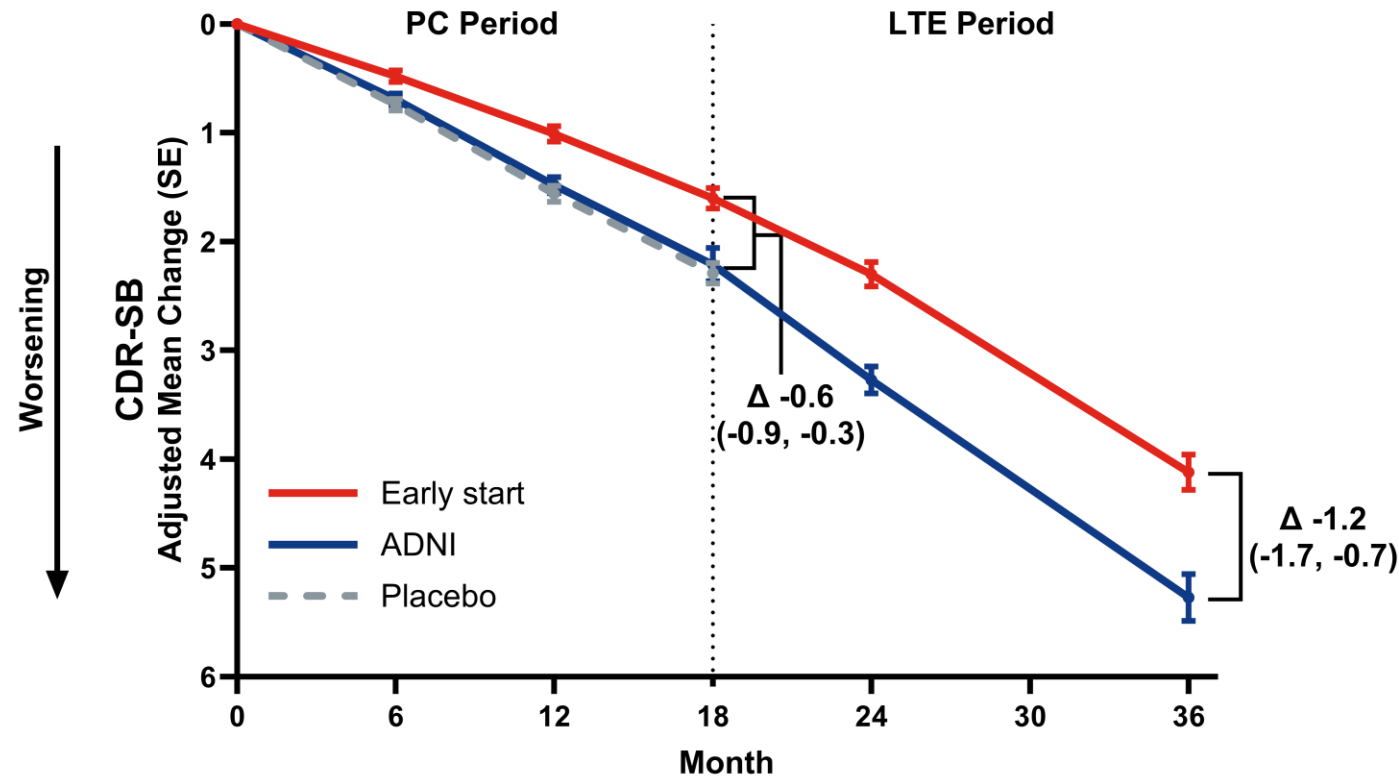
# Results from the TRAILBLAZER-ALZ 2 long-term extension



Zimmer JA et al. JAPD 2025

**Disclaimer:** Il trattamento con *donanemab* in Europa è approvato in pazienti MCI o early AD non-carrier o eterozigoti per APOE ε4 per un massimo di 18 mesi.

# EFFICACY: SLOWING OF CLINICAL DECLINE IN EARLY START DONANEMAB VS EXTERNAL ADNI COHORT

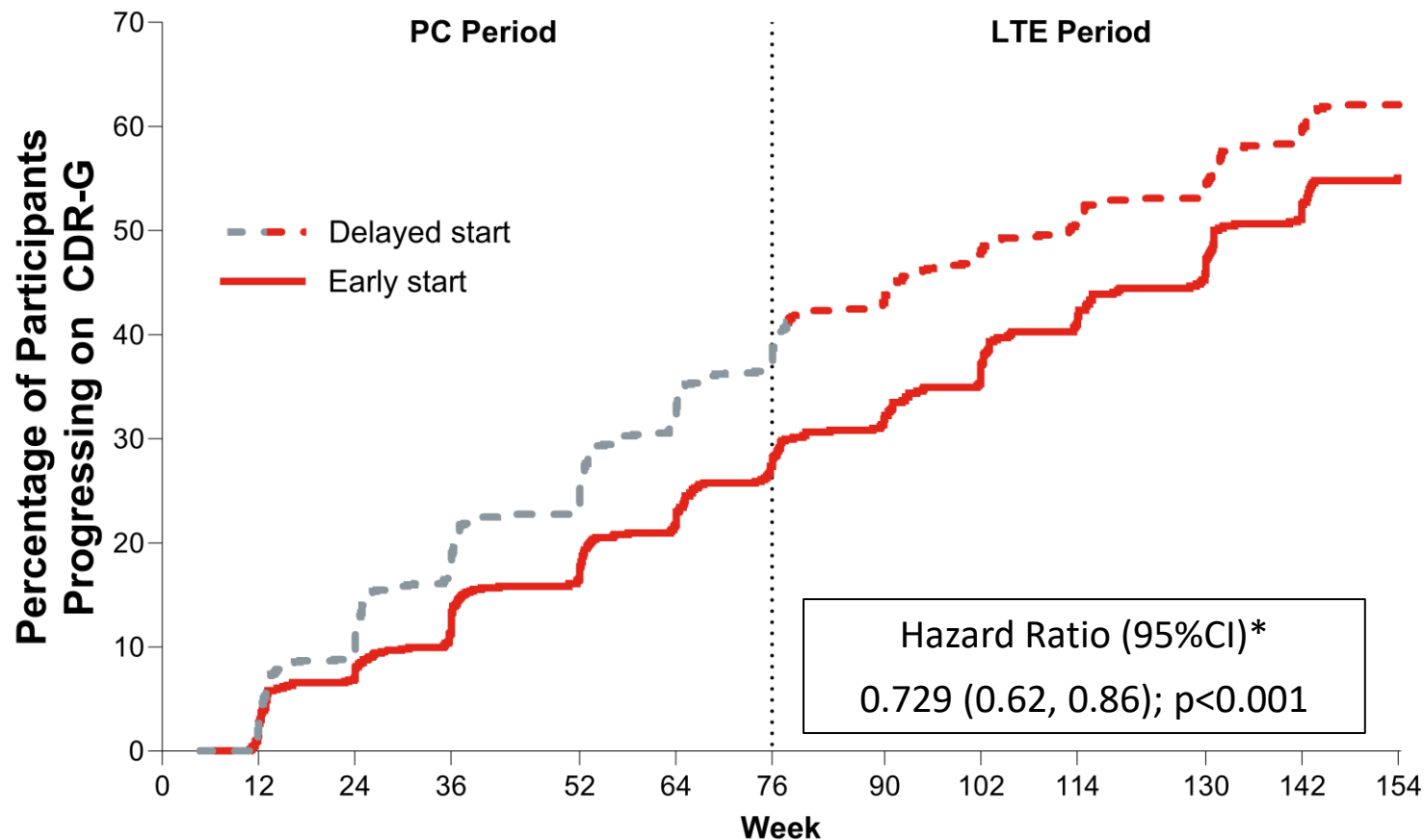


Early start (N):	794	731	650	604	507	417
ADNI (ESS):	268	255	237	200	183	122
Placebo (N):	840	783	714	680		

- Treatment benefit increased even after treatment regimen was completed in most participants
- **Donanemab benefit continued to grow over 3 years compared to external ADNI cohort with delta CDR-SB increasing from 0.6 at 18 months to 1.2 at 36 months**

Zimmer JA et al. JAPD 2025

# EFFICACY: REDUCED RISK OF PROGRESSION TO NEXT CLINICAL DISEASE STAGE



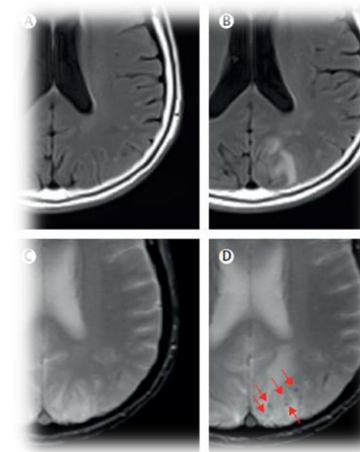
- Early start donanemab group showed 27% reduced risk of progression to next stage of disease compared to delayed start donanemab group
- Disease modification by donanemab was demonstrated by continued treatment differences between the early and delayed start groups

Zimmer JA et al. JAPD 2025

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# ARIA AND INFUSION-RELATED REACTION FREQUENCIES WITH LATER DONANEMAB INITIATION

Treatment Arm	Donanemab initiated in PC period*†	Donanemab initiated in LTE period*‡
Observation Period	PC Period	LTE Period
	N=853; n (%)	N=657; n (%)
<b>ARIA-E<sup>§</sup></b>	<b>205 (24.0)</b>	<b>171 (26.0)</b>
Symptomatic	52 (6.1)	40 (6.1)
SAE of ARIA-E <sup>¶</sup>	13 (1.5)	9 (1.4)
<b>ARIA-H<sup>§</sup></b>	<b>269 (31.5)</b>	<b>261 (39.7)</b>
Symptomatic	10 (1.2)	3 (0.5)
SAE of ARIA-H <sup>¶</sup>	4 (0.5)	0 (0.0)
<b>Macrohemorrhage<sup>§</sup></b>	<b>3 (0.4)</b>	<b>7 (1.1)</b>
SAE of Macrohemorrhage <sup>¶</sup>	1 (0.1)	1 (0.2)
<b>Infusion-related reaction</b>	<b>75 (8.8)</b>	<b>49 (7.5)</b>
<b>Anaphylactic reaction<sup>#</sup></b>	<b>3 (0.4)</b>	<b>4 (0.6)</b>



- **Comparable frequencies of ARIA and infusion-related reactions between early donanemab treatment initiation and later initiation**

\*Includes safety analysis population (i.e., all participants who received at least one infusion in the relevant study period).

†Includes events that occurred prior to the earlier of date of study withdrawal/completion, end of the placebo-controlled period + 57 days, or data cut-off. Includes additional data incorporated after primary outcome lock.

‡Includes events that occurred prior to the earlier of date of study withdrawal/completion, end of the extension period + 57 days, or data cut-off are included in this table.

§Based on MRI or TEAE cluster.

¶Based on TEAE cluster.

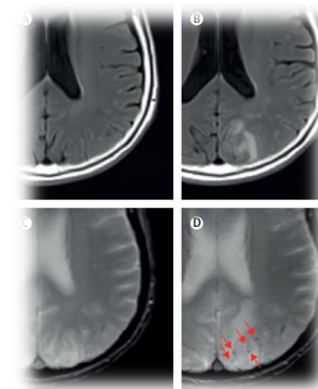
#Includes anaphylactic reaction and anaphylactic shock.

Zimmer JA et al. JAPD 2025

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# WITH LONGER OBSERVATION, ARIA FREQUENCY DECREASED

Treatment Arm	Placebo initiated in PC period* <sup>†</sup>	Donanemab initiated in PC period* <sup>‡</sup>
Observation Period	PC Period	LTE Period
	N=874; n (%)	N=550; n (%)
<b>ARIA-E<sup>§</sup></b>	<b>18 (2.1)</b>	<b>19 (3.5)</b>
Symptomatic	0 (0.0)	4 (0.7)
SAE of ARIA-E <sup>¶</sup>	0 (0.0)	1 (0.2)
<b>ARIA-H<sup>§</sup></b>	<b>119 (13.6)</b>	<b>105 (19.1)</b>
Symptomatic	3 (0.3)	1 (0.2)
SAE of ARIA-H <sup>¶</sup>	0 (0.0)	0 (0.0)
<b>Macrohemorrhage<sup>§</sup></b>	<b>2 (0.2)</b>	<b>0 (0.0)</b>
SAE of Macrohemorrhage <sup>¶</sup>	1 (0.1)	0 (0.0)
<b>Infusion-related reaction</b>	<b>4 (0.5)</b>	<b>13 (2.4)</b>
<b>Anaphylactic reaction<sup>#</sup></b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>



- During the LTE period, participants who initiated donanemab early had **ARIA and infusion-related reaction frequencies that began to approximate the safety profile of placebo** treated participants

\*Includes safety analysis population (i.e., all participants who received at least one infusion in the relevant study period).

<sup>†</sup>Includes events that occurred prior to the earlier of date of study withdrawal/completion, end of the placebo-controlled period + 57 days, or data cut-off. Includes additional data incorporated after primary outcome lock.

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<sup>§</sup>Based on MRI or TEAE cluster.

<sup>¶</sup>Based on TEAE cluster.

<sup>#</sup>Includes anaphylactic reaction and anaphylactic shock.

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# SUMMARY

## Clinical Efficacy

- Donanemab significantly slowed clinical progression in participants with early symptomatic AD
- Donanemab benefit continued to grow over 3 years (CDR-SB vs ADNI: -1.2 points)
- Delayed initiation of donanemab also provided benefit on CDR-SB
- Early initiation of donanemab reduced risk of progression by 27% on CDR-SB

## Biomarkers

- Early and delayed start of donanemab showed robust amyloid reduction (~86 CL)

## Safety

- ARIA 3-6% resulted in symptoms
- APO $\epsilon$  4 and microH are the major risk factors
- In LTE no new safety signals observed versus the established safety profile

ADNI: Alzheimer's Disease Neuroimaging Initiative (<https://adni.loni.usc.edu/>); CDR-G: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CL: Centiloids; PET: positron emission tomography.