HOSPITAL CLINIC UNIVERSITARI

CEAFA ALZHEIMER

integrando la innovación

X Congreso Nacional de ALZHEIMER

GIJÓN. 8, 9, 10 y 11 /NOV/ 2023

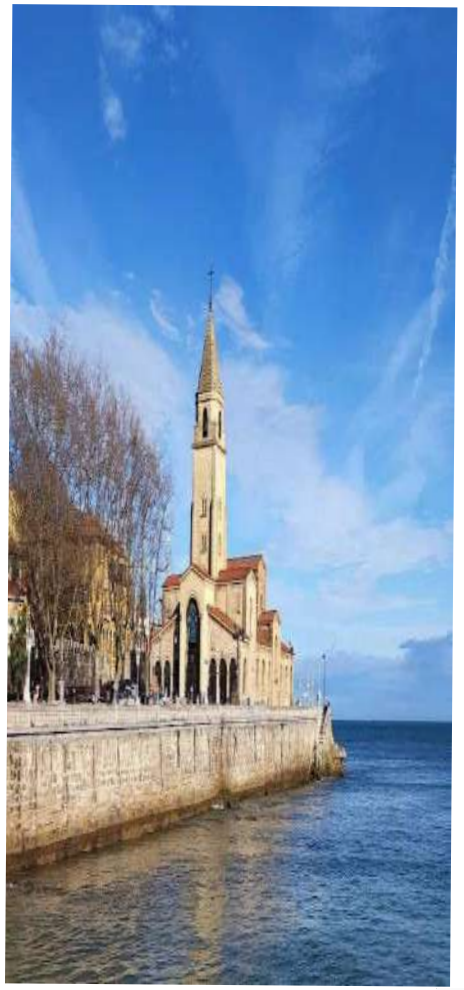
Universidad Católica de Valencia San Vicente Mártir

Los Nuevos Fármacos Frente al Alzheimer

Gijón, Noviembre, 2023

José Miguel Láinez, MD, PhD, FAAN, FANA, FAHS

Hospital Clínico Universitario
Universidad Católica de Valencia
España



HOSPITAL CLINIC UNIVERSITARI

Universidad Católica de Valencia San Vicente Mártir

:Disclosures

Honoraria, consultation fees and research grants from: Allergan, Amgen, ATI, Bial, Boehringher, Chiesi, ElectroCore, Eli Lily, Lumdbeck, Medtronic, Novartis, Otsuka, Roche, Teva and UCB

Key Pathological Features of AD

Amyloid Plaques[1-4]

Composed primarily of the insoluble **Aβ peptide $Aβ_{42}$**; extracellular

Neurofibrillary Tangles (NFT) of Tau[1,2]

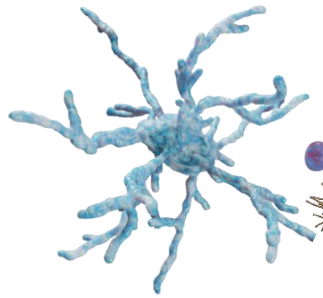
Composed of hyperphosphorylated microtubule-associated protein **tau (P-tau)**; intraneuronal filamentous inclusions

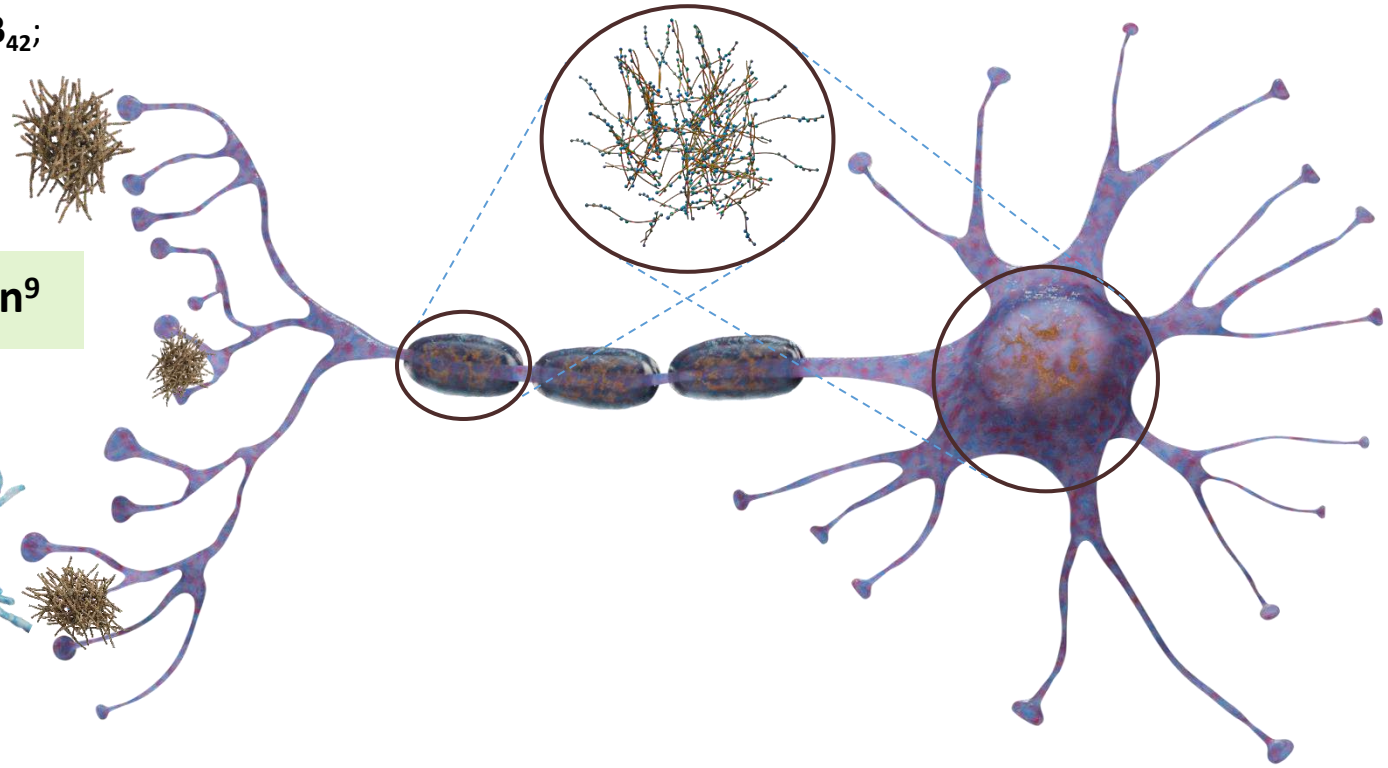
Neurodegeneration[5-8]

Cerebral **atrophy**, where sulci widen and gyri narrow,[6] is caused by a decrease in synaptic density and neuronal loss[7,8]

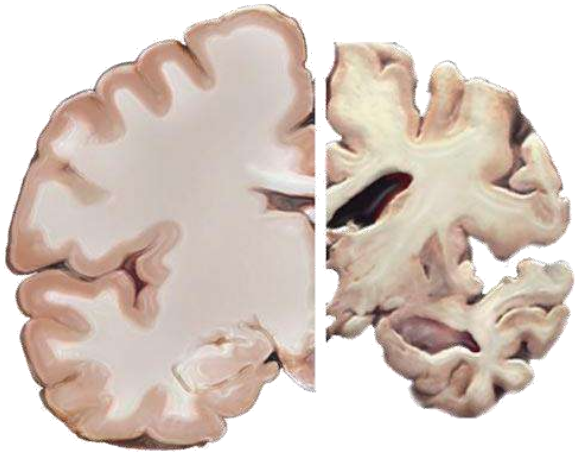
Neuroinflammation[9]

Gliosis





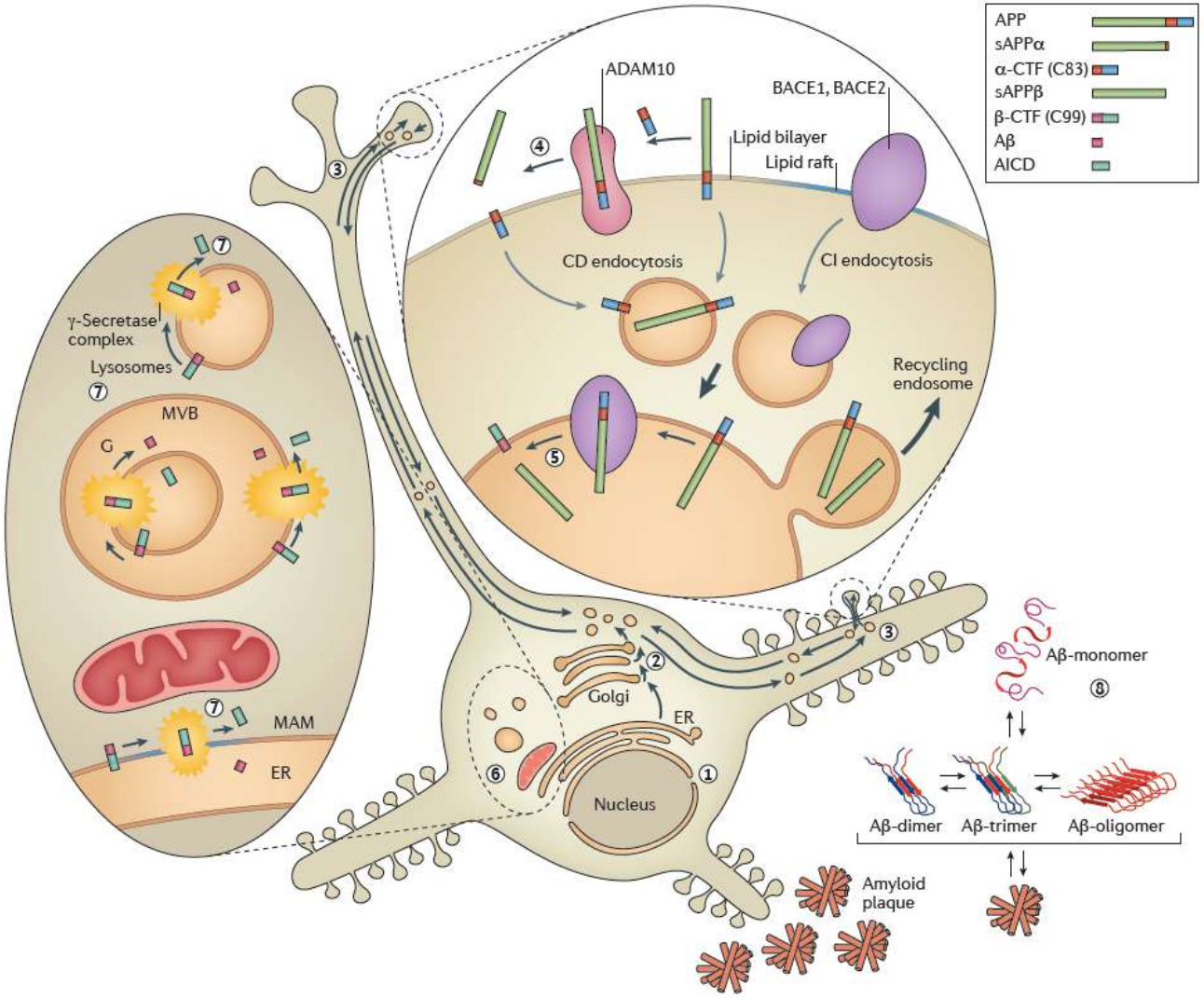
Healthy Brain **Severe AD**



Aβ=Amyloid Beta; AD=Alzheimer's Disease; NFTs=Neurofibrillary Tangles; P-tau=Phosphorylated-Tau.

1. Koper MJ, et al. *Acta Neuropathologica.* 2020;139:463-484. 2. Querfurth HW, LaFerla FM. *N Engl J Med.* 2010;362(4):329-344 (erratum in: *N Engl J Med.* 2011;364(6):588). 3. Raskin J, et al. *Curr Alzheimer Res.* 2015;12(8):712-722. 4. Kuo YM, et al. *J Biol Chem.* 1996;271(8):4077-4081. 5. Ferreira D, et al. *Front Neurol.* 2019;10:524. 6. Castellani RJ, et al. *Dis Mon.* 2010;56(9):484-546. 7. Serrano-Pozo A, et al. *Cold Spring Harb Perspect Med.* 2011;1(1):a006189. 8. Blinkouskaya Y, Weickenmeier *J. Front Mech Eng.* 2021;7:705653. 9. Kinney, JW, et al. *Alzheimers Dement (N Y).* 2018;4:575-590. Image used with permission from: https://commons.wikimedia.org/wiki/File:Alzheimers_brain.

Amiloide, exceso de producción, ¿causas?



Proteina Precursora Amiloide

Funciones

Actividad sináptica
Func. Protectora
Neurogénesis
Plasticidad
Nuevas Conexiones

Hiperproducción Aß

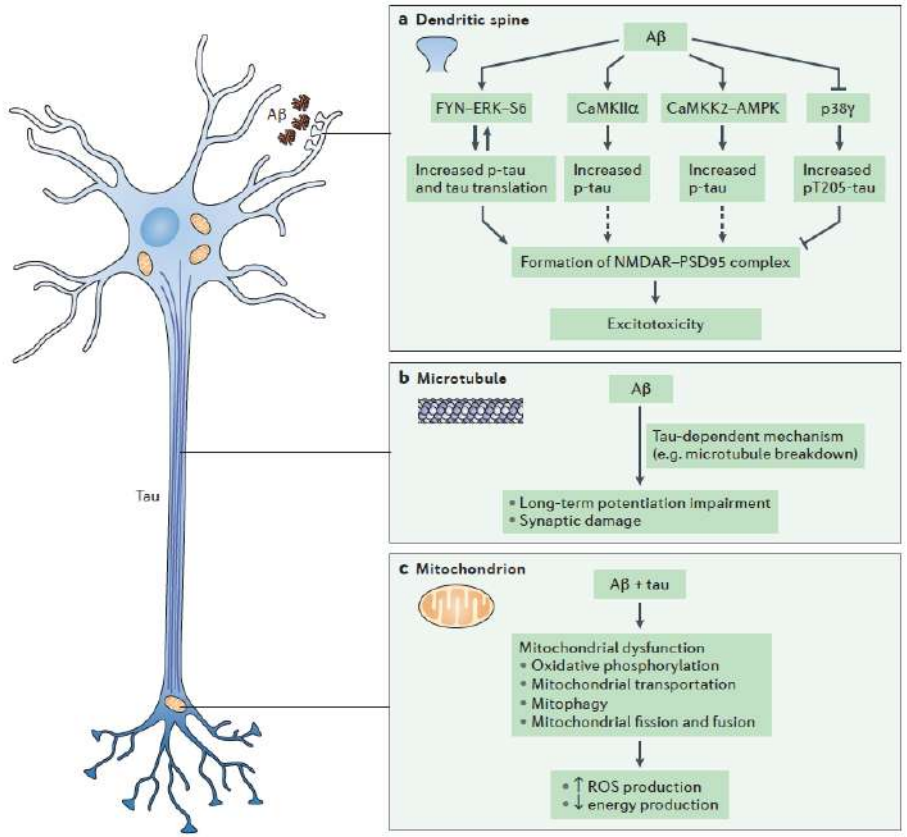
Causas genéticas

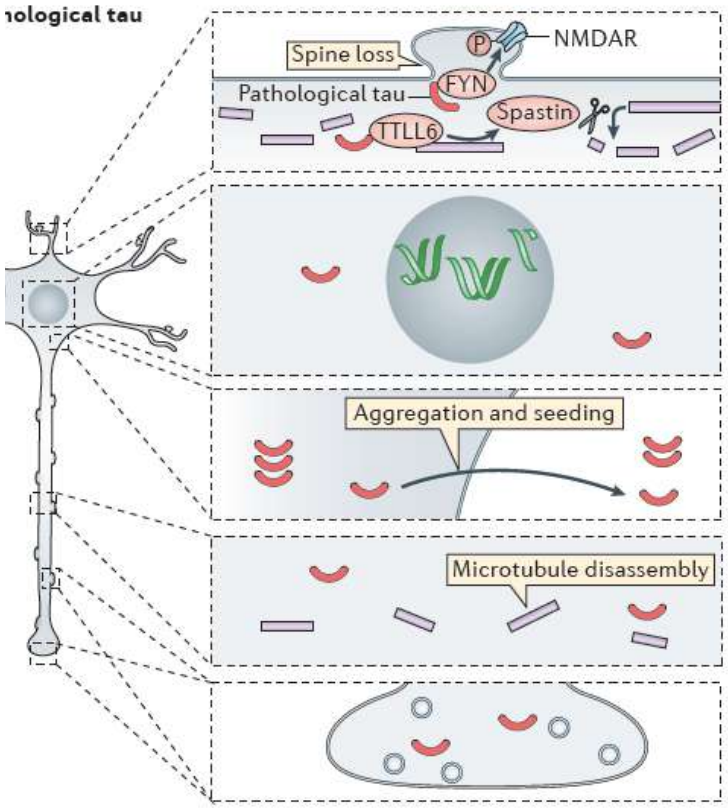
Isquemia
Traumatismo
Infecciones
Estados inflamatorios
¿?

Cortesía de Pablo Martinez-Lage,

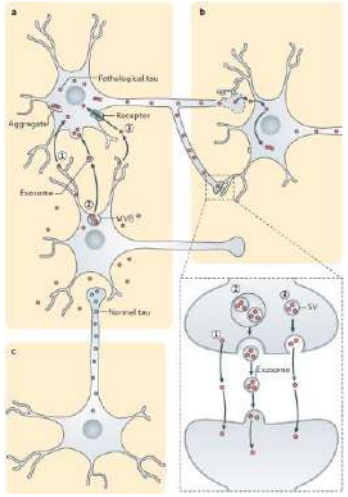
NATURE REVIEWS | NEUROLOGY Polanco JC, et al. Nat Rev Neurol. 2017; 14(1): 22-39.

Aß induce cambios que favorecen la patología tau (fosforilación, agregación...)





- **Estructural**
  - microtúbulos
  - espinas dendríticas,
  - vesículas sinápticas
- **Protección DNA nuclear**
- **Transporte axonal**.

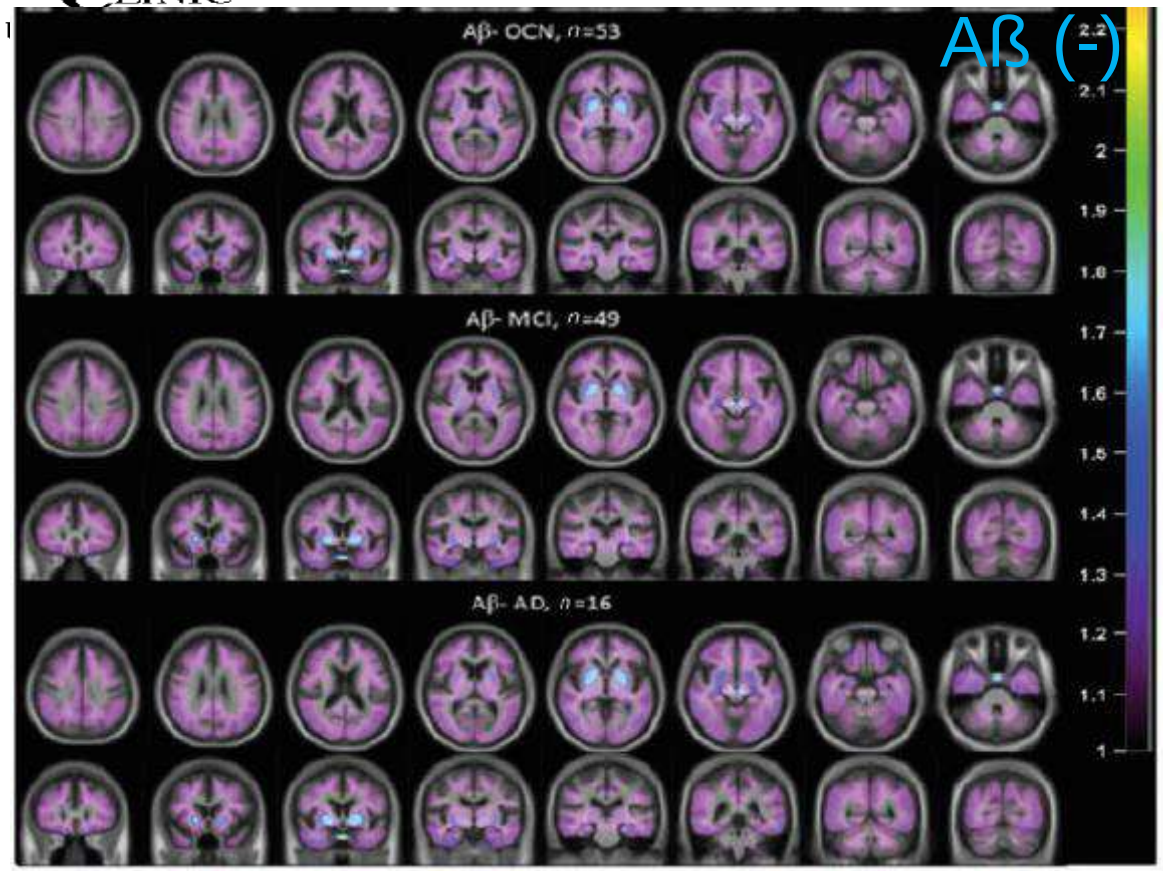


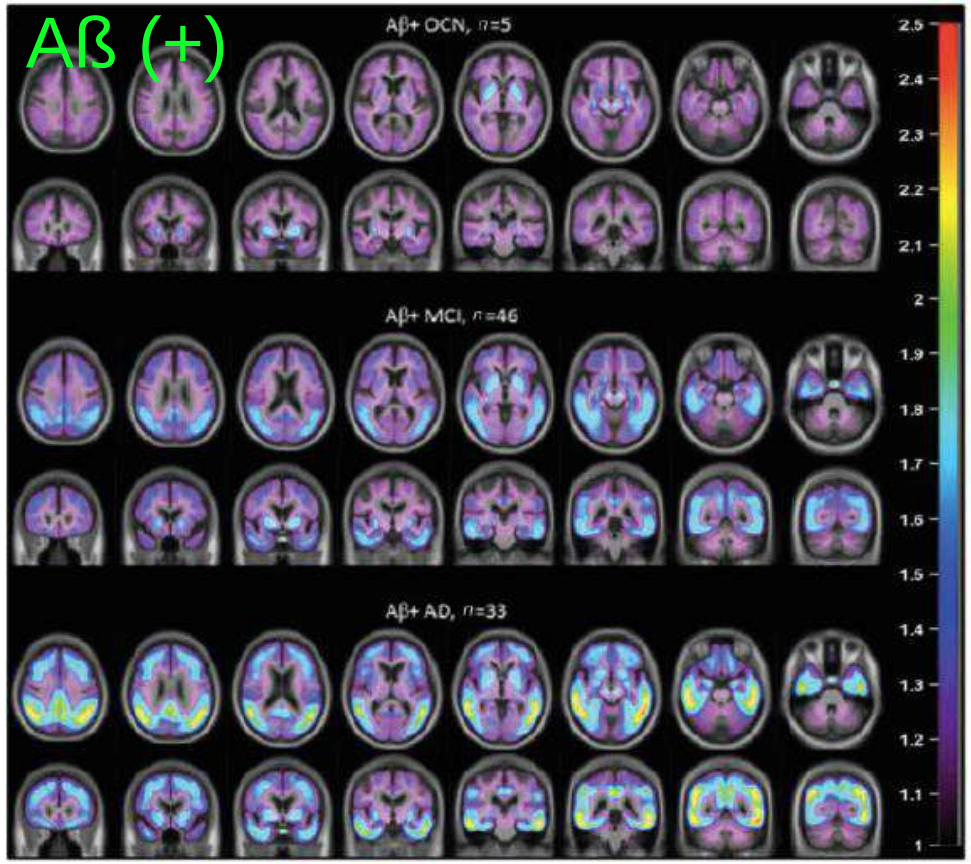
Formas truncadas de tau se transmiten de neurona a neurona.

NATURE REVIEWS | NEUROLOGY

Polanco JC, et al. Nat Rev Neurol. 2017; 14(1): 22-39.

Tau-PET. Topography of tau-pathology





AD (*n* = 48)	MCI (*n* = 95)	OCN (*n* = 58)	YCN (*n* = 16)

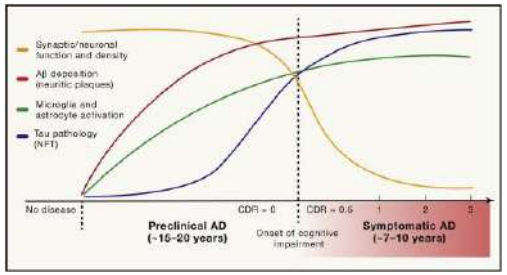
Pontecorvo MJ, et al. Brain 2017; 140: 748-763

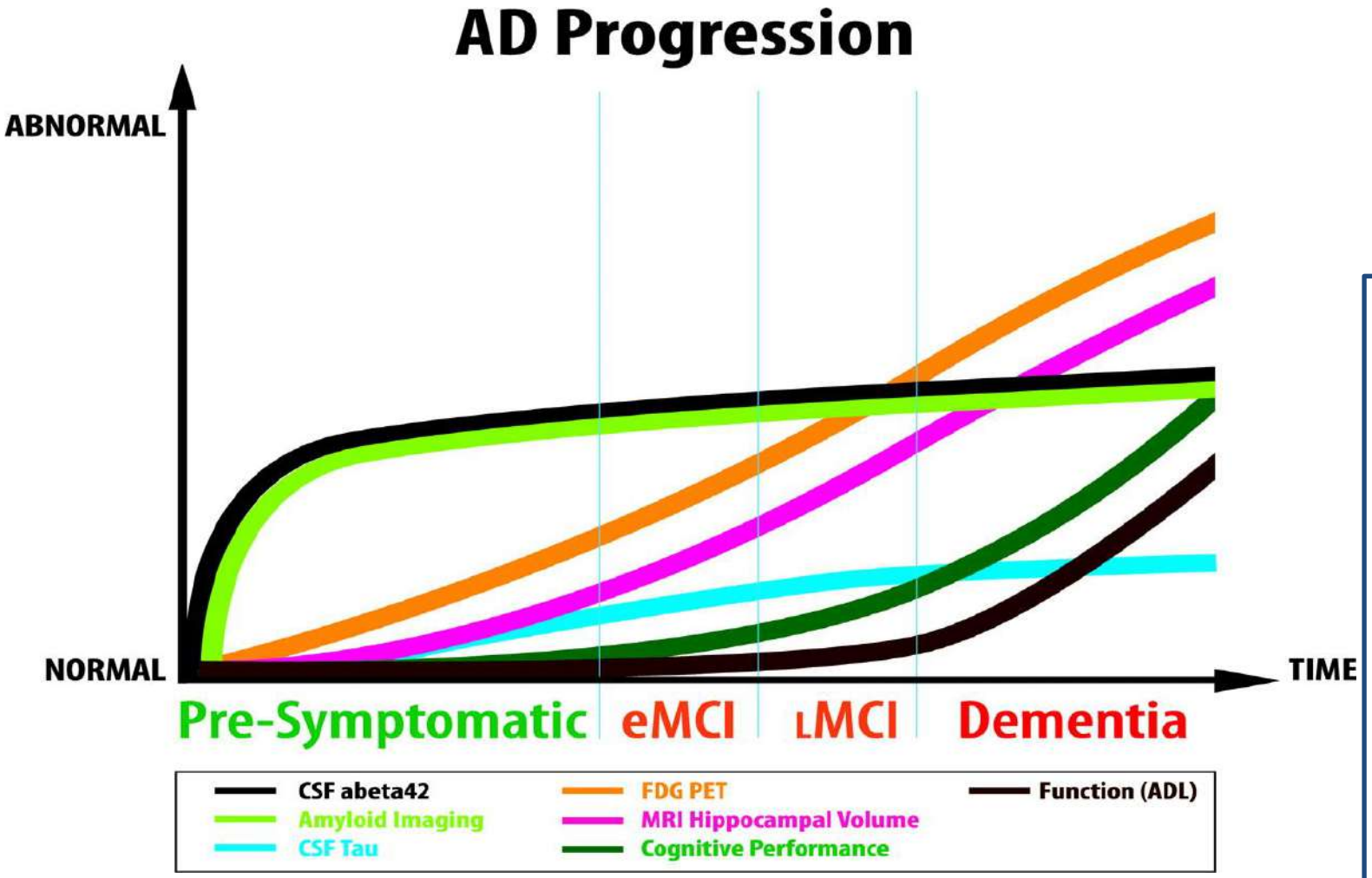
Modelo dinámico-secuencial de biomarcdores. Continuum EA

HOSPITAL CLINIC UNIVERSITARI

Universidad Católica de Valencia San Vicente Mártir

Long y Holtzman (2019) Cell Sep 25





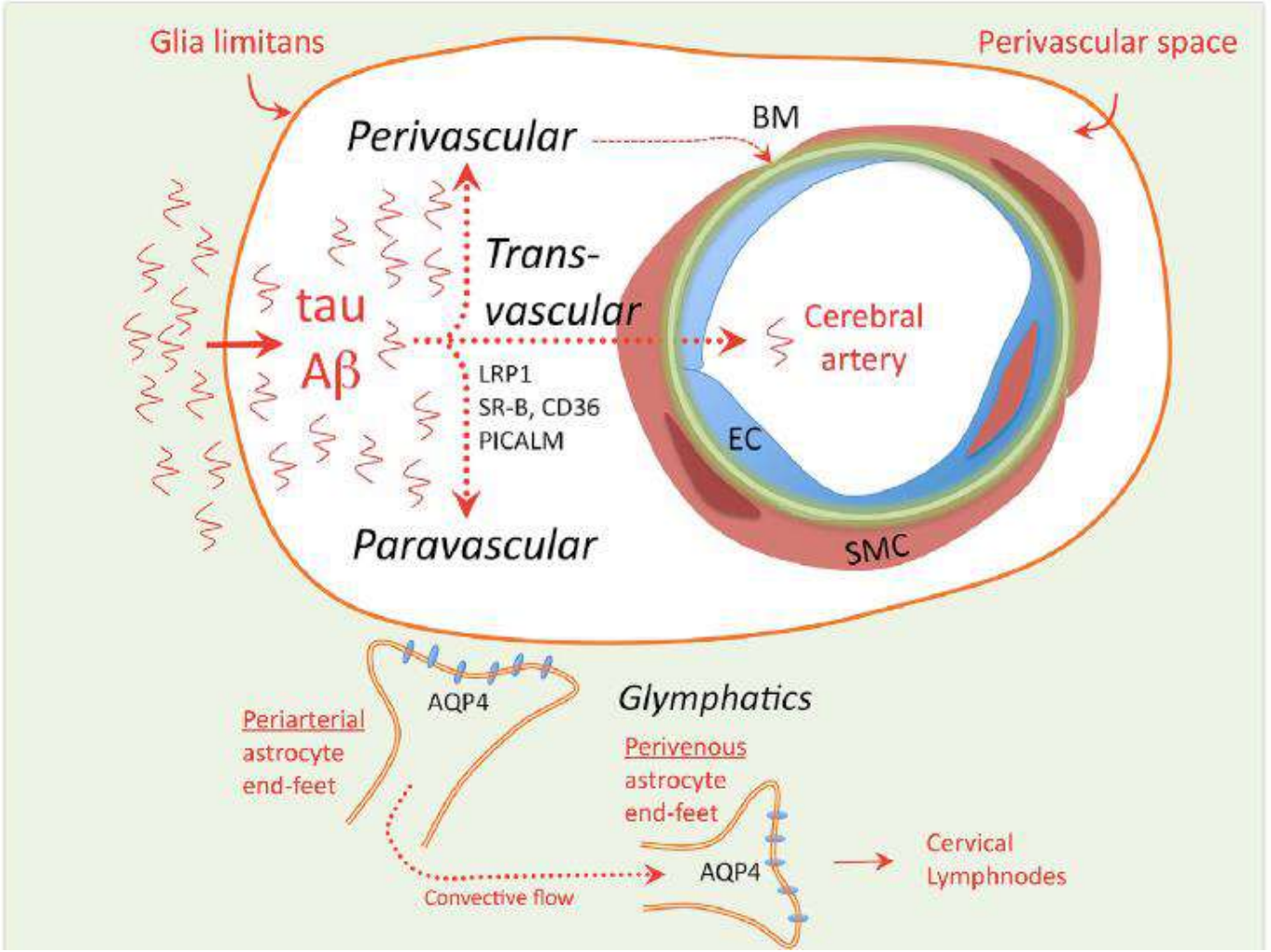
Aisen P et al. Neurology 2011;76:280-286

Causas/desencadenantes
Edad - Envejecimiento
Genética / Epigenética
Inflamación
Salud cerebral – (Vascular)
Copatologías
Comorbilidades
Infecciones
Microbioma
Metabolismo
Traumatismo
Reserva...

Jack CR, et al. Lancet Neurol. 2010;9(1):119-28.

Interacción bidireccional de patologías en la unidad Neuro-vascular

Neuron
Review



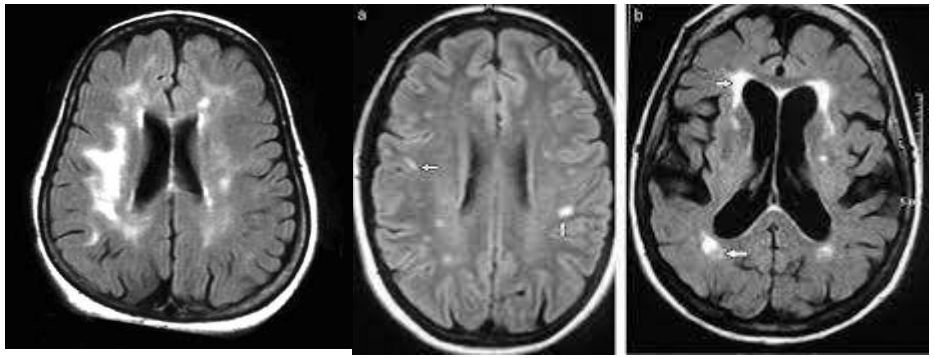
Iadecola C. Neuron 2017; 96(1): 17-42..

HOSPITAL CLINIC UNIVERSITARI

Universidad Católica de Valencia San Vicente Mártir

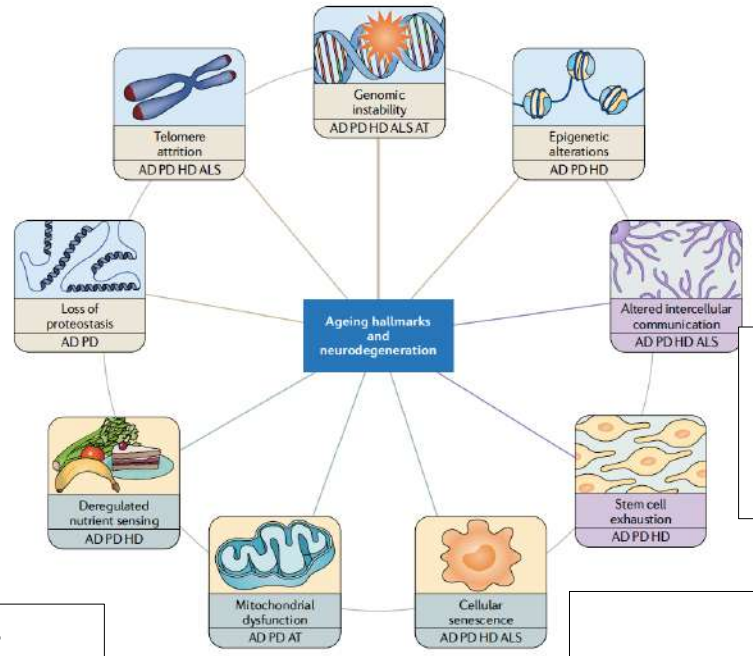
ctaalzheimer

La Patología vascular y la patología alzheimer interaccionan; una favorece la otra y viceversa y juntas producen más afectación clínica



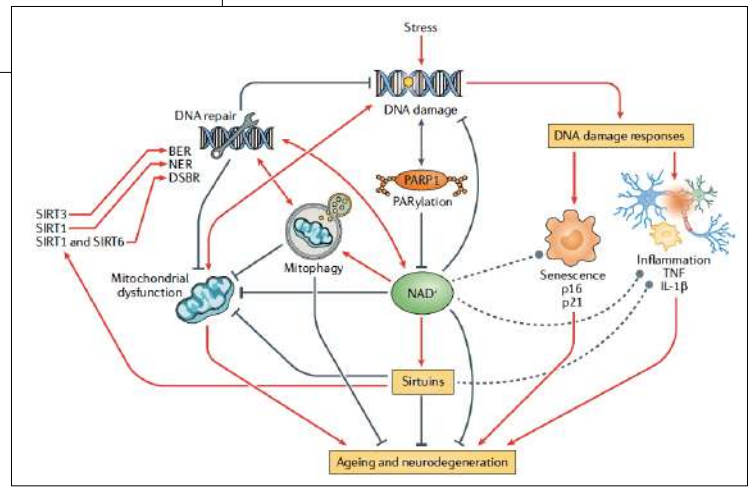
La edad/envejecimiento como factor de riesgo

Inestabilidad genómica
Telómeros
Cambios epigenéticos
Proteostasis



Comunicación intercelular
Inmunidad/inflamación
Neurogénesis

Senescencia celular
Disfunción mitocondrial
Señalización nutricional



Senescencia celular
Condiciones de estrés
Detención del estado proliferativo
Fenotipo secretor pro-inflamatorio
Activación inmunidad innata

Hou Y, et al. Nature Rev Neurol 2019; 15: 565-582.

Las personas (normales) con mejor reserva cognitiva tienen mejor cognición y menos alzheimer pre-clínico

HOSPITAL CLINIC

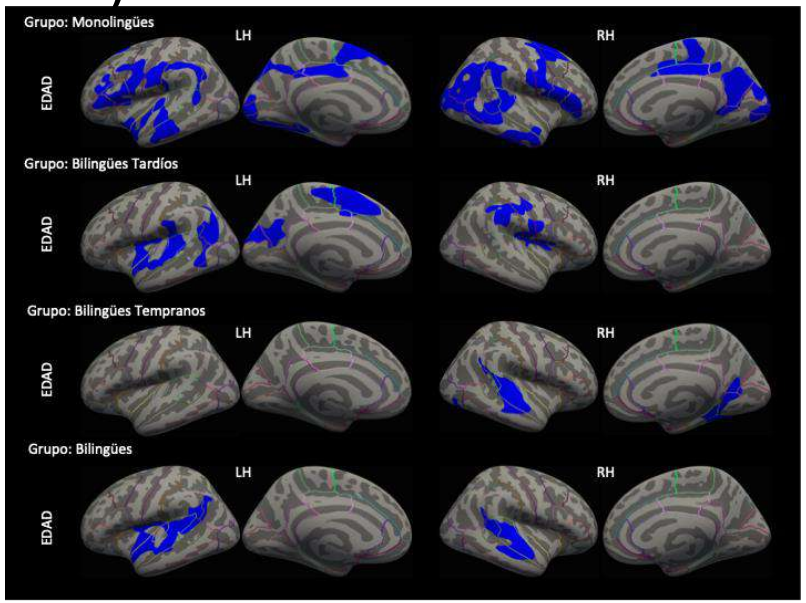
Beneficial effect of bilingualism on Alzheimer's disease CSF biomarkers and cognition

Ainara Estanga [a], Mirian Ecay-Torres [a], Almudena Ibañez [a], Andrea Izagirre [a], Jorge Villanua [b,c], Maite Garcia-Sebastian [b], M. Teresa Iglesias Gaspar [d], Ane Otaegui-Arrazola [a], Ane Iriondo [a], Monserrat Clerigue [a], Pablo Martinez-Lage [a,*]

Table 3
CSF biomarkers result comparison between monolinguals and early and late bilinguals

CSF data	Descriptives data			Generalized models			
	Monolinguals (n = 59)	Late bilinguals (n = 52)	Early bilinguals (n = 55)	Monolinguals versus late bilinguals		Monolinguals versus early bilinguals	
				B	p[a]	B	p[a]
Aβ1–42 pg/mL	853.39 (252.94)	846.03 (239.62)	819.70 (176.94)	−46.25	0.26	−60.38	0.14
t-tau pg/mL	240.49 (104.29)	237.10 (82.71)	198.18 (66.22)	0.23	0.99	−35.15	0.019[b]
p-tau pg/mL	45.49 (16.15)	45.69 (13.25)	40.64 (11.64)	−0.60	0.81	−3.88	0.11
t-tau/Aβ1–42 ratio	0.31 (0.22)	0.31 (0.18)	0.25 (0.12)	0.02	0.37	−0.03	0.24
p-tau/Aβ1–42 ratio	0.06 (0.03)	0.06 (0.03)	0.05 (0.02)	0.006	0.19	−0.002	0.65
Preclinical AD CSF stage, No. (%)							
Stage 0	44 (74.6%)	35 (67.3%)	51 (92.7%)	0.51	0.27	−1.63	0.02[b]
Stage 1	7 (11.9%)	9 (17.3%)	2 (3.6%)				
Stage 2	4 (6.8%)	1 (1.9%)	1 (1.8%)				
SNAP	4 (6.8%)	7 (13.5%)	1 (1.8%)				

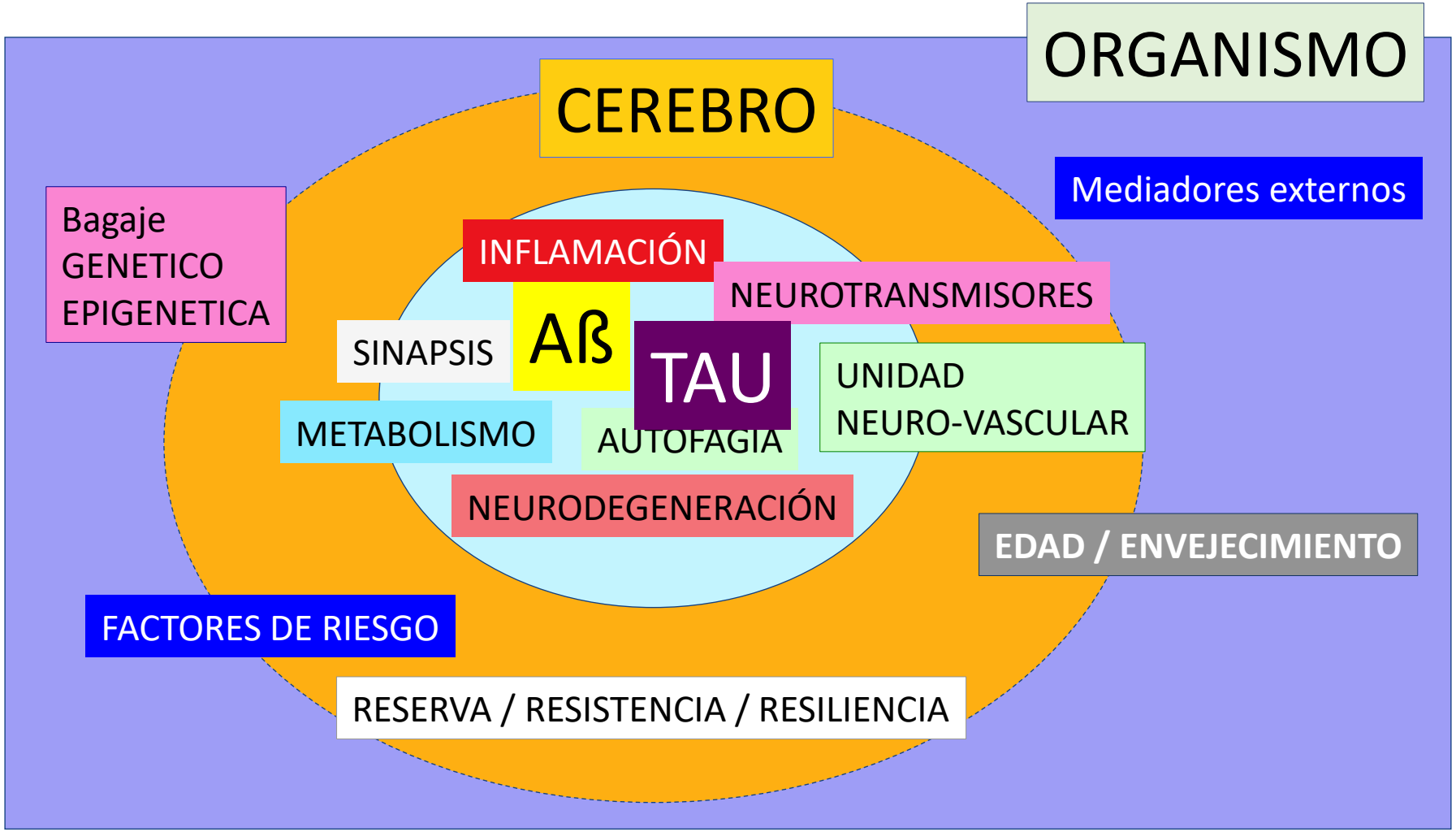
Correlación con la edad en cada grupo (sujetos con Fazekas=0; covariables sexo y vocabulario)

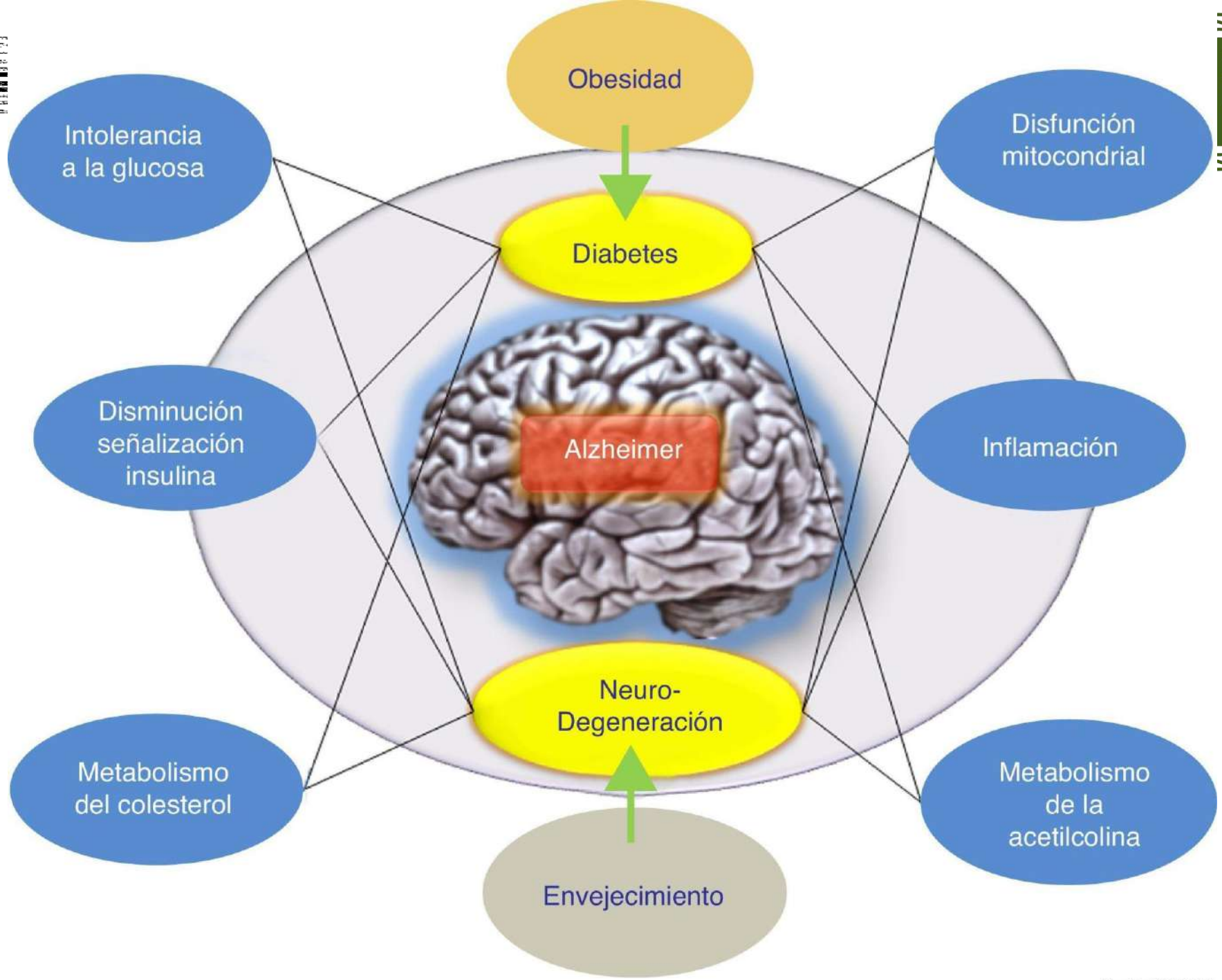


El bilingüismo "modera" la relación entre edad y grosor cortical

Estanga A, et al. Neurobiology of aging 2017; 50: 144-151

Puzzle etiopatogénico de la EA





Neurologia. 2018;33:47–58

Diana: Amiloide

Diana: Disminuir agregación-oligómeros

"ANTIAGREGANTES" DE AMILOIDE

- Tramiprosato/Gammataurina (Alzhemed)
- Clioquinol
- Scilo-inositol
- PBT2

Diana: Amiloide, disminuir formación

INHIBIDORES de GAMMA-SECRETASA

Semagacestat
Avagacestat

INHIBIDORES de ß-SECRETASA (BACE)

Verubecestat
Lanabacestat
Atabecestat
Elenbecestat
Umibecestat

Long JM, Holtzman DM. Cell 2019; 176: 312-339
Liu PP, et al. Signal Transduction and Targeted Therapy (2019) 4:29
Yiannopoulou KG, Papagiorgiou SG. Journal of Central Nervous System Disease 2020; 12: 1–12

Diana: Amiloide, eliminación, inmunoterapia

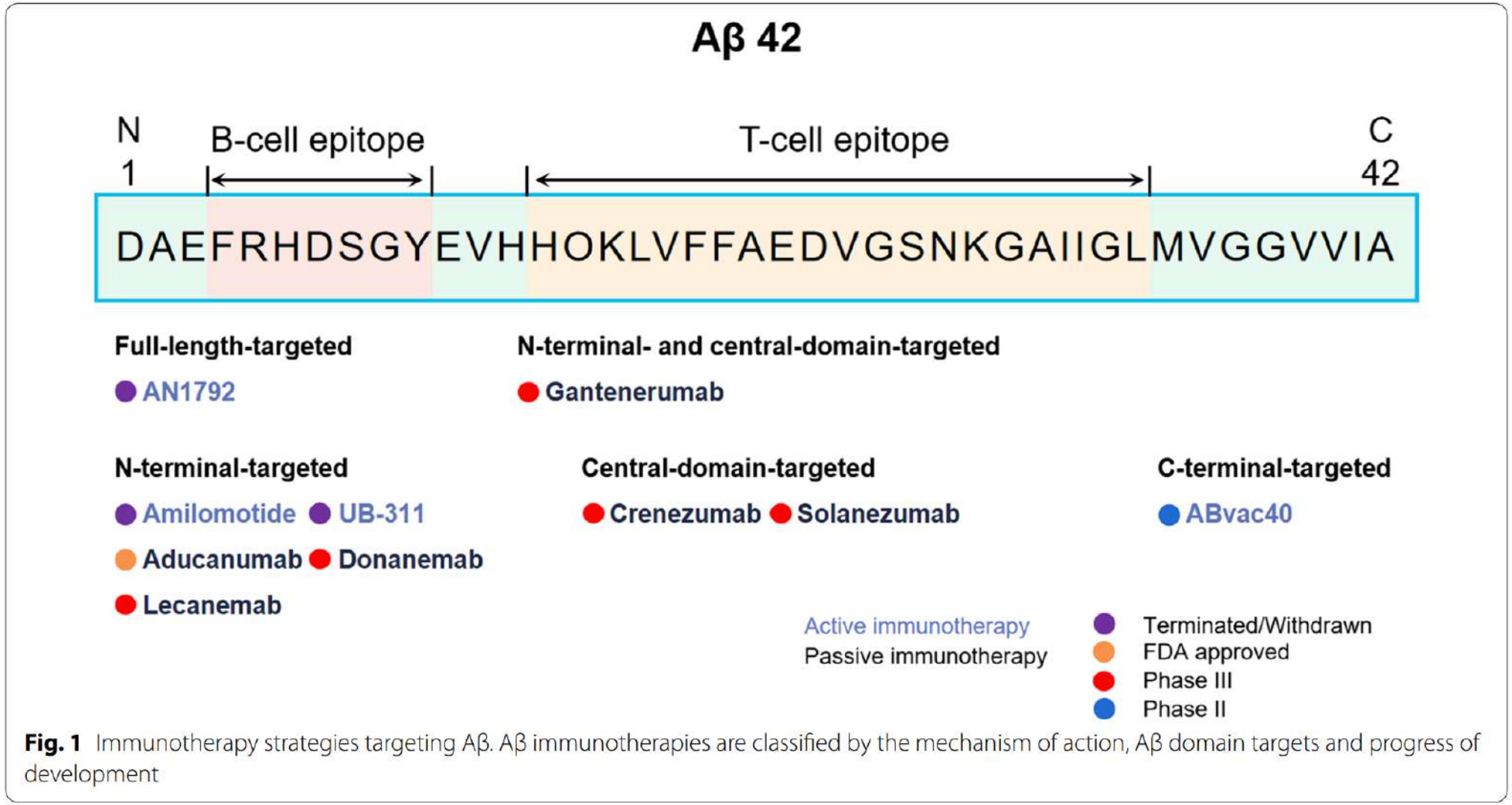


Fig. 1 Immunotherapy strategies targeting Aβ. Aβ immunotherapies are classified by the mechanism of action, Aβ domain targets and progress of development

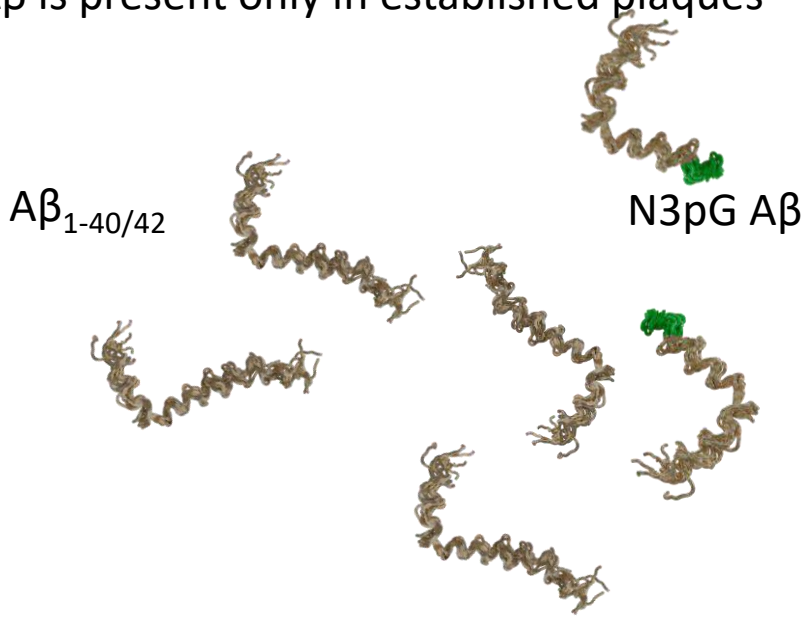
Song et al. Translational Neurodegeneration (2022) 11:18

Composition of Aβ Plaques

Amyloid plaques comprise a heterogenous mixture of post-translationally modified Aβ peptides[1,2]

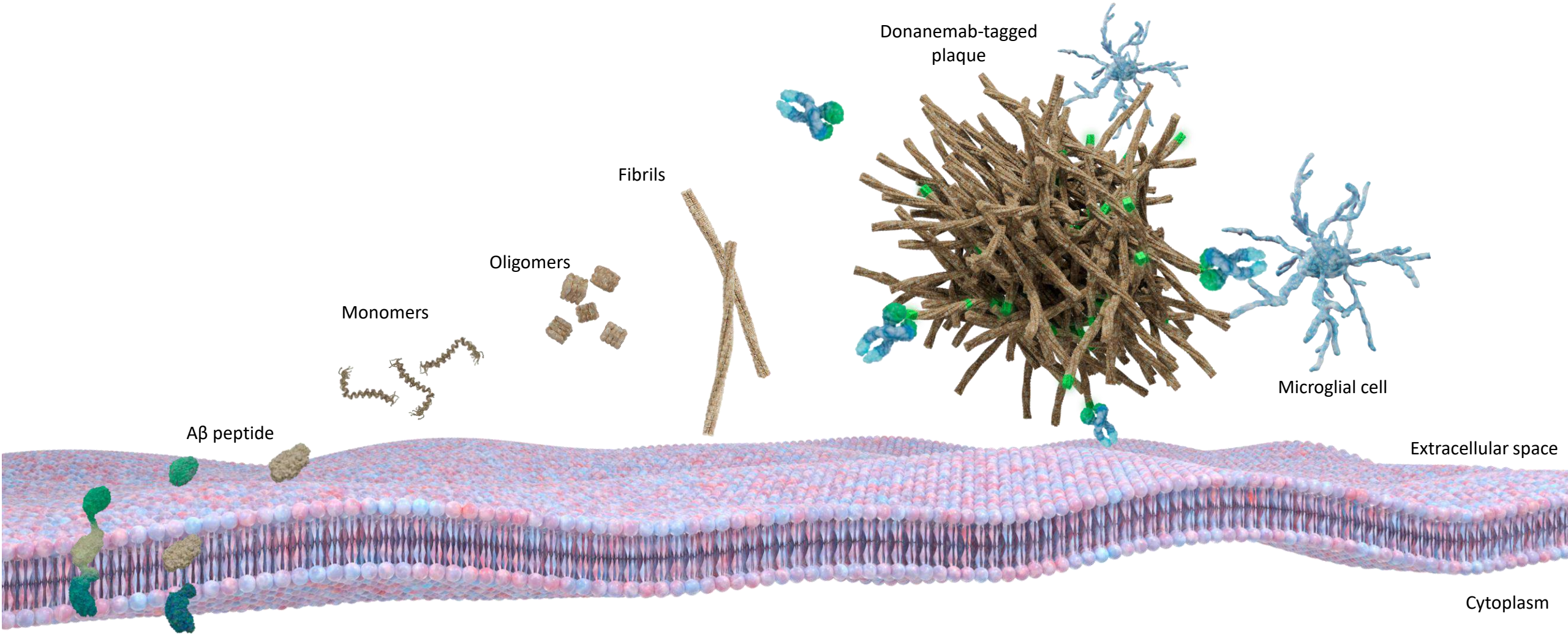
The isoforms $Aβ_{40}$ and $Aβ_{42}$, and N-terminal variants (eg, N3pG Aβ), are the primary constituents of amyloid plaques found in patients with AD[2-4]

N3pG Aβ is present only in established plaques[3,4]



1. Dammers C, et al. *Biophys J*. 2017;112(8):1621-1633. 2. Bayer TA. *Mol Psychiatry*. 2021;doi:10.1038/s41380-021-01409-2. 3. Portelius E, et al. *Acta Neuropathol*. 2010;120:185-193. 4. DeMattos RB, et al. *Neuron*. 2012;76(5):908-920.

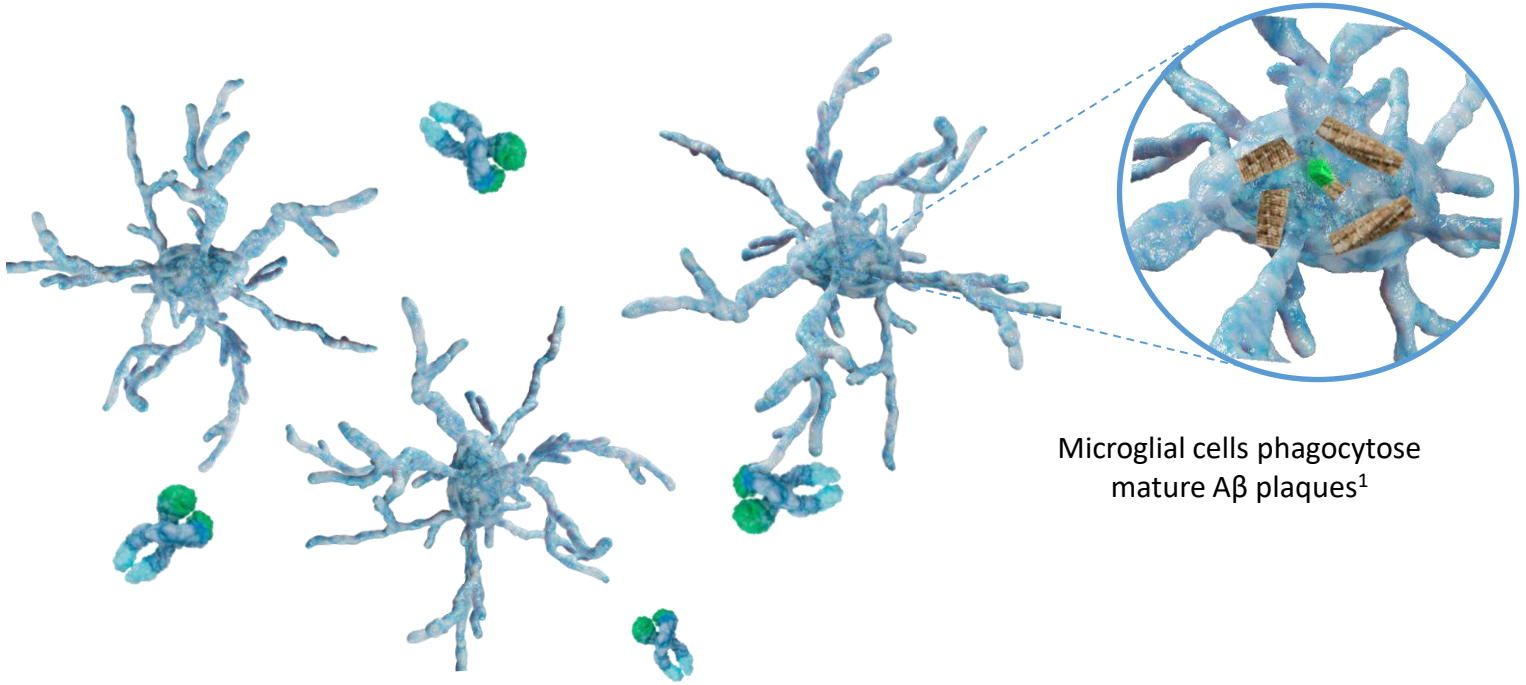
Aβ Plaque Initiates Phagocytosis by Microglia[1–3]



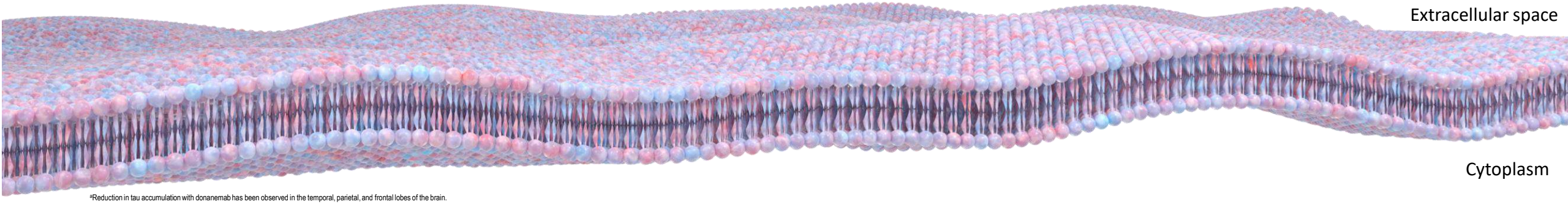
1. DeMattos RB, et al. *Neuron.* 2012;76(5):908-920. 2. Drolle E, et al. *Drug Metab Rev.* 2014;46(2):207-223. 3. Kent SA, et al. *Acta Neuropathol.* 2020;140(4):417-447.

Clearance of Aβ Plaques by Microglia May Slow the Progression of AD

By clearing mature Aβ plaques, treatment may lead to a reduction in other AD-related pathologies, eg, reduction in tau accumulation,[a] neuronal damage, and synaptic loss[1-4]



Microglial cells phagocytose mature Aβ plaques[1]

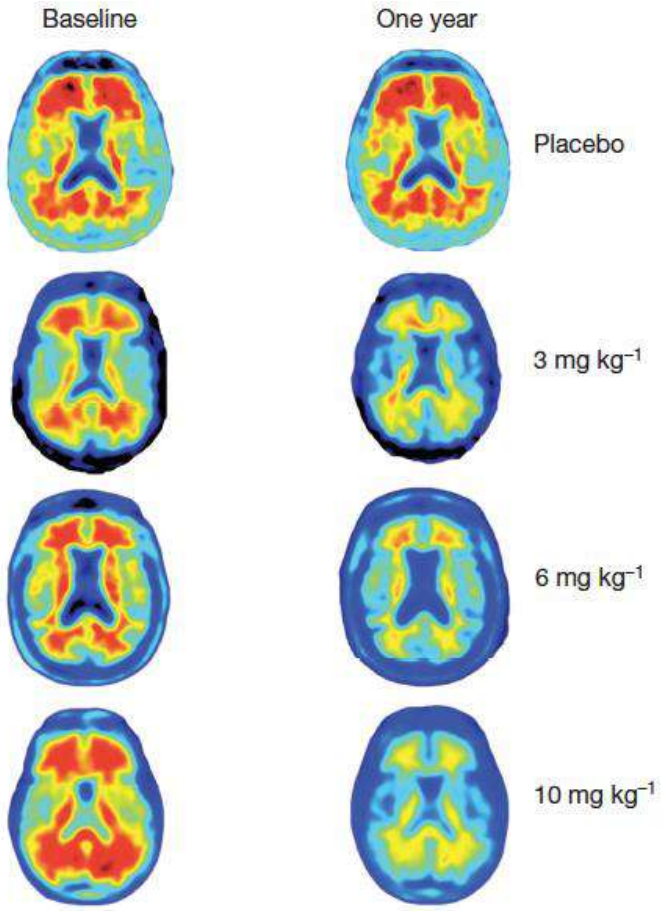


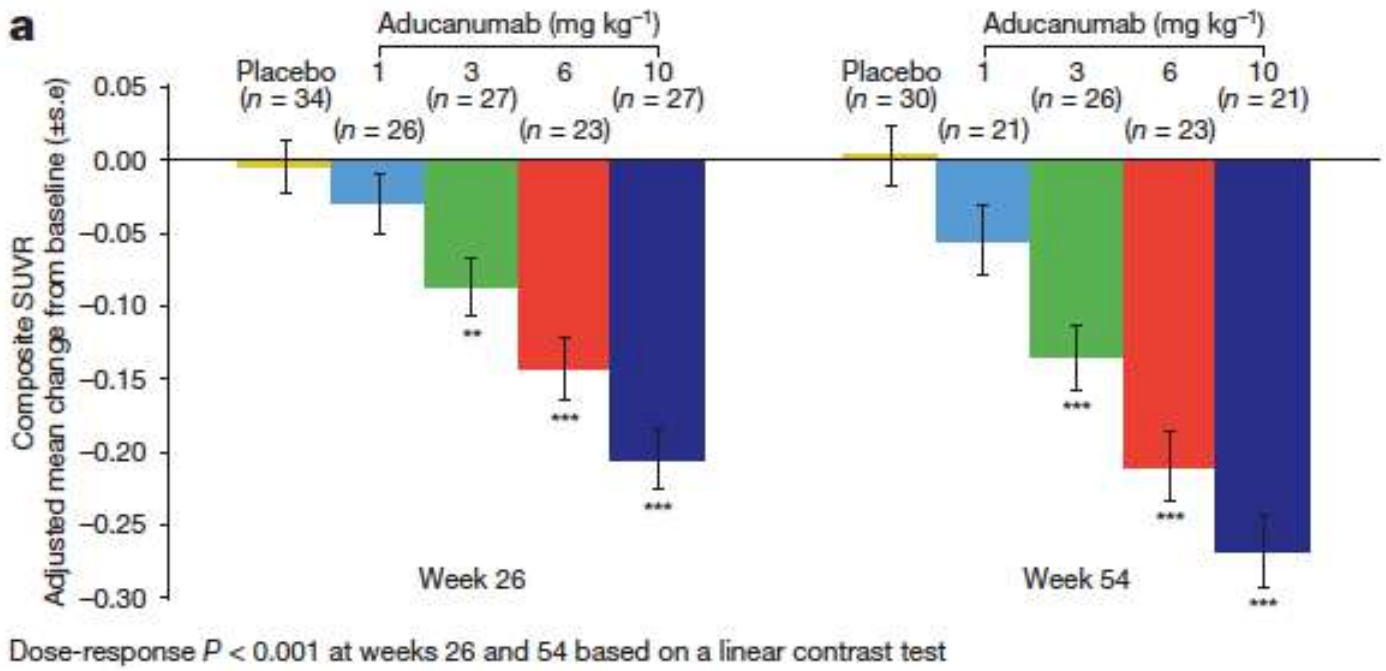
[a]Reduction in tau accumulation with donanemab has been observed in the temporal, parietal, and frontal lobes of the brain.

1. DeMattos RB, et al. *Neuron*. 2012;76(5):908-920. 2. Mintun MA, et al. *N Engl J Med*. 2021;384(18):1691-1704. 3. Jawhar S, et al. *J Biol Chem*. 2011;286(45):38825-38832. 4. Sims JR, et al. Oral presentation at: *AAIC 2021*.

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§



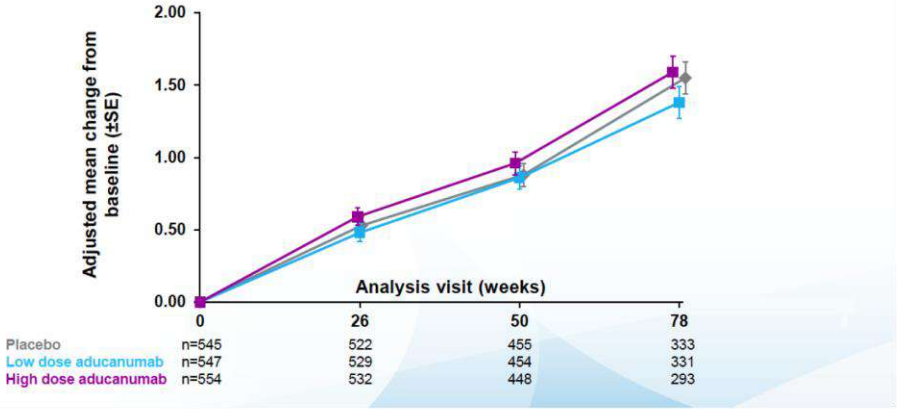


Dose-response $P < 0.001$ at weeks 26 and 54 based on a linear contrast test

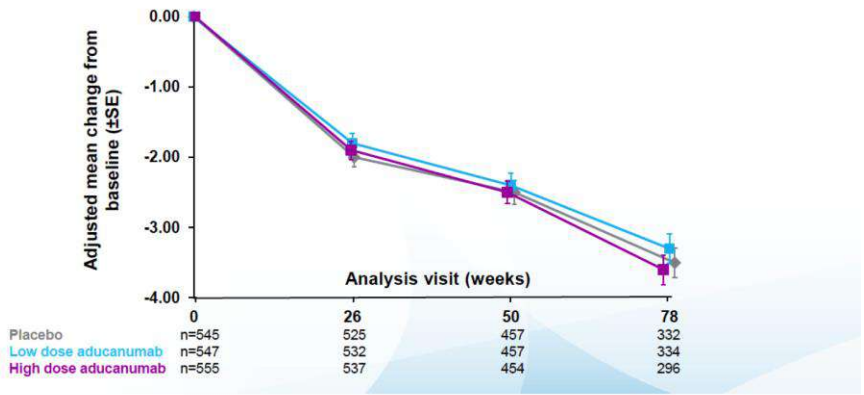
Sevigny J et al. Nature 2017; 537:50-56

Aducanumab. Ensayo ENGAGE (Negativo).

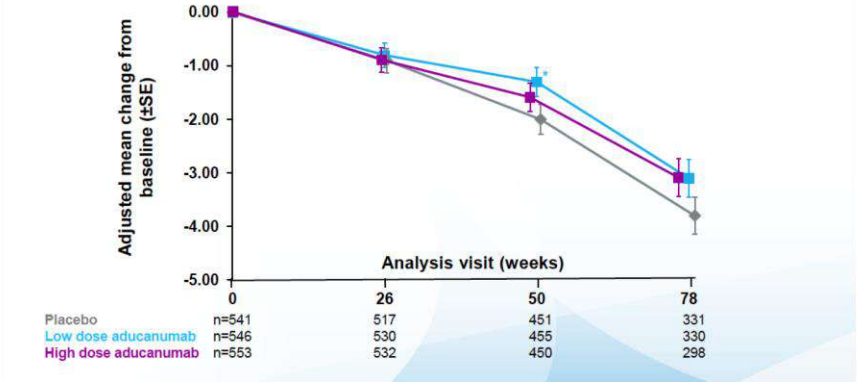
ENGAGE: Longitudinal change from baseline in CDR-SB



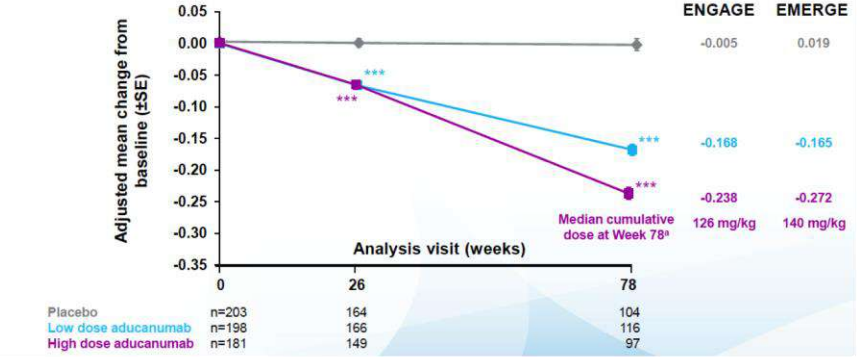
ENGAGE: Longitudinal change from baseline in MMSE



ENGAGE: Longitudinal change from baseline in ADCS-ADL-MCI



ENGAGE: Longitudinal change from baseline in amyloid PET SUVR

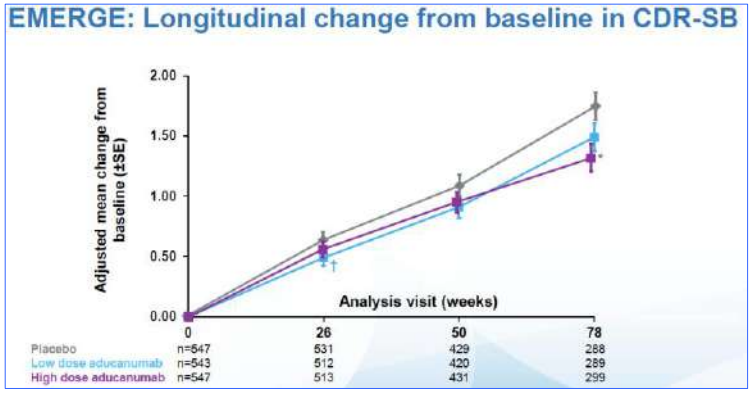


Aducanumab. Ensayo EMERGE (positivo).

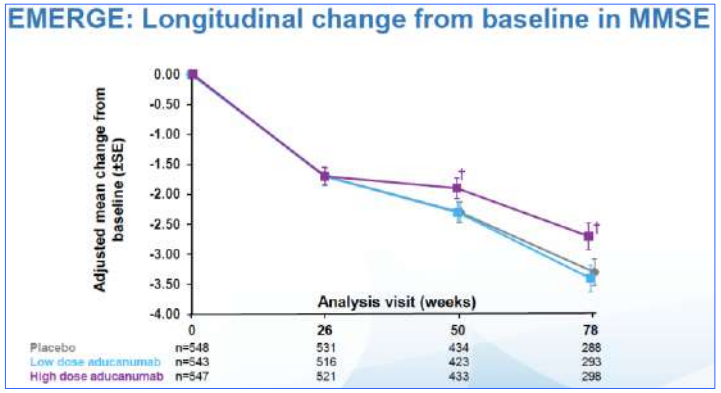
EMERGE: Primary and secondary endpoints from final data set at Week 78

	Placebo decline (n=548)	Difference vs. placebo (%)[a] p-value	
		Low dose (n=543)	High dose (n=547)
CDR-SB	1.74	**-0.26** (-15%) 0.0901	**-0.39** (-22%) 0.0120
MMSE	-3.3	**-0.1** (3%) 0.7578	**0.6** (-18%) 0.0493
ADAS-Cog 13	5.162	**-0.701** (-14%) 0.1962	**-1.400** (-27%) 0.0097
ADCS-ADL-MCI	-4.3	**0.7** (-16%) 0.1515	**1.7** (-40%) 0.0006

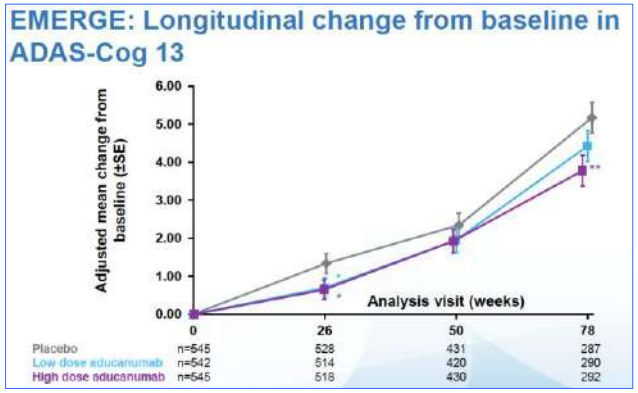
EMERGE: Longitudinal change from baseline in CDR-SB



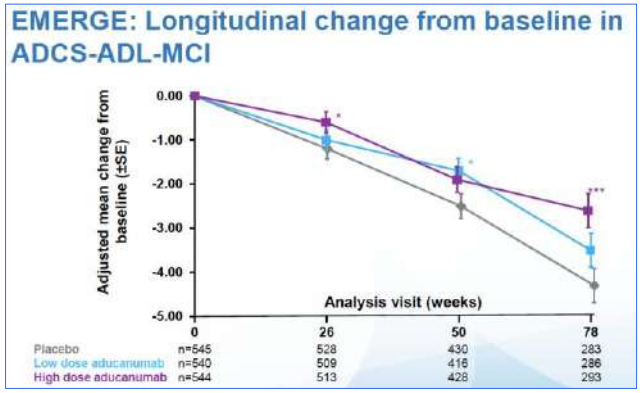
EMERGE: Longitudinal change from baseline in MMSE



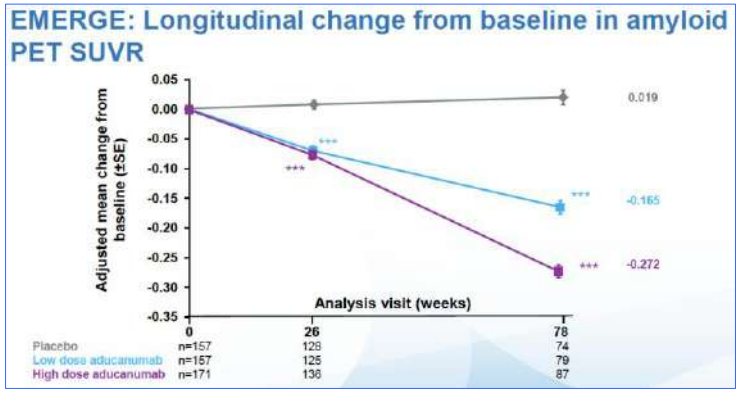
EMERGE: Longitudinal change from baseline in ADAS-Cog 13



EMERGE: Longitudinal change from baseline in ADCS-ADL-MCI



EMERGE: Longitudinal change from baseline in amyloid PET SUVR

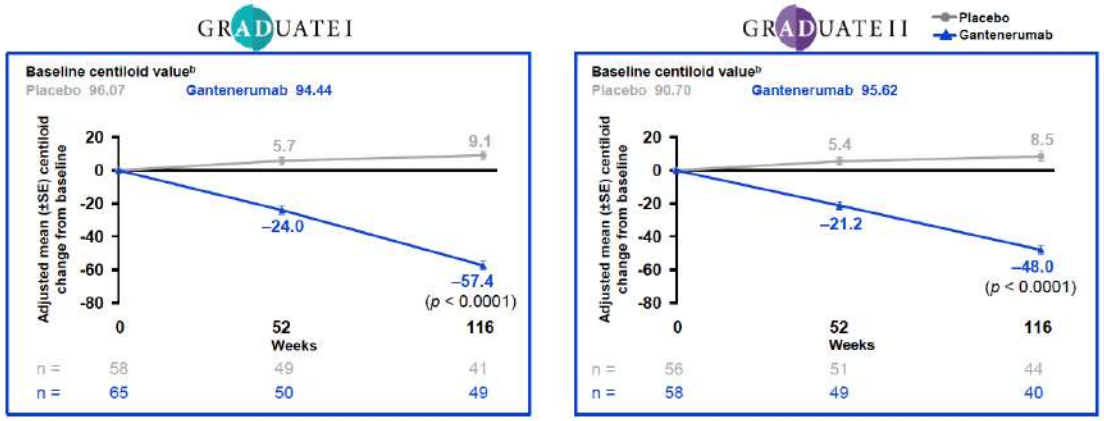


https://www.alzforum.org/news/conference-coverage/exposure-exposure-exposure-ctad-aducanumab-scientists-make-cas;
https://investors.biogen.com/static-files/8e58afa4-ba37-4250-9a78-2ecfb63b1dcb;

Phase III Trials of Subcutaneous Gantenerumab

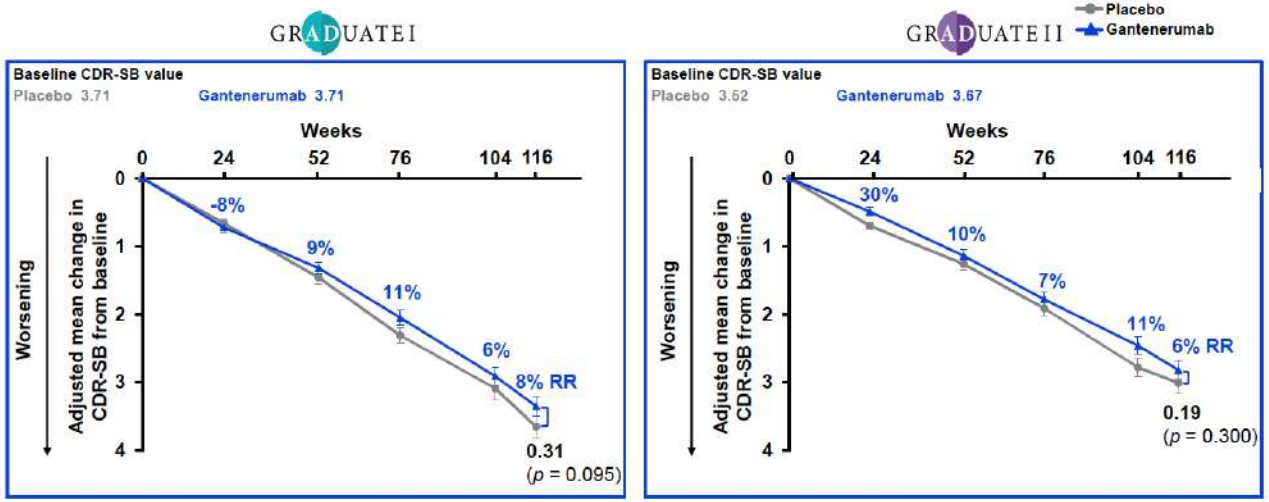
Amyloid PET change from baseline

Gantenerumab significantly reduced amyloid plaque but below expectations[a]



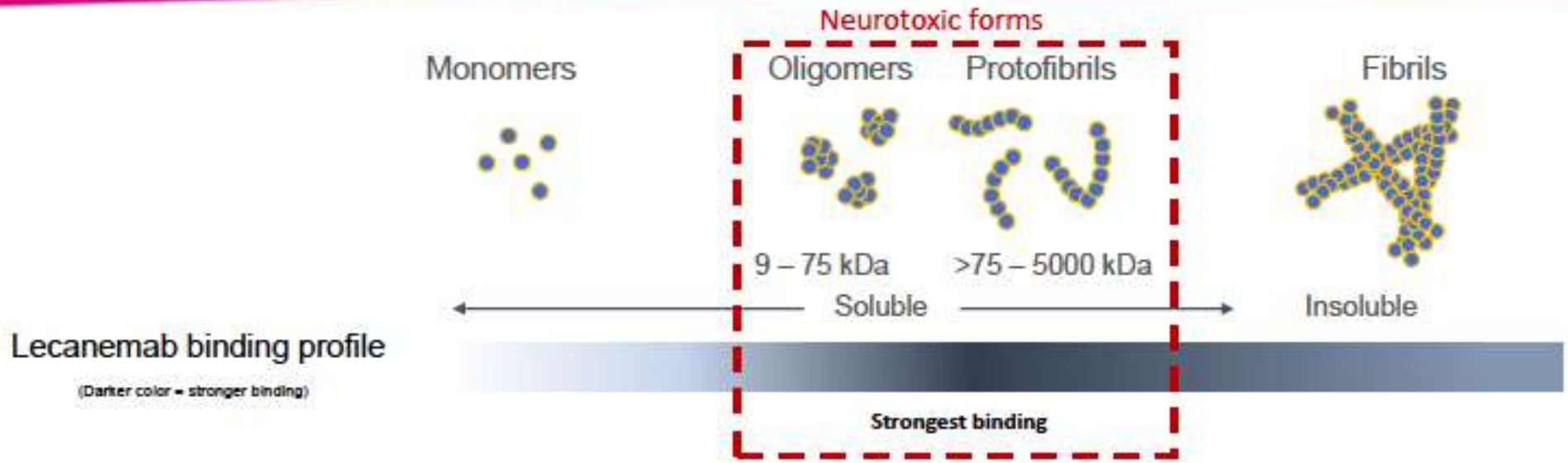
GRADUATE I and II did not meet the primary endpoint of change from baseline on CDR-SB at Week 116

Non-significant trend towards clinical effect of 6–8% relative reduction across studies



Lecanemab: Unique Selectivity Towards Toxic Soluble Species of Aβ

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



Aβ pathway in Alzheimer's Disease

- Aβ dynamically evolves through different conformational states, including:[1,2]
  - Soluble monomers
  - Soluble aggregates of increasing size (eg, dimers, trimers, oligomers, protofibrils)
  - Protofibrils are defined as large (>75-100kDa), soluble, aggregated Aβ filaments[1]
  - Insoluble fibrils and amyloid plaques
- Recent studies have garnered considerable interest in the role of protofibrils in the pathophysiology of Alzheimer's disease[2-4]

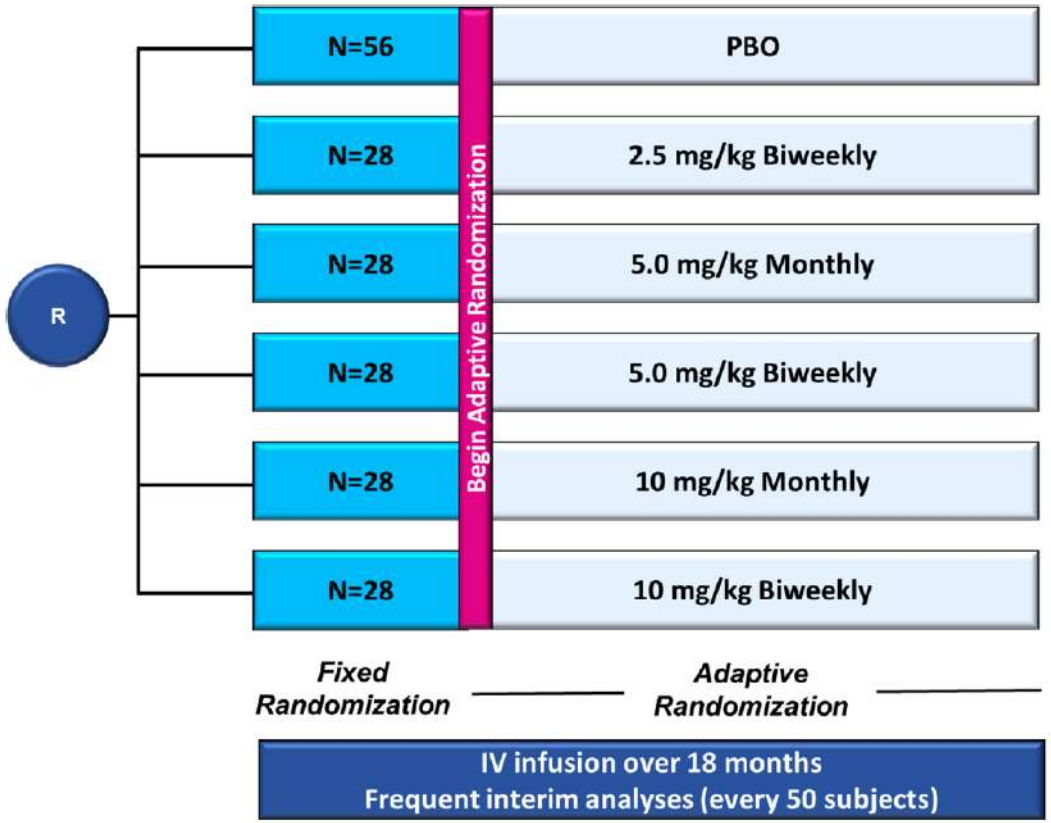
Lecanemab

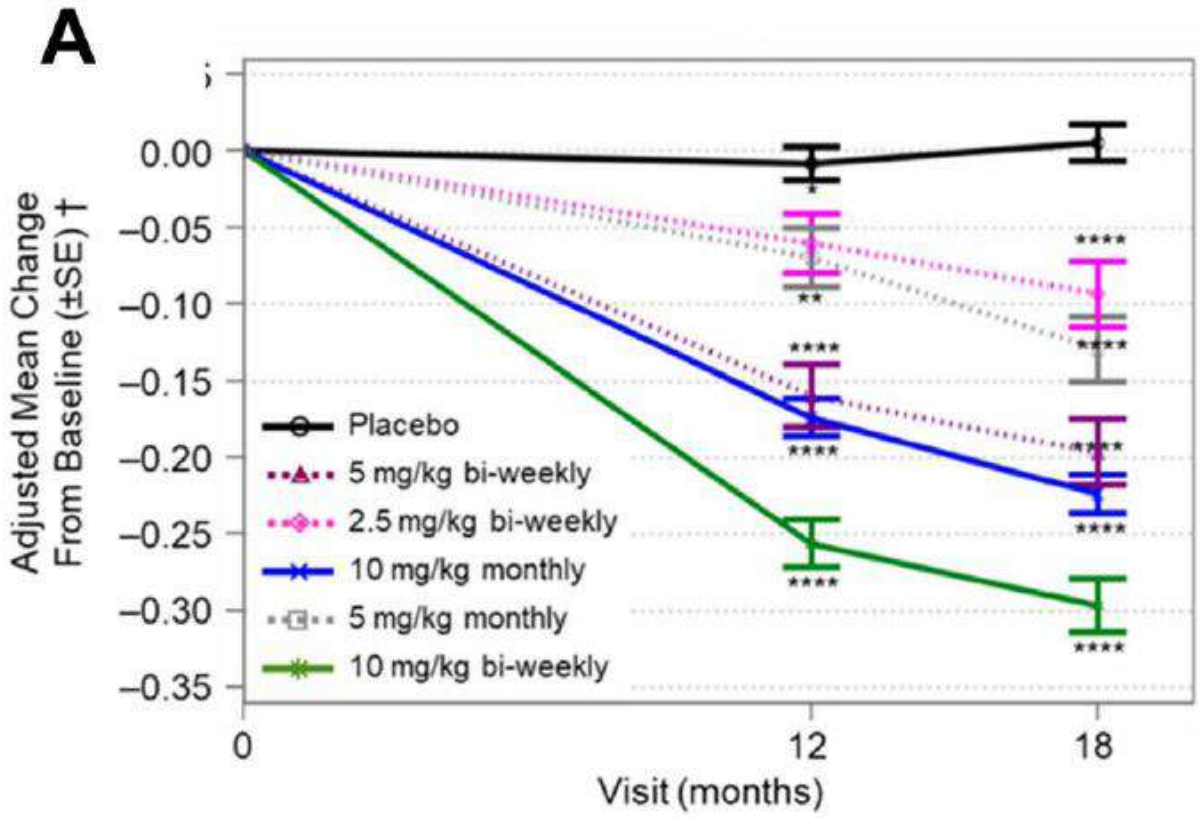
- Lecanemab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody
- Selectively binds to soluble Aβ aggregate species
  - >1000-fold selectivity for protofibrils over Aβ monomers (low affinity for Aβ monomer[5])
  - Preferential activity for Aβ protofibrils over fibrils (>10x)[6-10]
- Initiates 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. 10. Söderberg L, et al. *Neurotherapeutics*. 2022 Oct 17. Epub ahead of print.

Estudio 201 fase 2 con Lecanemab en enfermedad de Alzheimer





Swanson et al. Alz Res & Ther 2021; 13:80

CLARITY – Estudio fase 3 de Lecanemab en enfermedad de Alzheimer

HOSPITAL CLINIC UNIVERSITARI

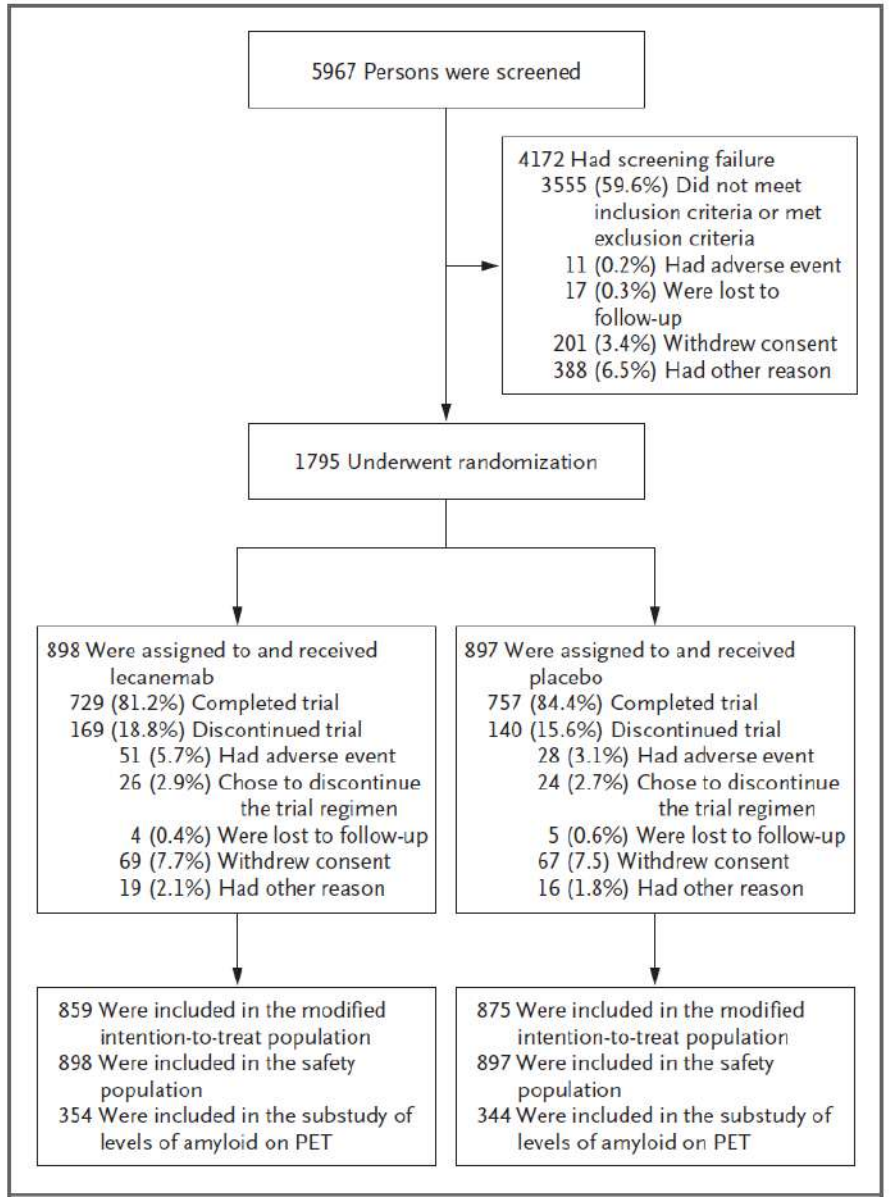
Universidad Católica de Valencia San Vicente Mártir

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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



Van Dick et al. N Eng J Med 2022

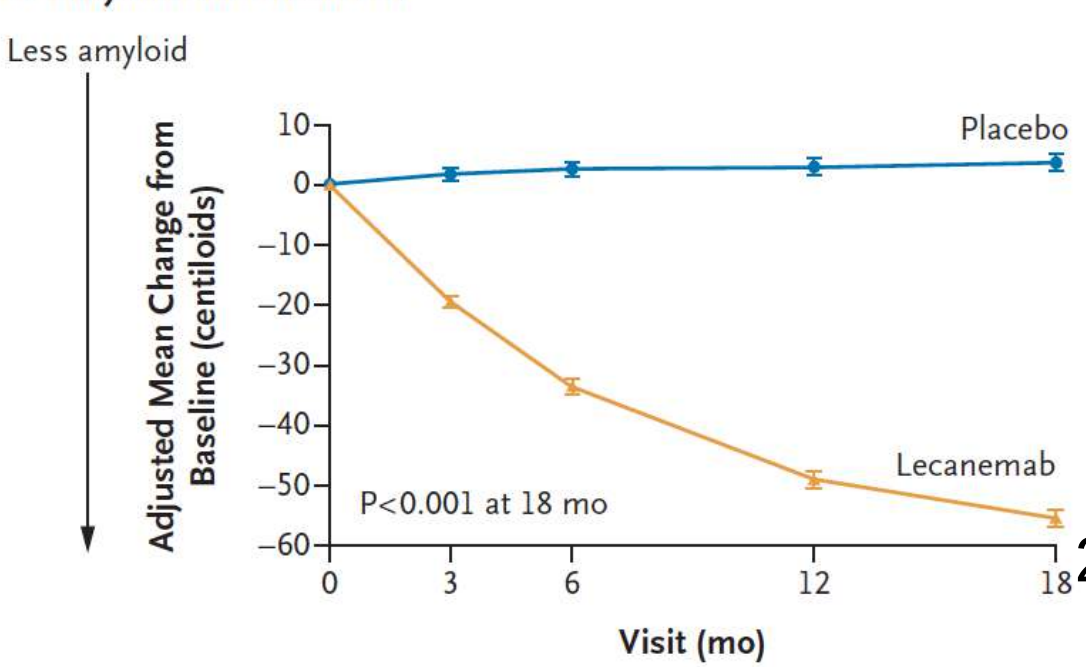
CLARITY – Estudio fase 3 de Lecanemab en enfermedad de Alzheimer

HOSPITAL CLINIC UNIVERSITARI

Universidad Católica de Valencia San Vicente Mártir

ctad alzheimer

B Amyloid Burden on PET



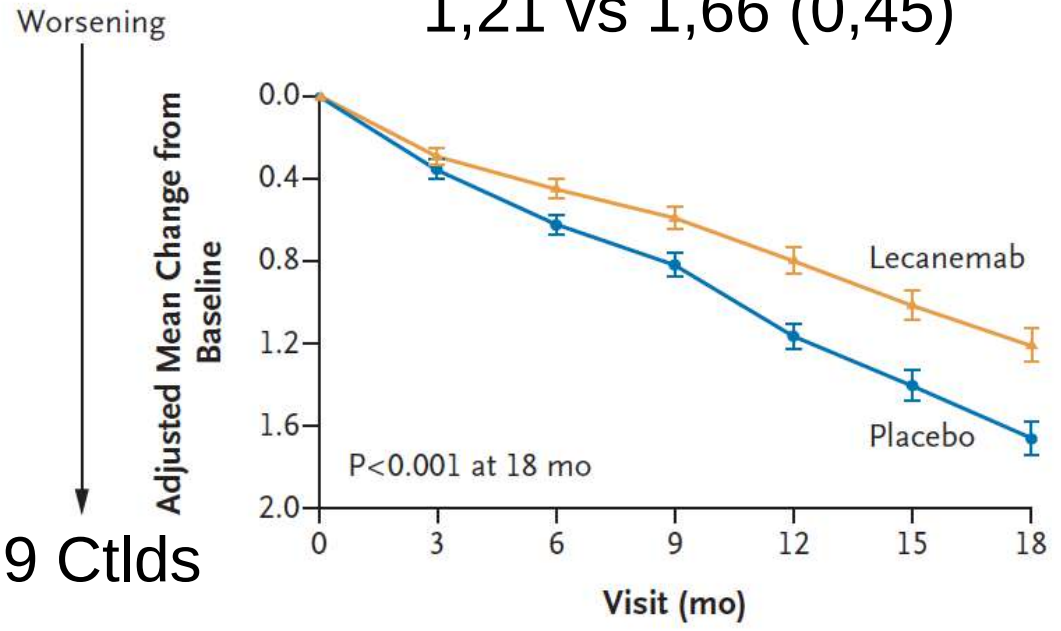
No. of Participants

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

22,9 Ctlds

CDR-SB Score

1,21 vs 1,66 (0,45)



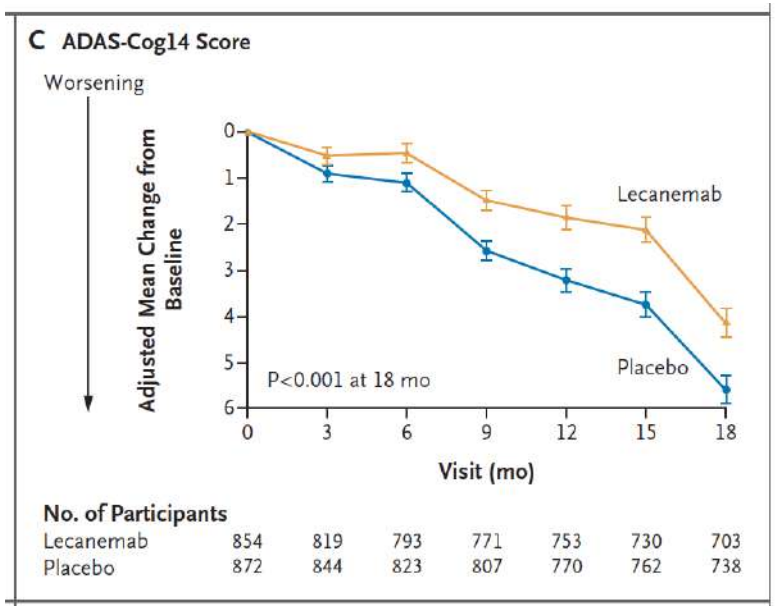
No. of Participants

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

Van Dick et al. N Eng J Med 2022

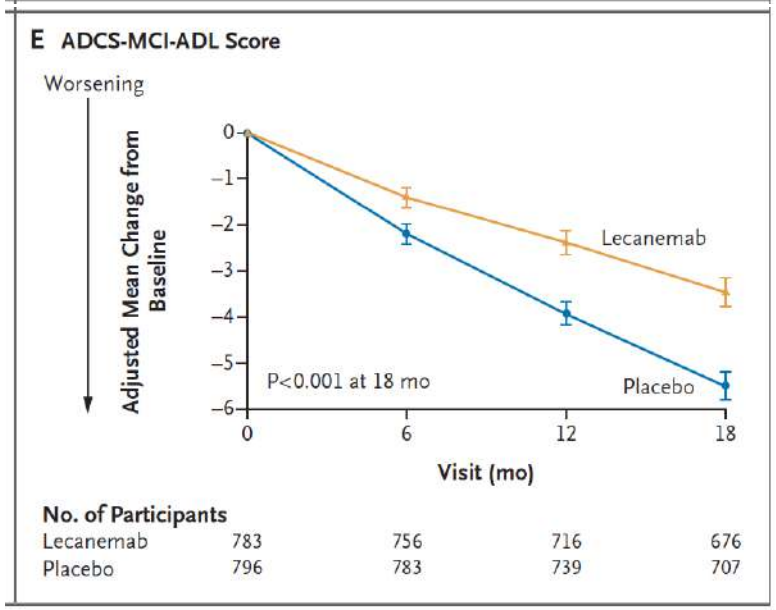
CLARITY – Estudio fase 3 de Lecanemab en enfermedad de Alzheimer

Rango (0-90)



- 1,44 (95% CI, −2.27 to −0.61; P<0.001)

Rango (0-53)



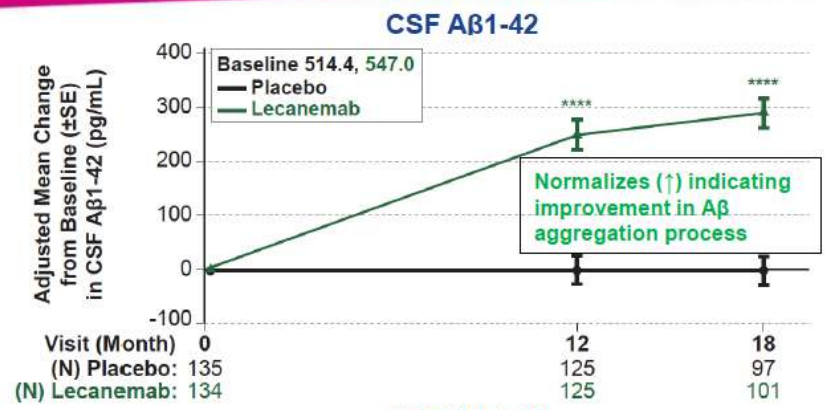
2.0 (95% CI, 1.2 to 2.8; P<0.001)

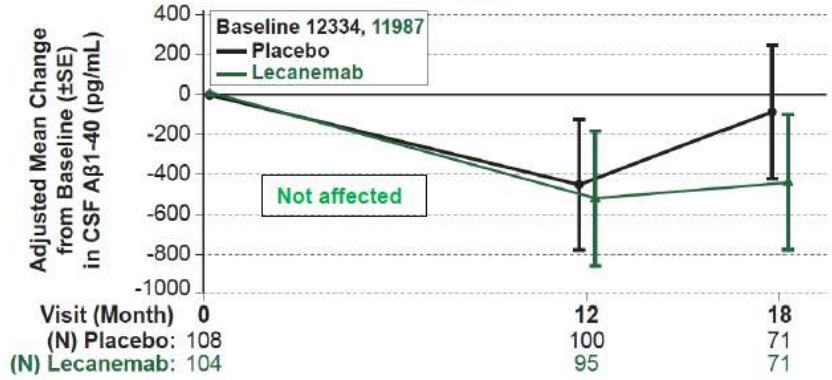
Van Dick et al. N Eng J Med 2022

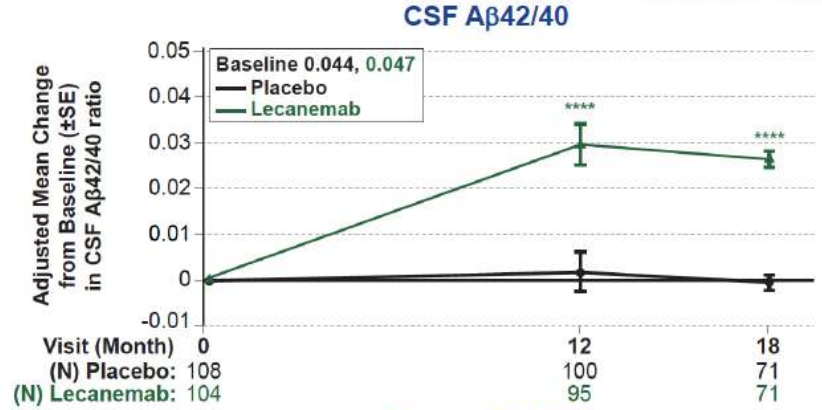
CLARITY – Estudio fase 3 de Lecanemab en enfermedad de Alzheimer Biomarcadores. Amiloide

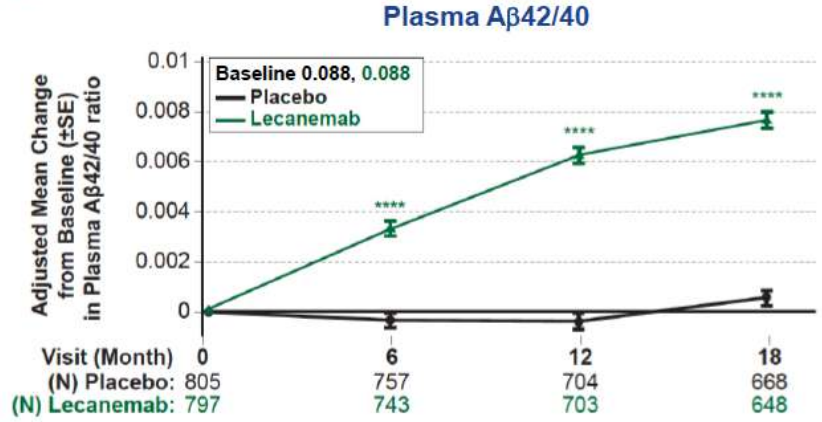
Amyloid Biomarkers

CSF and Plasma Aβ42/40 Improves Indicating Early/Sustained Amyloid Reversal Effects





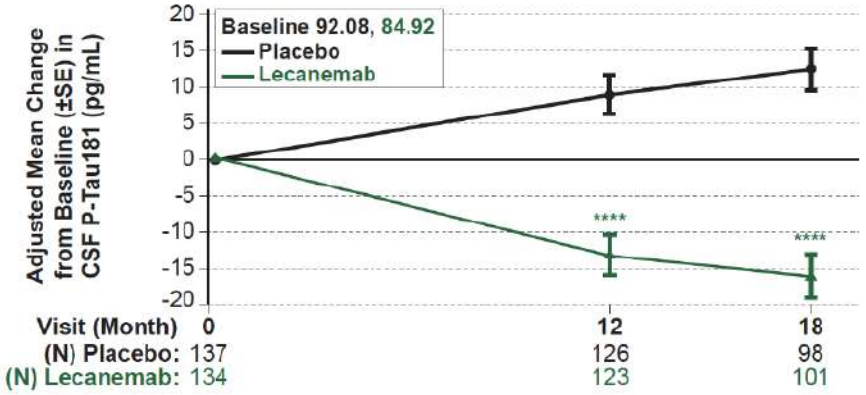




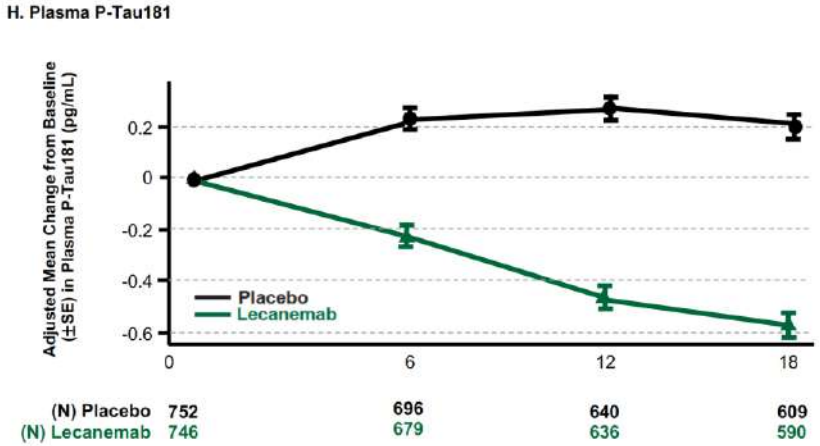
52 **** P<0.0001 Aβ, amyloid beta; CSF, cerebrospinal fluid, SE, standard error.

CLARITY – Estudio fase 3 de Lecanemab en enfermedad de Alzheimer
Biomarcadores. Tau

CSF P-Tau181

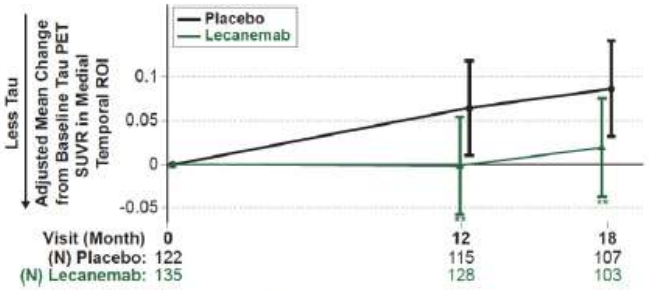


Plasma p-tau181

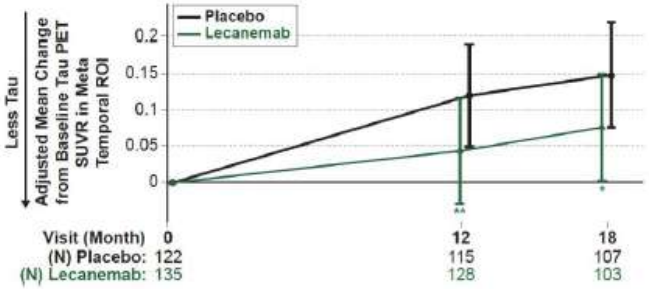


PET-tau

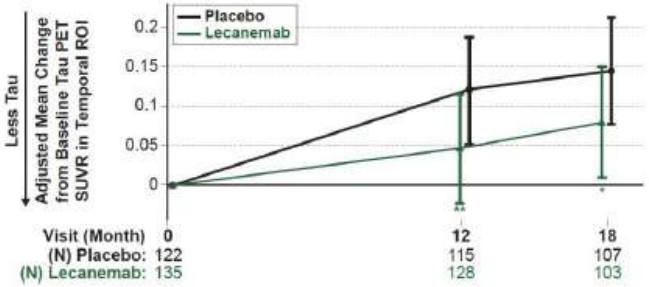
Medial Temporal



Meta Temporal



Temporal

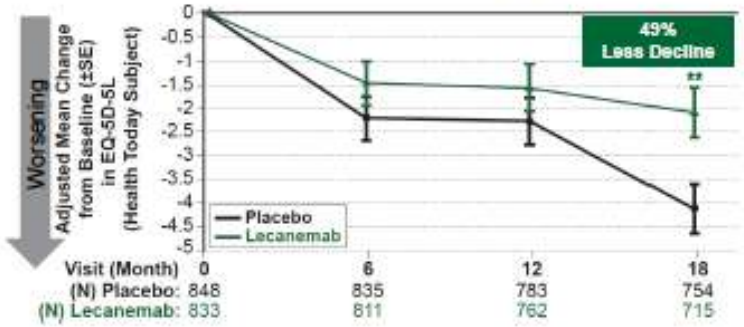


Van Dick et al. N Eng J Med 2022

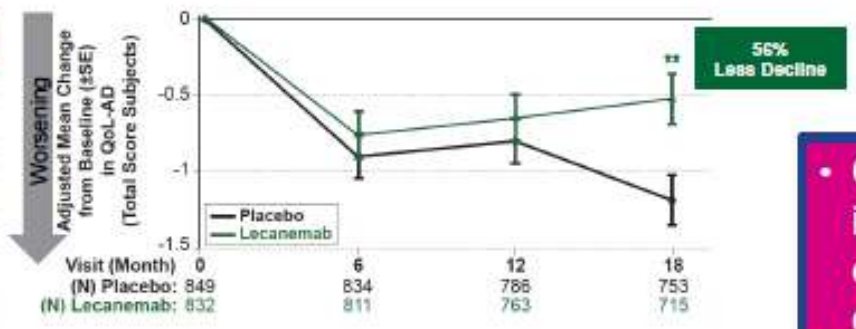
Health-Related Quality of Life Measures

Slowing of Health Decline with Lecanemab on Subject and Study Partner Burden

EQ-5D-5L (Subject)



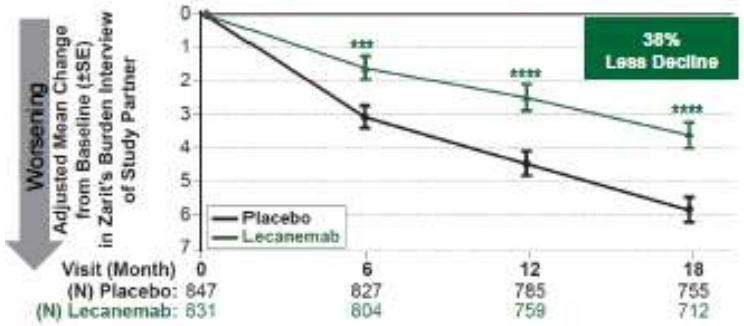
QOL-AD (Subject)



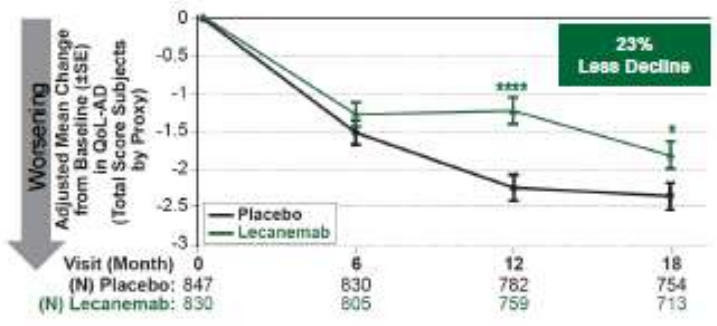
- **Consistent benefits seen in quality of life and caregiver burden across different scales**

Zarit Burden Interview

Study Partner Burden (total score)



QOL-AD (Subject by Proxy)

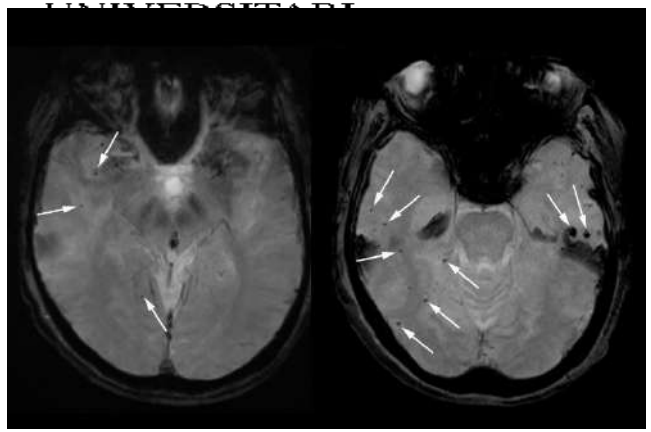


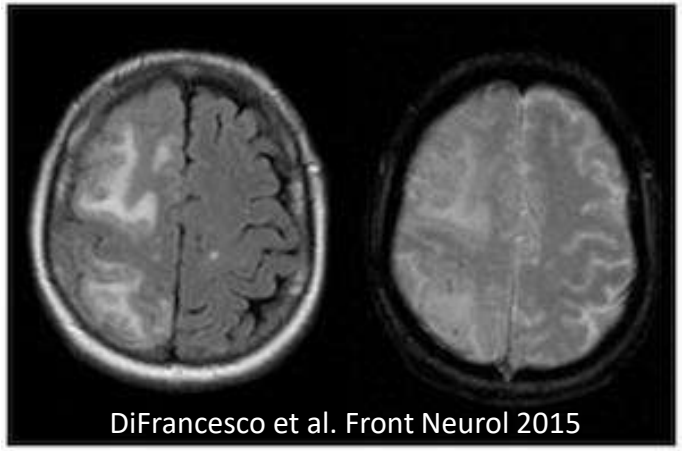
- **EQ-5D-5L:** European Quality of Life–5 Dimensions (5 Level version): The descriptive system covers 5 dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with 5 levels of severity in each dimension (no problems, slight problems, moderate problems, severe problems, and unable to perform or extreme problems). The score being presented is the VAS: Health Today (Visual Analog Scale subtotal).
- **QOL-AD:** Quality of Life in Alzheimer's Disease: A 13-item questionnaire designed to provide both a patient and a caregiver report of the quality of life (QOL) for patients who have been diagnosed with Alzheimer Disease
- **Zarit Burden Interview:** The 22-item instrument used in dementia caregiving research used to assess the stresses experienced by study partners of subjects with dementia.

SE, standard error.

* P<0.05; ** P<0.01; *** P<0.001; **** P<0.0001

CLARITY Seguridad





DiFrancesco et al. Front Neurol 2015

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)
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)
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)

Reacción a la infusión
75 % en la primera administración

ARIA-H: 17,3 % (Leca) vs 9 % (placebo)

ARIA-E: 12,6 % (Leca) vs 1,7% (placebo)

78 % asintomáticas

Van Dick et al. N Eng J Med 2022

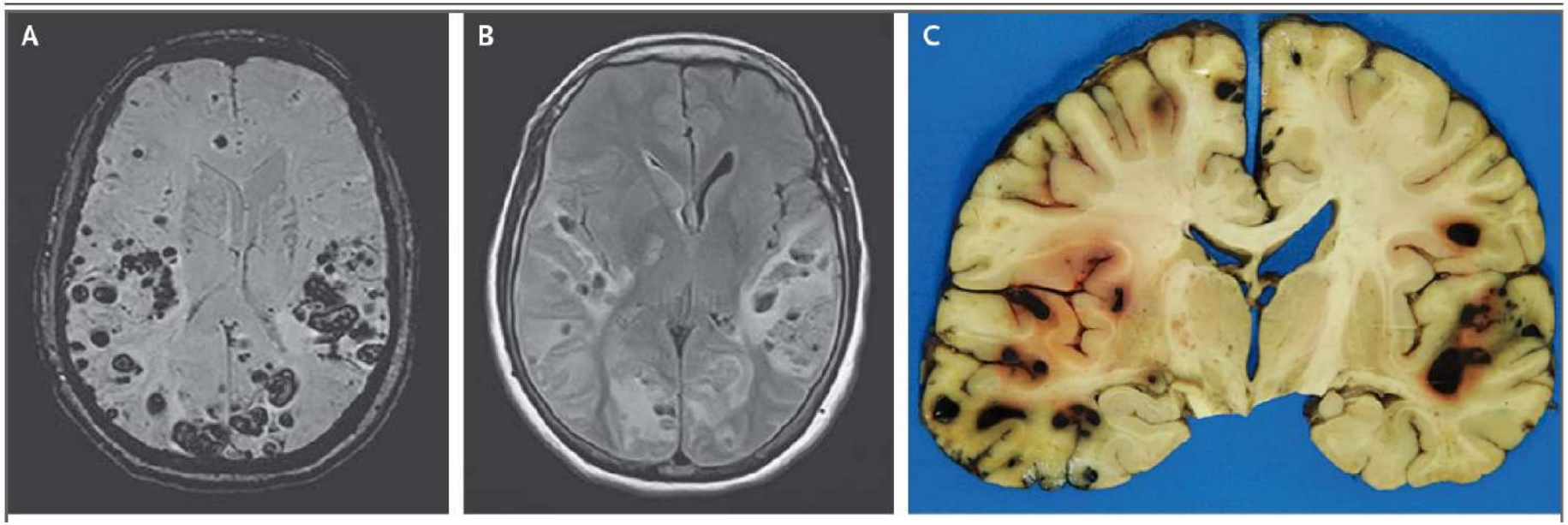
CLARITY. Seguridad

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke

65 años
APOE ε4ε4
Afasia



Reish et al. N Eng J Med 2022

Donanemab Clinical Pharmacology Program Overview

Characterization of Donanemab Pharmacokinetics and Pharmacodynamics

	AACC[1,2] Phase 1a		AACD[2] Phase 1b	AACG[3] TRAILBLAZER-ALZ, Phase 2
Region(s)	Japan, US		Japan, US	North America
N	63 (incl. 6 healthy volunteers)		61	257
Population(s)	Amyloid+ adults with mild MCI due to AD or mild/moderate AD dementia; healthy volunteers		Amyloid+ adults with mild MCI due to AD or mild/moderate AD dementia	Amyloid+/Tau+ adults with mild MCI due to AD or mild AD dementia, and MMSE score 20-28
Study arm(s)	SAD phase PBO DON 0.1 mg/kg IV[a] DON 0.3 mg/kg IV DON 1 mg/kg IV DON 3 mg/kg IV DON 10 mg/kg IV DON 3 mg/kg SC DON 1 mg/kg IV[b]	MAD phase PBO DON 0.3 mg/kg Q4W DON 0.3 mg/kg Q4W DON 1 mg/kg Q4W DON 3 mg/kg Q4W DON 10 mg/kg Q4W	PBO DON 10 mg/kg IV (SD) DON 20 mg/kg IV (SD) DON 40 mg/kg IV (SD) DON 10 mg/kg Q2W DON 10 mg/kg Q4W DON 20 mg/kg Q4W	PBO DON 700 mg/1400 Q4W
PK and PD outcome(s)	C_{max}, $AUC_{[0-\infty]}$, terminal $t_{1/2}$, change in amyloid burden, TE-ADA impact on PK/PD		C_{max}, $AUC_{[0-\infty]}$, terminal $t_{1/2}$, change in amyloid burden, TE-ADAs	Population PK analysis, change in amyloid and tau burden, TE-ADAs
Duration of treatment and follow-up	SAD + 12 weeks' FU	MAD approx. once/month for up to 4 doses + 12 weeks' FU	See Notes	72 weeks' treatment; FU at 76 weeks

[a]Sentinel dosing: first 2 patients dosed with donanemab or PBO during SAD phase, then 0.3 mg/kg during MAD phase. [b]In healthy volunteers. AD=Alzheimer's Disease; AUC=Area; Under the Concentration-Time Curve $AUC_{(0-\infty)}$=AUC from Zero to Infinity; DON=Donanemab; C_{max}=Maximum Observed Drug Concentration; FU=Follow-Up; MAD=Multiple-Ascending Dose; IV=Intravenous; MCI=Mild Cognitive Impairment; MMSE=Mini-Mental State Examination; PBO=Placebo; PD=Pharmacodynamics; PK=Pharmacokinetics; Q2W=Every 2 Weeks; Q4W=Every 4 Weeks; SAD=Single-Ascending Dose; SC=Subcutaneous; SD=Single Dose; $t_{1/2}$=Half-Life; TE-ADA=Treatment-Emergent Antidrug Antibody. 1. Lowe SL, et al. *Alzheimer's Dement.* 2021;7:e12112. 2. Lowe SL, et al. *J Prev Alz Dis.* 2021;4(8):414-424. 3. Mintun MA, et al. *N Engl J Med.* 2021;384(18):1691-1704.

Overview

Donanemab Phase 2 and Phase 3 Clinical Trials Program

Study Name	Phase	Participants	Intervention	Primary Outcome	Current Status[a]
TRAILBLAZER-ALZ[1]	2	Early symptomatic AD	DON vs. PBO	Change in iADRS from baseline to Week 76	Complete; primary outcome data published
TRAILBLAZER-EXT[2]	2	Symptomatic AD	Part A: None Part B: DON	Part A: Correlation between video teleconference and on-site assessment for ADAS-Cog_{13}, ADCS-iADL, MMSE, and CDR-SB Part B: Safety	Ongoing; estimated primary completion May 2023
TRAILBLAZER-ALZ 2 + TRAILBLAZER-ALZ 2-EXT[3]	3	Early symptomatic AD with presence of brain tau pathology	DON vs. PBO	Change in iADRS from baseline to Week 76	Ongoing; estimated primary completion April 2023
TRAILBLAZER-ALZ 3[4]	3	At risk of AD (due to presence of amyloid and early tau pathology); prevention study	DON vs. PBO	Time to clinical progression (CDR-GS)	Ongoing; estimated primary completion September 2027
TRAILBLAZER-ALZ 4[5]	3	Early symptomatic AD	DON vs. ADU	Percentage of participants who reach complete amyloid plaque clearance at 6 months in overall and intermediate tau subpopulations with DON vs. ADU	Ongoing; estimated primary completion June 2022

[a]As of February 2022.

AD=Alzheimer's Disease; ADAS-Cog_{13}=13-Item Cognitive Subscale of the Alzheimer's Disease Assessment Scale; ADCS-iADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory, Instrumental Items; ADU=Aducanumab; CDR-GS=Clinical Dementia Rating Scale – Global Score; CDR-SB=Clinical Dementia Rating Scale – Sum of Boxes; DON=Donanemab; iADRS= Integrated Alzheimer's Disease Rating Scale; MMSE=Mini-Mental State Exam; PBO=Placebo.

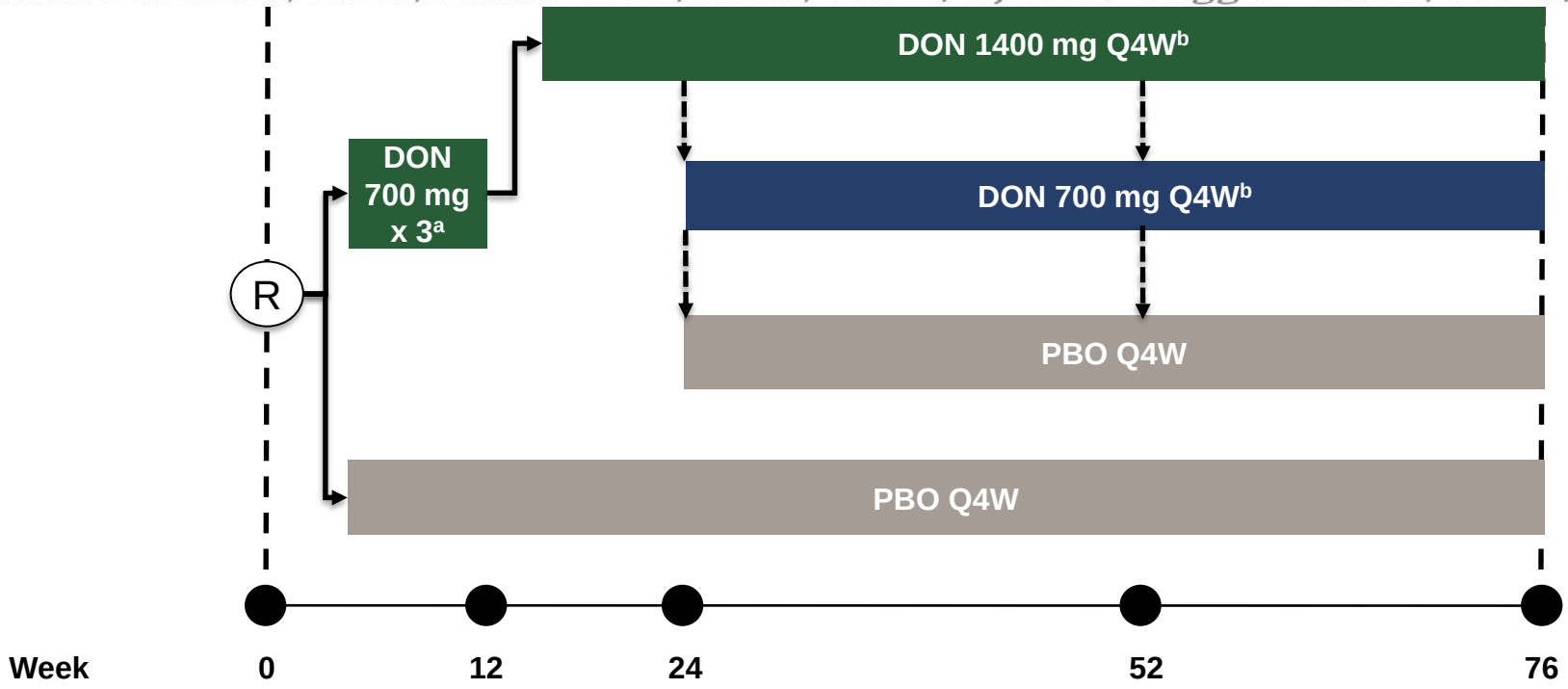
1. Mintun MA, et al. *N Engl J Med*. 2021;384(18):1691-1704. 2. https://clinicaltrials.gov/ct2/show/NCT04640077 (Accessed February 3, 2022). 3. https://clinicaltrials.gov/ct2/show/NCT04437511 (Accessed February 1, 2022). 4. https://clinicaltrials.gov/ct2/show/NCT05026866 (Accessed February 1, 2022). 5. https://clinicaltrials.gov/ct2/show/NCT05108922 (Accessed February 2, 2022).

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 6, 2021 VOL. 384 NO. 18

Donanemab in Early Alzheimer's Disease

Mark A. Mintun, M.D., Albert C. Lo, M.D., Ph.D., Cynthia Duggan Evans, Ph.D., Alette M. Wessels, Ph.D.,



[a]DON 700 mg Q4W for 3 doses. [b]In participants who were treated with DON, if the amyloid plaque level as assessed by florbetapir PET (performed at 24 and 52 weeks) was 11 to less than 25 centiloids, indicating removal of amyloid plaques, the dose was lowered to 700 mg. If the amyloid plaque level was less than 11 centiloids on any one scan or was 11 to less than 25 centiloids on two consecutive scans, DON was switched to PBO.

AD=Alzheimer's Disease; DON=Donanemab; PBO=Placebo; R=Randomization; Q4W=Every 4 Weeks.

Mintun MA, et al. *N Engl J Med.* 2021;384(18):1691-1704.

Baseline Patient Demographics

mITT Population (TRAILBLAZER-ALZ)

	PBO N=126	DON N=131
Sex (female), n (%)	65 (51.6)	68 (51.9)
Age (years), mean (SD)	75.4 (5.4)	75.0 (5.6)
Race, n (%)		
Asian	2 (1.6)	1 (0.8)
Black or African American	3 (2.4)	5 (3.8)
White	121 (96.0)	122 (93.1)
Other[a]	0	3 (2.3)
Hispanic ethnic group, n (%)	3 (2.4)	5 (3.8)
Education (≥13 years), n (%)	102 (81.0)	97 (74.0)
AChEI use, n (%)	74 (58.7)	78 (59.5)

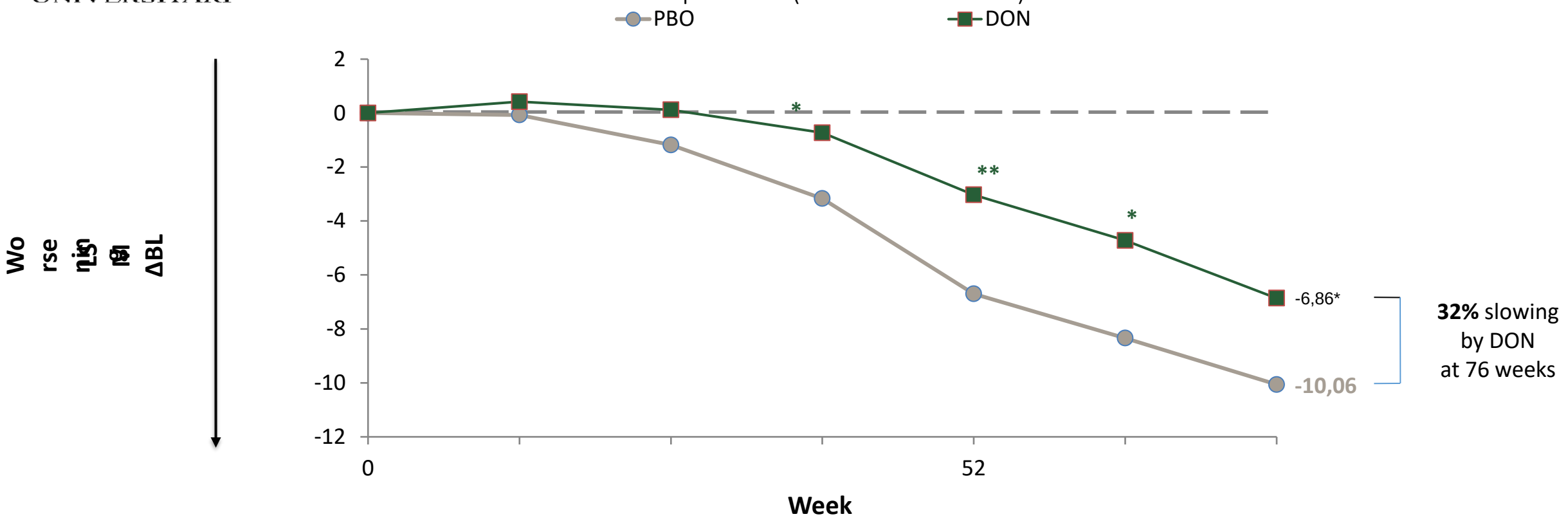
Note: Patients randomized to study drug received DON 700 mg Q4W for the first three doses and DON 1400 mg Q4W from Week 12 up to Week 72.

[a]Included multiple and American Indian or Alaska Native.

AChEI=Acetylcholinesterase Inhibitor; DON=Donanemab; mITT=Modified Intent-to-Treat; PBO=Placebo; Q4W=Every 4 Weeks; SD=Standard Deviation.

Mintun MA, et al. *N Engl J Med*. 2021;384(18):1691-1704.

Primary Endpoint: iADRS Through Week 76, MMRM[1,2]

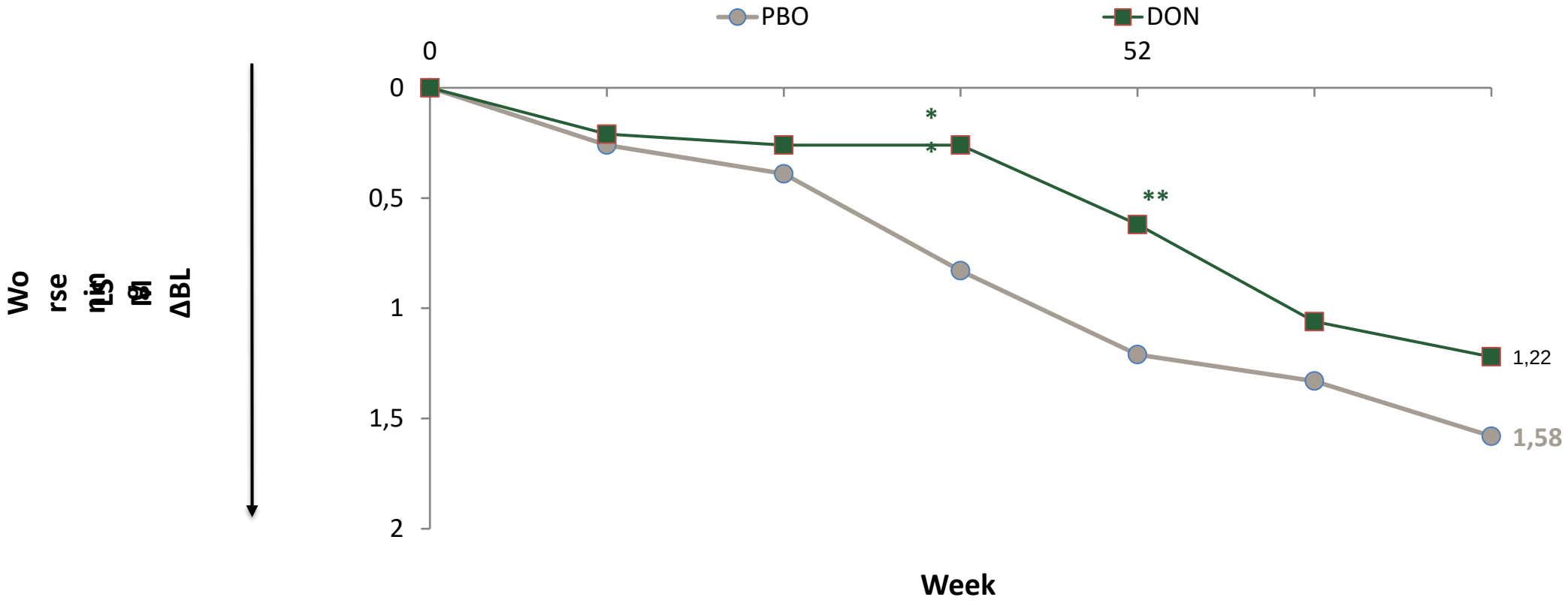


PBO, N	120			113			110			103			90			90			91
DON, N	115			110			112			102			88			89			93

vs. PBO: *p≤0.05, **p≤0.01. Note: Patients randomized to study drug received DON 700 mg Q4W for the first three doses and DON 1400 mg Q4W from Week 12 up to Week 72.
ΔBL=Change From Baseline; DON=Donanemab. iADRS=Integrated Alzheimer's Disease Rating Scale; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model for Repeated Measures; PBO=Placebo; Q4W=Every 4 Weeks.
1. Mintun MA, et al. *N Engl J Med*. 2021;384(18):1691-1704. 2. Mintun MA, et al. Oral presentation at: *AD/PD 2021*.

Key Secondary Endpoint: CDR-SB Through Week 76, MMRM[1,2]

mITT Population (TRAILBLAZER-ALZ)



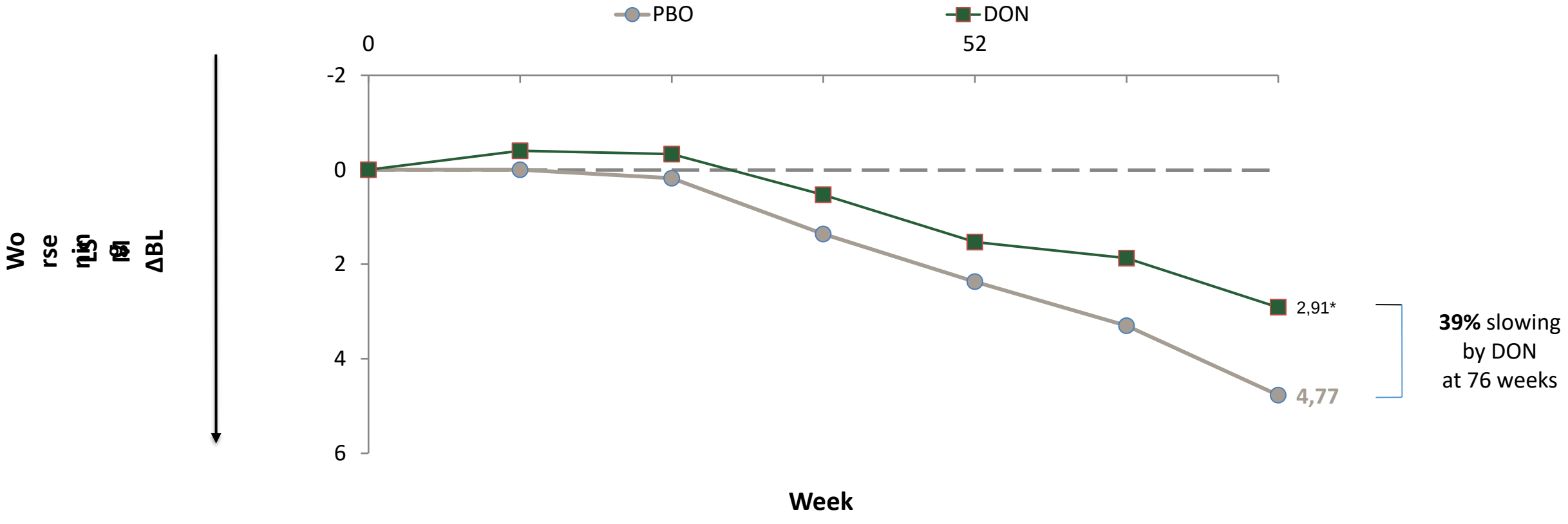
23% slowing by DON at 76 weeks

PBO, N	120			115			111			104				91			90			90
DON, N	125			122			114			102				90			92			93

vs. PBO; **p≤0.01. Note: Patients randomized to study ΔBL=Change From Baseline; CDR-SB=Clinical Dementia Rating-Sum of Boxes; LS Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model for Repeated Measures; PBO=Placebo; Q4W =Every 4 Weeks.

1. Mintun MA, et al. *N Engl J Med.* 2021;384(18):1691-1704.

Key Secondary Endpoint: ADAS-Cog$_{13}$ Through Week 76, MMRM[1,2]



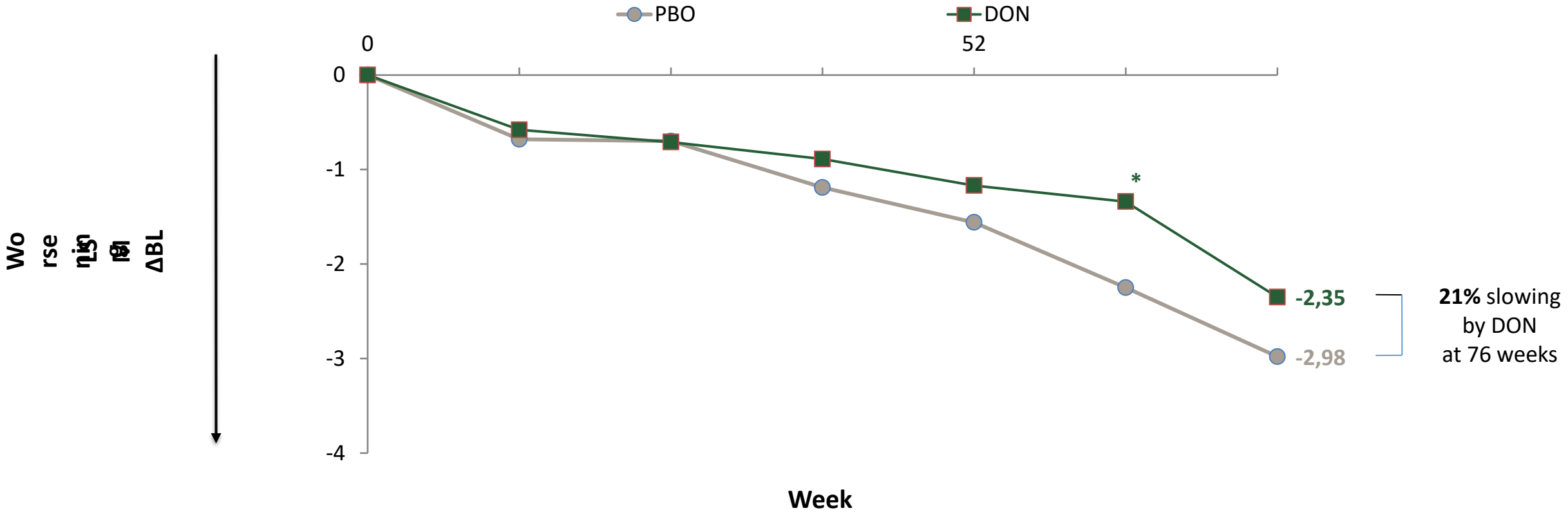
PBO, N	120			116			111			104				92			90			93
DON, N	125			121			112			103				89			91			93

vs. PBO: *p≤0.05. Note: Patients randomized to stud (12 up to Week 72.

ΔBL=Change From Baseline; ADAS-Cog$_{13}$=13-item est Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model for Repeated Measures; PBO= Placebo; Q4W=Every 4 W eeks.

1. Mintun MA, et al. *N Engl J Med.* 2021;384(18):169

Key Secondary Endpoint: MMSE Through Week 76, MMRM[1,2]



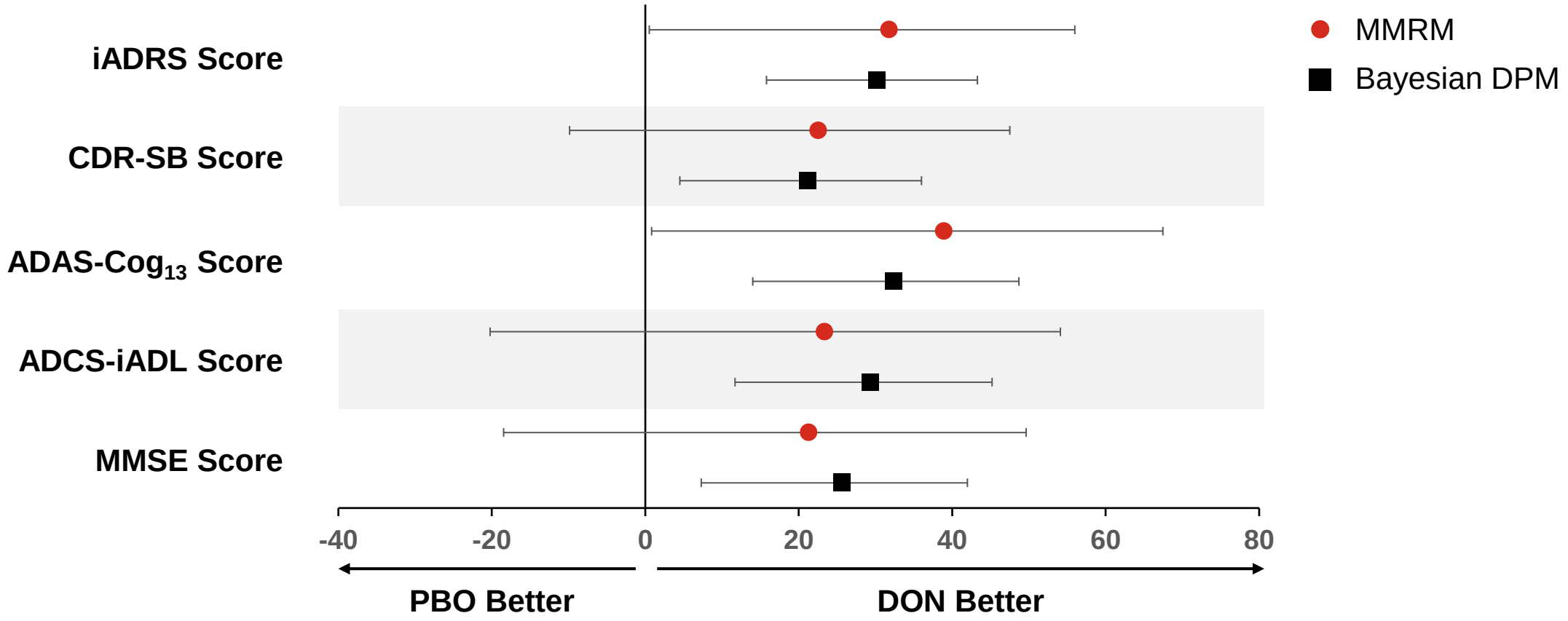
PBO, N	115			112			107			101			89			87		90
DON, N	121			118			108			100			86			89		91

vs. PBO: *p≤0.05. Note: Patients randomized to stud (12 up to Week 72.

ΔBL=Change From Baseline; DON=Donanemab; LS esures; MMSE=Mini-Mental State Examination; PB >Placebo; Q4W=Every 4 Weeks.

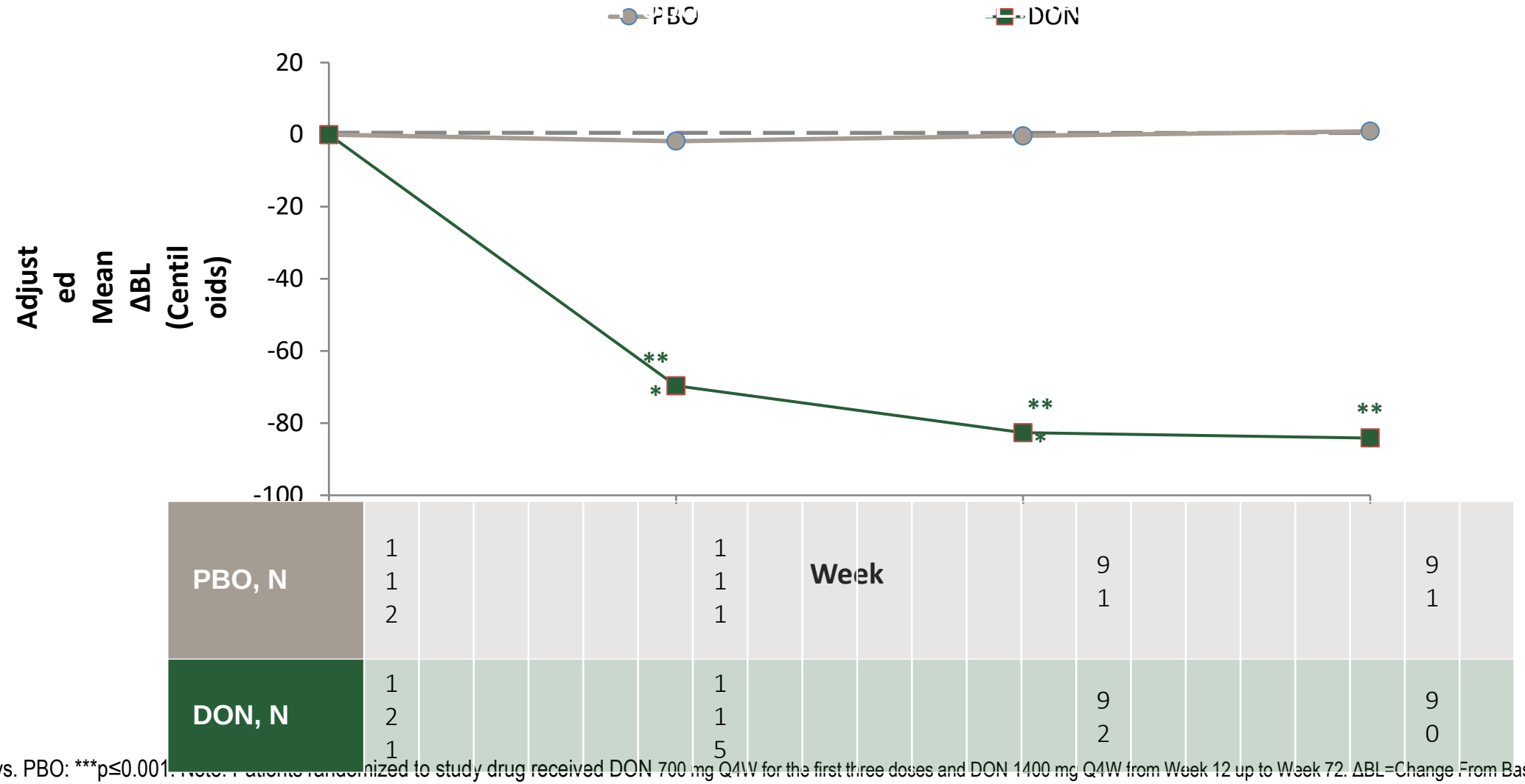
1. Mintun MA, et al. *N Engl J Med.* 2021;384(18):169

Estimated Percent Change in Clinical Scores at Week 76 (MMRM) or From Baseline to Week 76 (Bayesian DPM)



ADAS-Cog_{13}=13-item Cognitive Subscale of the Alzheimer's Disease Assessment Scale; ADCS-iADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory, Instrumental Items; CDR-SB=Clinical Dementia Rating Scale – Sum of Boxes; DON=Donanemab; DPM=Disease Progression Model; iADRS=Integrated Alzheimer's Disease Rating Scale; mITT=Modified Intent-to-Treat; MMRM=Mixed Model for Repeated Measures; MMSE=Mini-Mental State Examination; PBO=Placebo.
Mintun MA, et al. *N Engl J Med*. 2021;384(18):1691-1704.

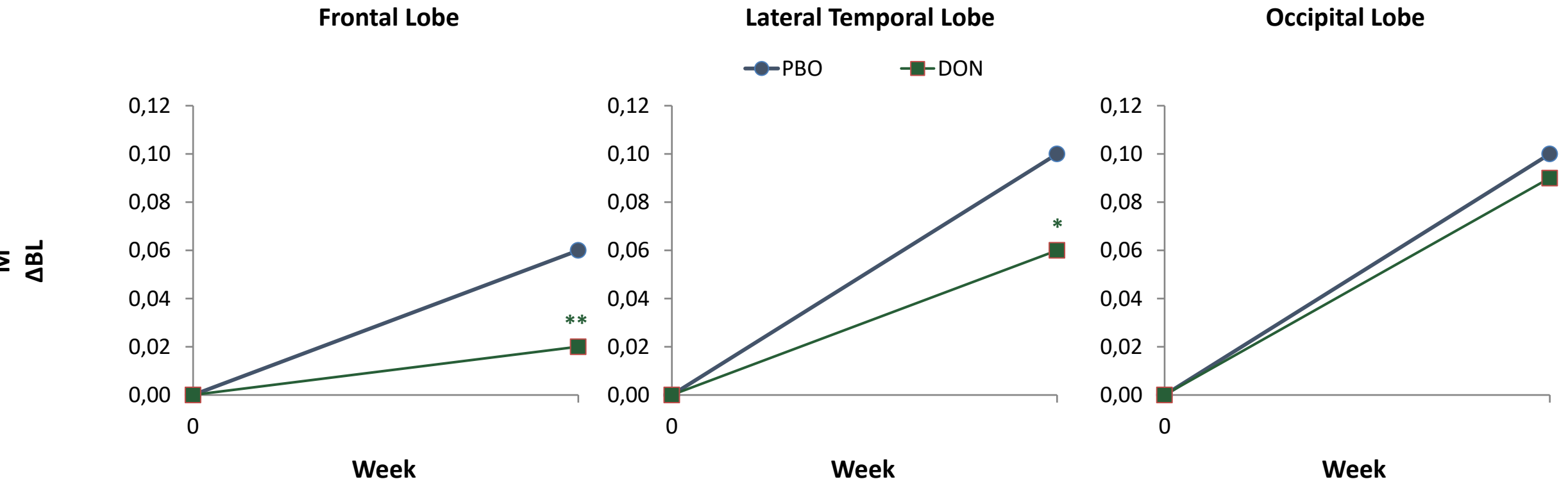
Secondary Endpoint: Change in Amyloid Plaque on Florbetapir PET Through Week 76, MMRM[1,2]



vs. PBO: ***p≤0.001. Note: Patients randomized to study drug received DON 700 mg Q4W for the first three doses and DON 1400 mg Q4W from Week 12 up to Week 72. ΔBL=Change From Baseline; DON=Donanemab; mITT=Modified Intent-to-Treat; MMRM=Mixed Model for Repeated Measures; PBO=Placebo; PET=Positron Emission Tomography; Q4W=Every 4 Weeks.

1. Mintun MA, et al. *N Engl J Med*. 2021;384(18):1691-1704. 2. Mintun MA, et al. Oral presentation at: *AD/PD 2021*.

Regional Tau Load on Flortaucipir PET at Week 76, MMRM[1,2]



vs. PBO: *p≤0.05, **p≤0.01. Note: Patients randomized to study drug received DON 700 mg Q4W for the first three doses and DON 1400 mg Q4W from Week 12 up to Week 72.
ΔBL=Change From Baseline; DON=Donanemab; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; PET=Positron Emission Tomography; PBO=Placebo; Q4W=Every 4 Weeks.

1. Mintun MA, et al. *N Engl J Med.* 2021;384(18):1691-1704. 2. Mintun MA, et al. Oral presentation at: *AD/PD* 2021.

Adverse Events of Special Interest

TRAILBLAZER-ALZ

- Adverse events of special interest were prespecified and subject to enhanced surveillance in order to capture key data points for analysis to improve understanding of the events:
  - ARIA-E (Amyloid-Related Imaging Abnormalities – Edema or Effusion)
  - ARIA-H (Amyloid-Related Imaging Abnormalities – Hemorrhage)
  - Hypersensitivity (immediate and non-immediate), including infusion-related reactions

ARIA-E=Amyloid-Related Imaging Abnormalities-Edema/Effusion; ARIA-H=Amyloid-Related Imaging abnormalities-Hemorrhage.

Mintun MA, et al. *N Engl J Med*. 2021;384(18):1691-1704.

Overview of Safety Outcomes Through Week 76

Safety Population (TRAILBLAZER-ALZ)

Event	PBO N=125	DON N=131
AEs during treatment period, n (%)	113 (90.4)	119 (90.8)
SAEs, n (%)	22 (17.6)	23 (17.6)
Discontinuation of treatment due to AE, n (%)[a]	9 (7.2)	40 (30.5)
Discontinuation of trial due to AE, n (%)[a]	6 (4.8)	20 (15.3)
Death, n (%)	2 (1.6)	1 (0.8)

Note: Patients randomized to study drug received DON 700 mg Q4W for the first 3 doses and DON 1400 mg Q4W from Week 12 up to Week 72.

[a]Discontinuation was based on protocol-defined criteria or reasons cited by the patient or principal investigator.
AE=Adverse Event; DON=Donanemab; PBO=Placebo; Q4W=Every 4 Weeks; SAE=Serious Adverse Event.
Mintun MA, et al. *N Engl J Med*. 2021;384(18):1691-1704.

Adverse Events Reported in ≥5% of Patients Through Week 76

Safety Population (TRAILBLAZER-ALZ) (1 of 2)

Event	PBO N=125	DON N=131
AEs reported in ≥5% of patients[a], n (%)		
ARIA-E	1 (0.8)	35 (26.7)
Fall	19 (15.2)	17 (13.0)
Dizziness	15 (12.0)	11 (8.4)
Headache	15 (12.0)	10 (7.6)
Superficial siderosis of CNS	4 (3.2)	18 (13.7)
Arthralgia	10 (8.0)	10 (7.6)
Nausea	4 (3.2)	14 (10.7)
Upper respiratory tract infection	9 (7.2)	9 (6.9)
Urinary tract infection	5 (4.0)	13 (9.9)
Diarrhea	5 (4.0)	11 (8.4)
ARIA-H	4 (3.2)	11 (8.4)

Note: Patients randomized to study drug received DON 700 mg Q4W for the first 3 doses and DON 1400 mg Q4W from Week 12 up to Week 72.
[a]Neither arm. AE=Adverse Event; ARIA-E=Amyloid-Related Imaging Abnormalities-Edema/Effusion; ARIA-H=Amyloid-Related Imaging abnormalities-Hemorrhage; CNS=Central Nervous System; DON=Donanemab; PBO=Placebo; Q4W=Every 4 Weeks.

Mintun MA, et al. *N Engl J Med.* 2021;384(18):1691-1704.

ARIA[a] Events Detected By MRI Through Week 76

Safety Population (TRAILBLAZER-ALZ) (1 of 2)

	PBO N=125	DON N=131
ARIA-E or ARIA-H, no. (%)	10 (8.0)	51 (38.9)
Any ARIA-E, no. (%)	1 (0.8)	36 (27.5)
ARIA-E symptom status, no. (%)		
Asymptomatic	0	28 (21.4)
Symptomatic	1 (0.8)	8 (6.1)
ARIA-E by APOE genotype, no./total no. (%)		
ε2/ε3	0/1	0/1
ε2/ε4	0/2	0/2
ε3/ε3	0/31	4/35 (11.4)
ε3/ε4	0/62	21/68 (30.9)
ε4/ε4	1/28 (3.6)	11/25 (44.0)

Note: Patients randomized to study drug received DON 700 mg Q4W for the first 3 doses and DON 1400 mg Q4W from Week 12 up to Week 72.

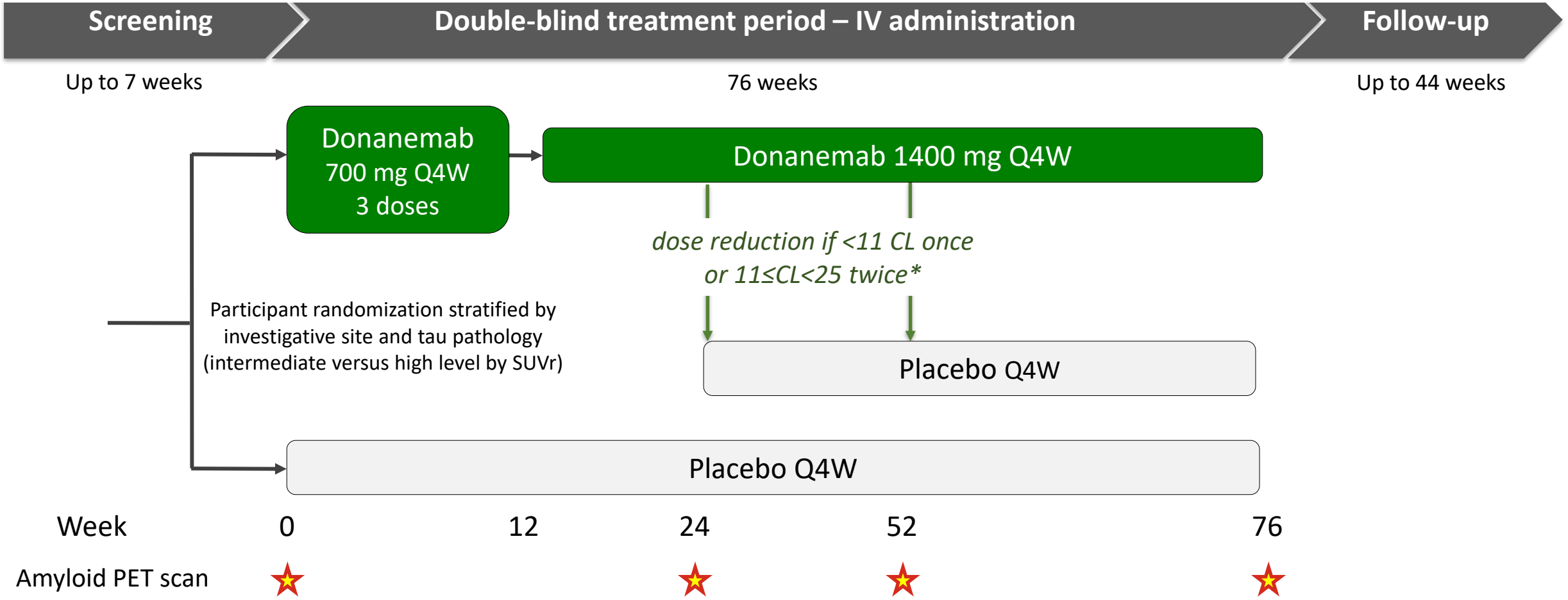
[a]ARIA events were based on central review of MRI studies and include events that occurred beyond the double-blind intervention period.
APOE=Apolipoprotein E; ARIA=Amyloid-Related Imaging Abnormalities; ARIA-E=Amyloid-Related Imaging Abnormalities-Edema/Effusion; ARIA-H=Amyloid-Related Imaging abnormalities-Hemorrhage; DON=Donanemab; MRI=Magnetic Resonance Imaging; No.=Number; PBO=Placebo; Q4W=Every 4 Weeks.

Mintun MA, et al. *N Engl J Med.* 2021;384(18):1691-1704.

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;



Abbreviations: CL=centiloid unit; IV=intravenous; PET=positron emission tomography; Q4W=every 4 weeks; SUVr=Standardized Uptake Value ratio

*Potential blinded dose reduction to placebo based on amyloid plaque burden at 24 and 52 weeks

TRAILBLAZER-ALZ 2: Outcome Measures

Primary Outcome

iADRS

Composite measure combining the ADAS-Cog$_{13}$ and the ADCS-iADL, to assess cognition and function, respectively

Secondary Outcomes

Clinical

CDR-SB
ADAS-Cog$_{13}$
ADCS-iADL
MMSE

Biomarkers

Amyloid PET
Flortaucipir PET
Volumetric MRI

Safety

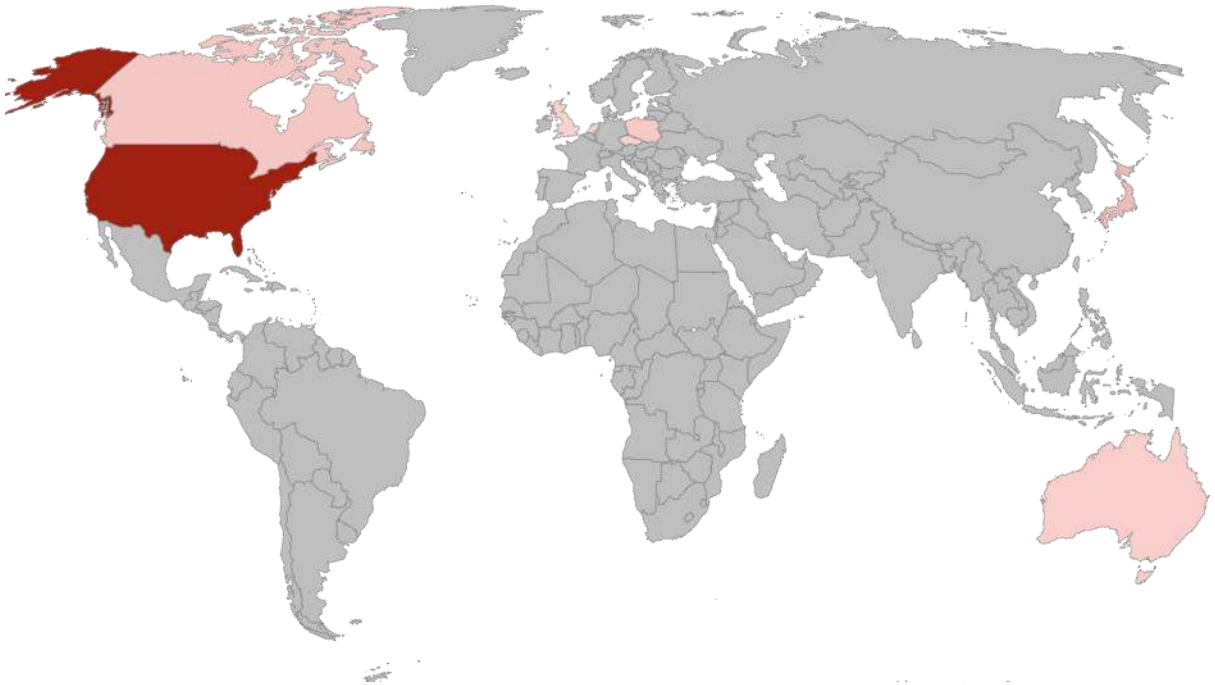
PK
ADAs

Tertiary Outcomes

Blood-based biomarkers including P-tau217
DSST

Abbreviations: ADA=anti-drug antibody; ADAS-Cog$_{13}$=Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-iADL=Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living Inventory; CDR-SB=Clinical Dementia Rating Scale Sum of Boxes; DSST=Digit Symbol Substitution Test; iADRS=Integrated Alzheimer's Disease Rating Scale; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; PET= positron emission tomography; PK=pharmacokinetics

TRAILBLAZER-ALZ 2: Geographies



Country	# Sites	# Screened	# Randomized	%*
United States	193	6381	1253	72%
Japan	31	307	88	5%
Canada	17	678	136	8%
Poland	14	514	158	9%
Australia	9	44	17	1%
Czech Republic	6	53	22	1%
United Kingdom	4	222	39	2%
Netherlands	4	47	22	1%

*percent of randomized

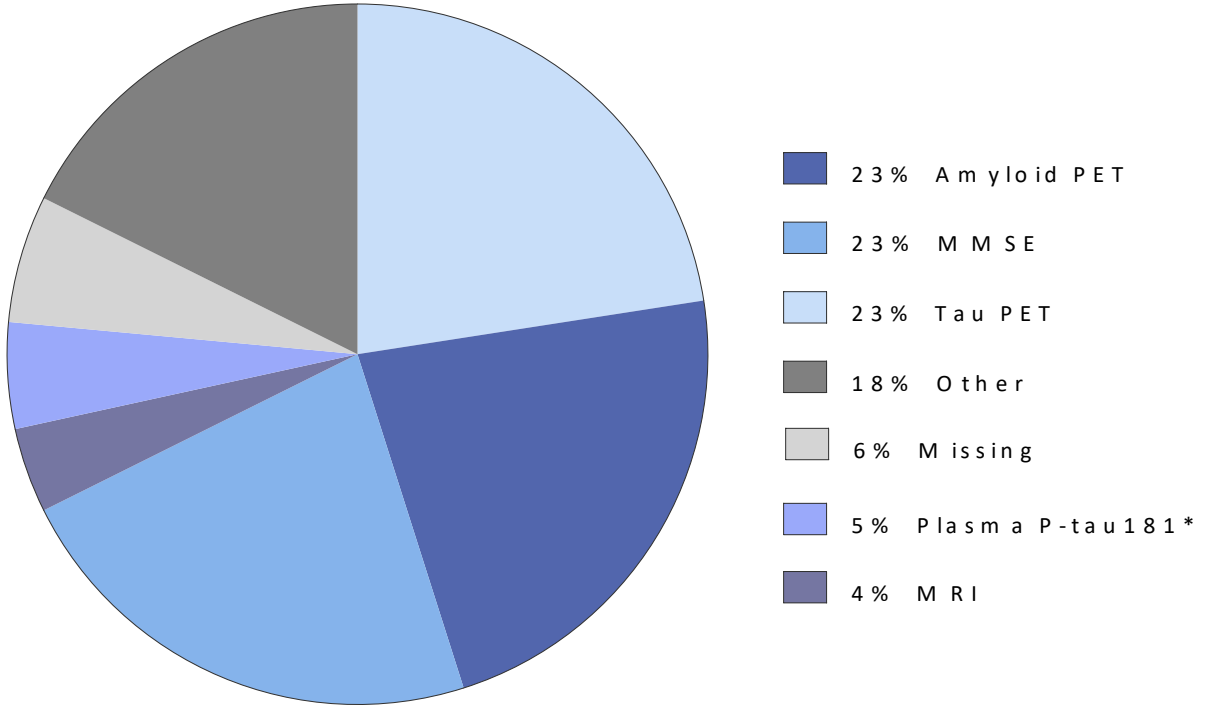
TRAILBLAZER-ALZ enrolled only in United States (92%) and Canada (8%)

TRAILBLAZER-ALZ 2: Screening & Enrollment

Screened
N=8246

Screen Failures
N=6511

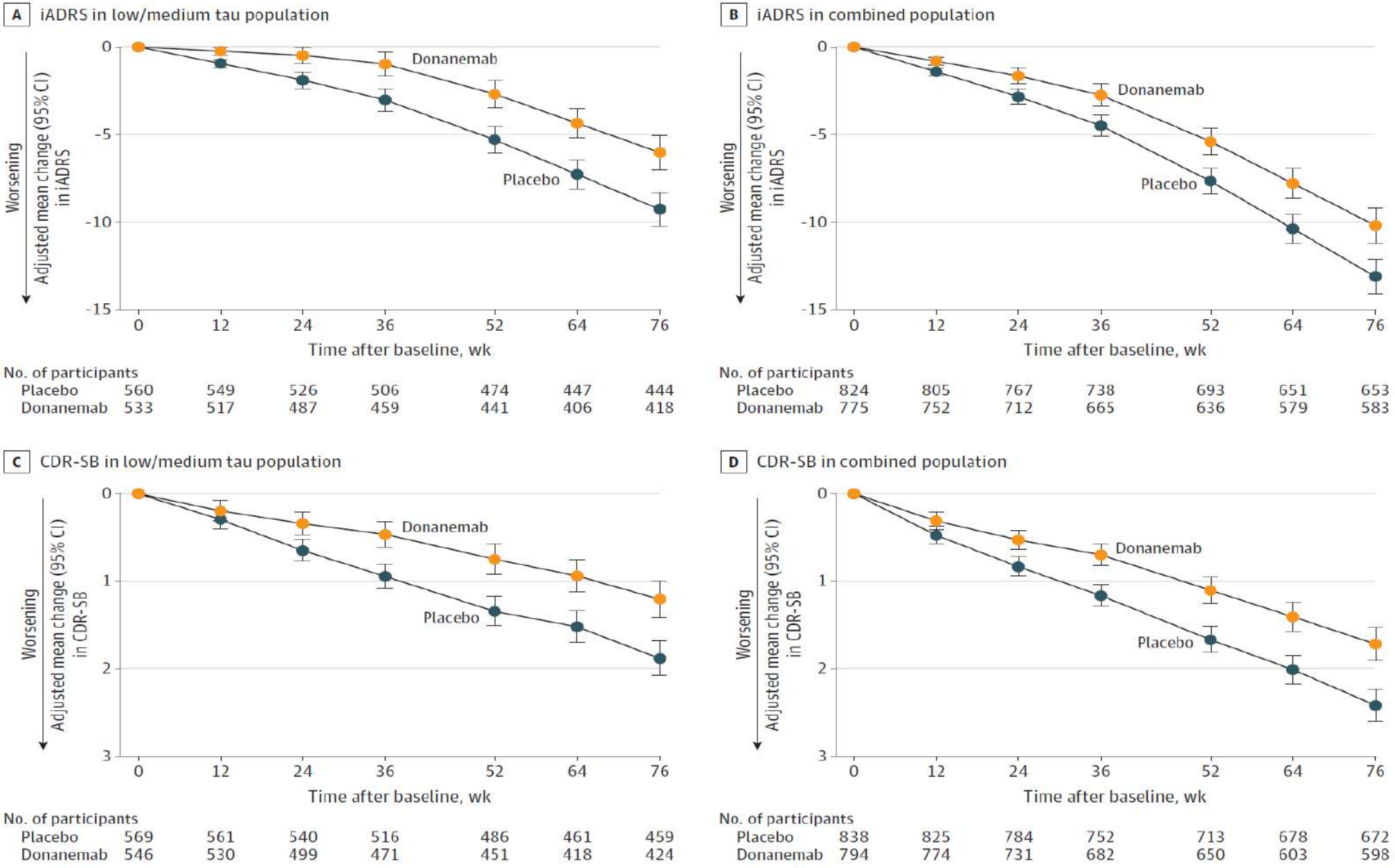
Randomized
N=1735



Abbreviations: MMSE=Mini-Mental State Examination; PET= positron emission tomography; MRI=magnetic resonance imaging

*Early version of protocol required presence of plasma P-tau181 before tau PET scan

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

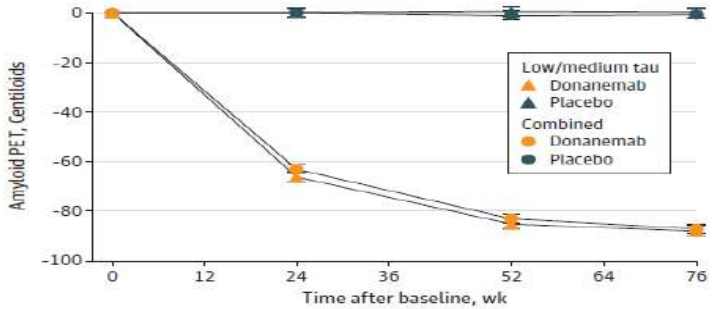


HOSPITAL CLINIC UNIVERSITARI

Universidad Católica de Valencia San Vicente Mártir

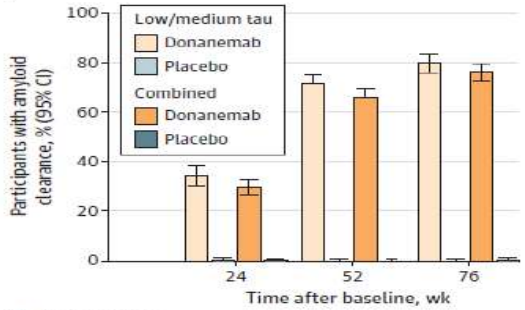
Figure 3. Brain Amyloid, Plasma Phosphorylated Tau 217 (P-tau217), and Hazard Ratios for Risk of Disease Progression

A Adjusted mean change (95% CI) in amyloid PET



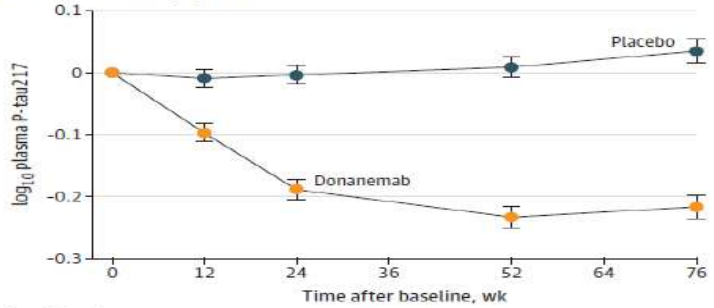
No. of participants					76-wk value, Centiloids	Difference from baseline %
Low/medium tau						
Donanemab	525	521	463	433	-88.0	-85.5
Placebo	556	552	498	470	0.2	0.2
Combined						
Donanemab	765	760	670	614	-87.0	-83.7
Placebo	812	805	729	690	-0.7	-0.7

B Participants with amyloid clearance (<24.1 Centiloids)



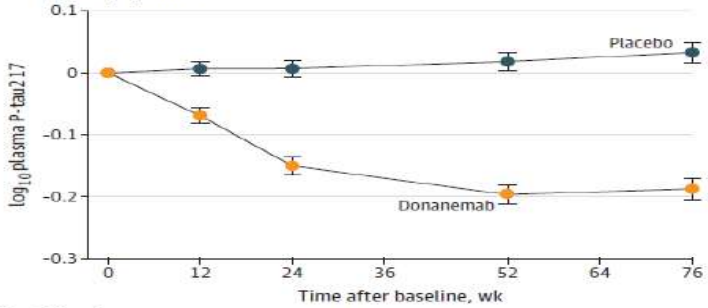
No. of participants			
Low/medium tau			
Donanemab	521	463	433
Placebo	553	498	470
Combined			
Donanemab	761	670	614
Placebo	805	730	690

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



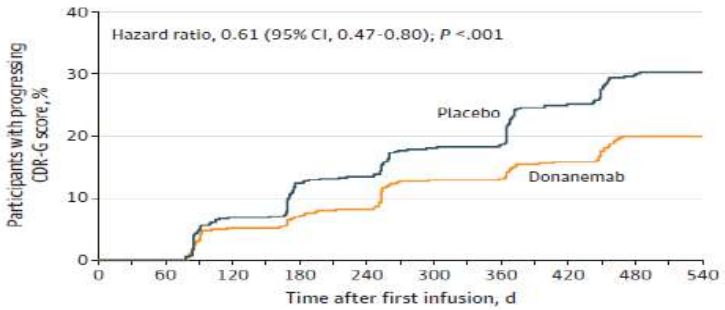
No. of participants					
Placebo	537	517	511	449	429
Donanemab	522	493	464	410	395

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



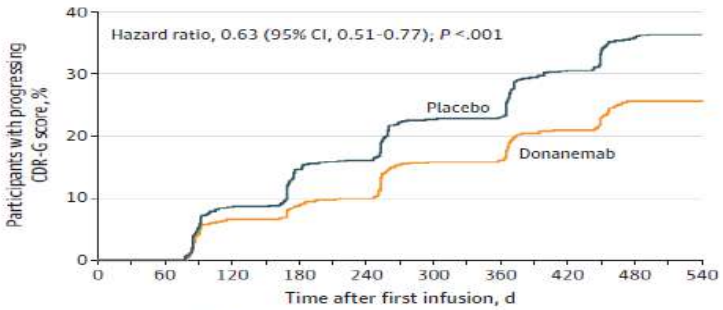
No. of participants					
Placebo	786	758	734	658	620
Donanemab	758	717	686	602	568

E CDR-G score in low/medium tau population



Treatment	No. of participants at risk					
	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

F CDR-G score in combined population

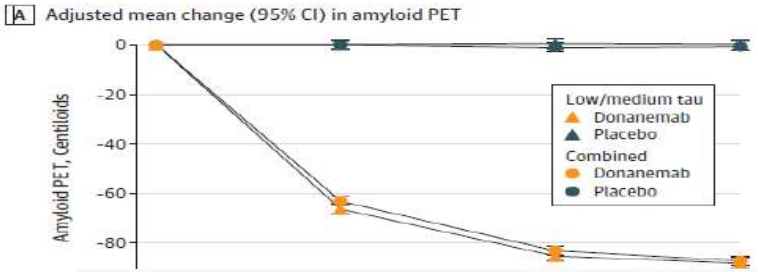


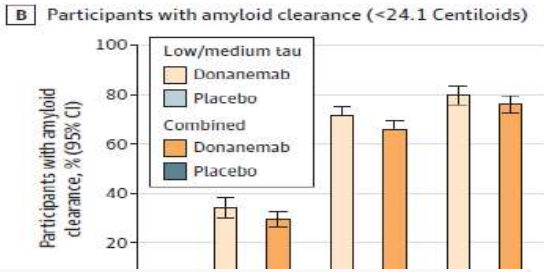
Treatment	No. of participants at risk					
	60 d	120 d	180 d	240 d	360 d	480 d
Placebo	840	764	700	671	587	462
Donanemab	801	737	696	696	575	474

HOSPITAL CLINIC UNIVERSITARI

Universidad Católica de Valencia San Vicente Mártir

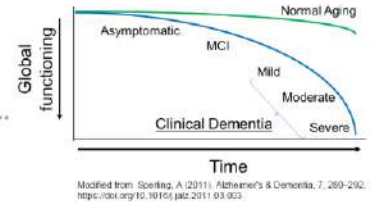
Figure 3. Brain Amyloid, Plasma Phosphorylated Tau 217 (P-tau217), and Hazard Ratios for Risk of Disease Progression

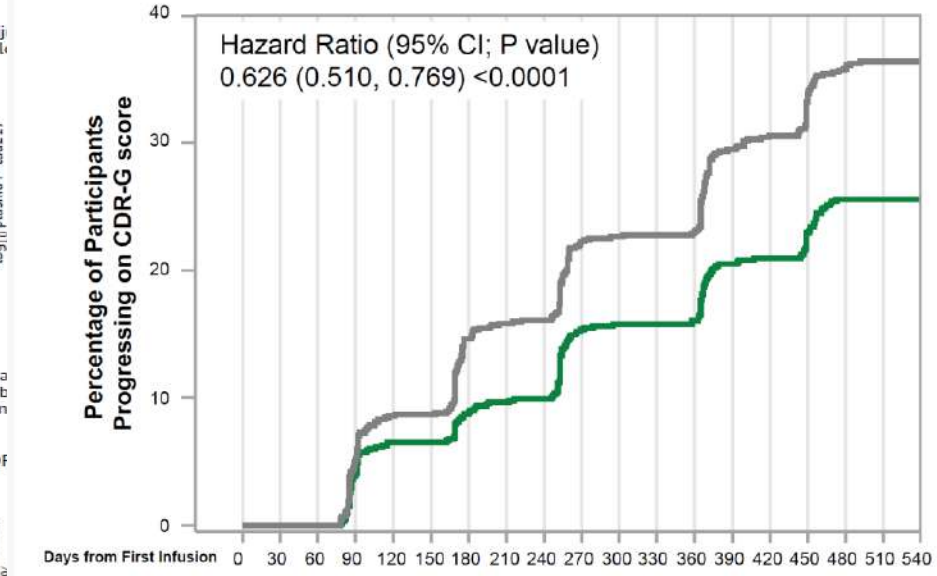




Risk of Progression: CDR-Global score

Combined Tau population

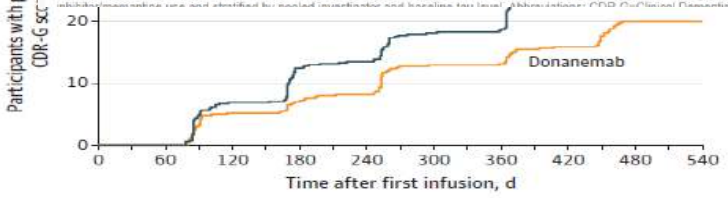




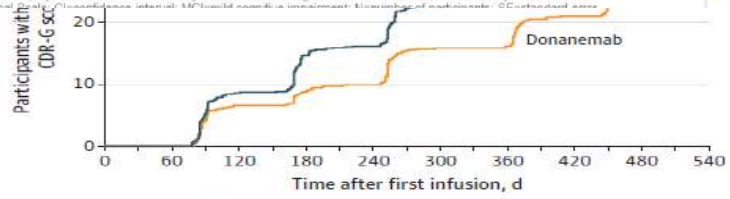
37.4% lower risk of progression over 76 weeks

	Placebo	Donanemab
N	844	805
Event	288	186
Time	% (SE) n at risk	% (SE) n at risk
60 days	0.0 (0.00) 840	0.0 (0.00) 801
120 days	8.6 (0.97) 764	6.5 (0.88) 737
180 days	14.6 (1.22) 700	8.9 (1.01) 696
240 days	16.1 (1.27) 671	9.9 (1.07) 668
360 days	23.0 (1.47) 587	16.1 (1.33) 575
480 days	35.8 (1.72) 462	25.6 (1.63) 474

Definition of event: an increase from baseline in CDR-G score at two consecutive visits. Hazard ratio and P-value were generated using a Cox proportional hazards model adjusted for baseline age, baseline value, and baseline acetylcholinesterase



	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

HOSPITAL CLINIC UNIVERSITARI

Universidad Católica de Valencia San Vicente Mártir

Table 3. Summary of Adverse Events (AEs) by Treatment Group

Event	Donanemab (n = 853)[a]	Placebo (n = 874)[a]
Overview of AEs, No. (%)		
Death[b]	16 (1.9)[c]	10 (1.1)
Death considered related to treatment[d]	3 (0.4)	1 (0.1)
Participants with ≥1 serious AE[e]	148 (17.4)	138 (15.8)
Treatment discontinuations due to AEs	112 (13.1)	38 (4.3)
Study discontinuations due to AEs	69 (8.1)	32 (3.7)
Participants with ≥1 treatment-emergent AE[f]	759 (89.0)	718 (82.2)
Treatment-emergent AEs ≥5% incidence, No. (%)		
ARIA-E	205 (24.0)	17 (1.9)
ARIA-H	168 (19.7)	65 (7.4)
COVID-19	136 (15.9)	154 (17.6)
Headache	119 (14.0)	86 (9.8)
Fall	114 (13.4)	110 (12.6)
Infusion-related reaction	74 (8.7)	4 (0.5)
Superficial siderosis of central nervous system	58 (6.8)	10 (1.1)
Dizziness	53 (6.2)	48 (5.5)
Arthralgia	49 (5.7)	42 (4.8)
Urinary tract infection	45 (5.3)	59 (6.8)
Diarrhea	43 (5.0)	50 (5.7)
Fatigue	42 (4.9)	45 (5.1)
Overview of ARIA[g]		
Microhemorrhage or superficial siderosis present at baseline, No. (%)	124 (14.5)	161 (18.4)
ARIA-E by *APOE* ε4 allele status, No./total No. (%)		
Noncarrier	40/255 (15.7)	2/250 (0.8)
Heterozygous carrier	103/452 (22.8)	9/474 (1.9)
Homozygous carrier	58/143 (40.6)	5/146 (3.4)
Any ARIA, No. (%)[h]	314 (36.8)	130 (14.9)
ARIA-E, No. (%)	205 (24.0)	18 (2.1)
Asymptomatic	153 (17.9)	17 (1.9)
Symptomatic	52 (6.1)	1 (0.1)[i]
ARIA-H, No. (%)	268 (31.4)	119 (13.6)
Microhemorrhage	229 (26.8)	109 (12.5)
Superficial siderosis	134 (15.7)	26 (3.0)
Intracerebral hemorrhage >1 cm	3 (0.4)	2 (0.2)

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

HOSPITAL CLINIC UNIVERSITARI

Estudios comparativos

Universidad Católica de Valencia San Vicente Mártir

P-81

TRAILBLAZER-ALZ 4: Directly comparing donanemab to aducanumab on amyloid lowering in early, symptomatic Alzheimer's disease - Results from 12-months

Andrew Pain[1], Margaret B. Ferguson[1], Hong Wang[1], Stephen Salloway[2], Elly Lee[3], Michelle Papka[4], Haoyan Hu[1], Ming Lu[1], Ena Oru[1], Emily C. Collins[1], Dawn A. Brooks[1], John R. Sims[1], Martin Pan (Non-Author Presenter)[1]

[1]Eli Lilly and Company, Indianapolis, IN, USA; [2]Department of Neurology and Department of Psychiatry, Alpert Medical School of Brown University, Providence, RI, USA; Butler Hospital, Providence, RI, USA; [3]Irvine Clinical Research, Irvine, CA, USA; [4]The Cognitive and Research Center of New Jersey LLC, Springfield, NJ, USA

BACKGROUND

- TRAILBLAZER-ALZ 4 demonstrated superiority of donanemab versus aducanumab at the 6-month primary endpoint of the percentage of participants achieving amyloid plaque clearance (<24.1 Centiloids [CL]) in patients with early symptomatic AD (Salloway et al. CTAD 2022)

CONCLUSION

The TRAILBLAZER-ALZ 4 study provides the first active comparator data on amyloid plaque clearance in patients with early symptomatic AD.

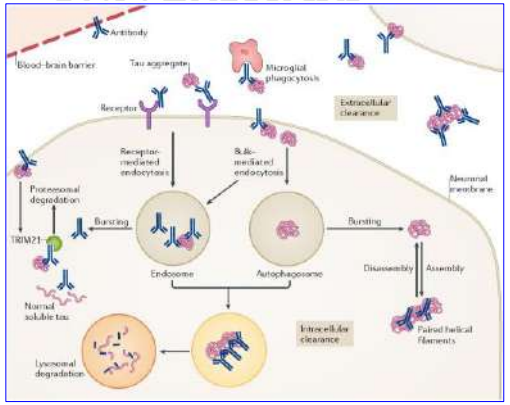
- Significantly more donanemab-treated participants reached amyloid plaque clearance, with larger amyloid reductions from baseline, than aducanumab at 12 months
- Safety profiles of both treatments were consistent with their previously published studies and TRAILBLAZER-ALZ 4 6-month data
  - Speed and depth of amyloid removal is not driving ARIA when comparing between molecules.
- TRAILBLAZER-ALZ 4 is ongoing and will have 18m secondary analyses

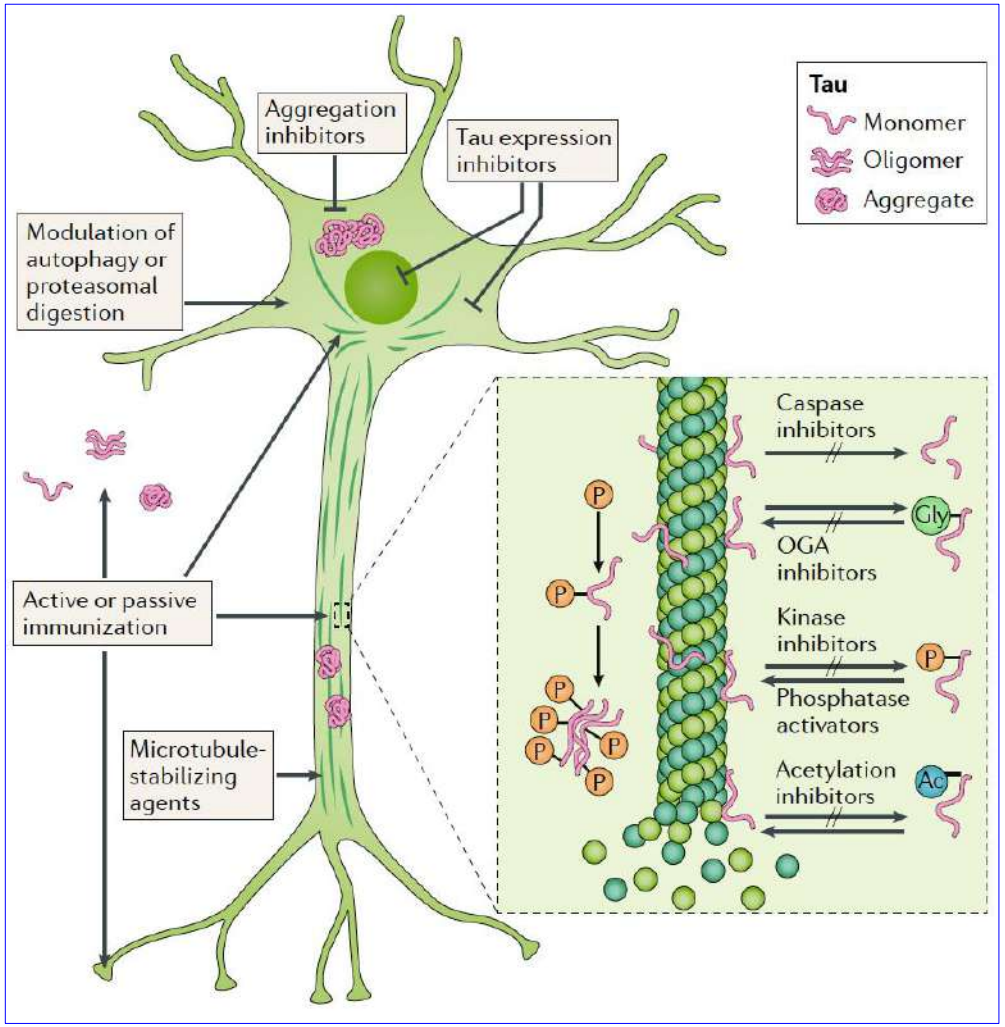
Sponsored by Eli Lilly and Company

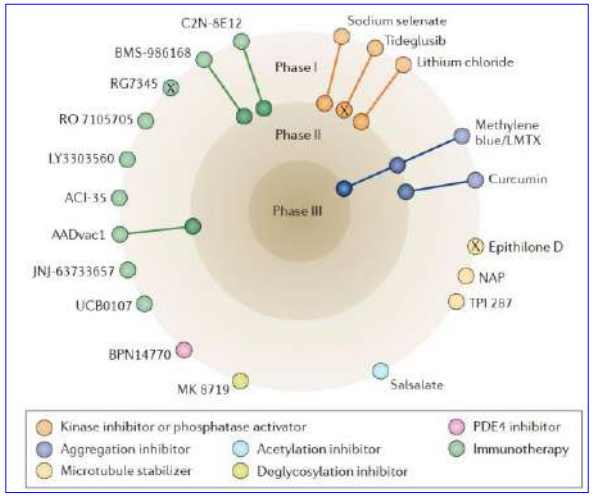
International Congress on Neurodegenerative Diseases (CIBERNED 2023); Málaga, Spain; September 19 – 22, 2023

Ensayos clínicos en alzhéimer temprano

Diana: tau. Fosforilación, agregacion, propagación...







- **Antibodies targeting Tau's middle:**
  - DIAN-TU trial chose Eisai's E2814, which recognizes a motif in the MTBR, for its anti-tau arm
  - Janssen JNJ-63733657, that has just begun Phase 2.
  - Biogen's mid-domain BIIB076 completed Phase 1 in AD in 2020.
  - Lilly's zagotenemab will read out for Phase 2 in AD later this year
  - Pinteon Therapeutics' PNT001 having completed Phase 1.
  - UCB's bepranemab is in Phase 1 for PSP is expected to complete this year. UCB put in hold a Phase 3 PSP trial, and is now prioritizing Phase 2b for AD

Congdon EE and Sigurdsson EM. Nature Rev Neurology 2018; 14: 399.
https://www.alzforum.org/news/conference-coverage/n-terminal-tau-antibodies-fade-mid-domain-ones-push-fore (Mar 2021)

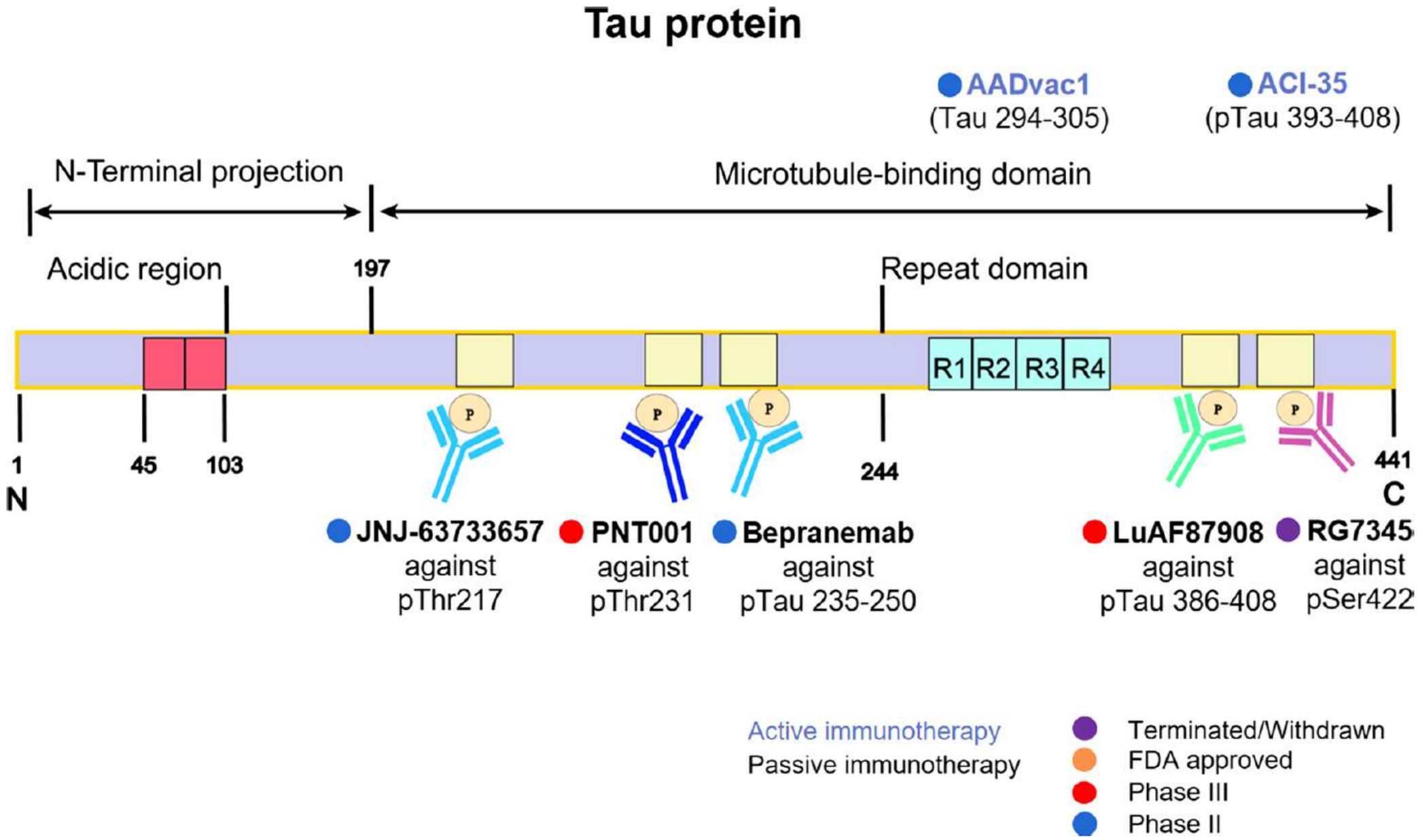
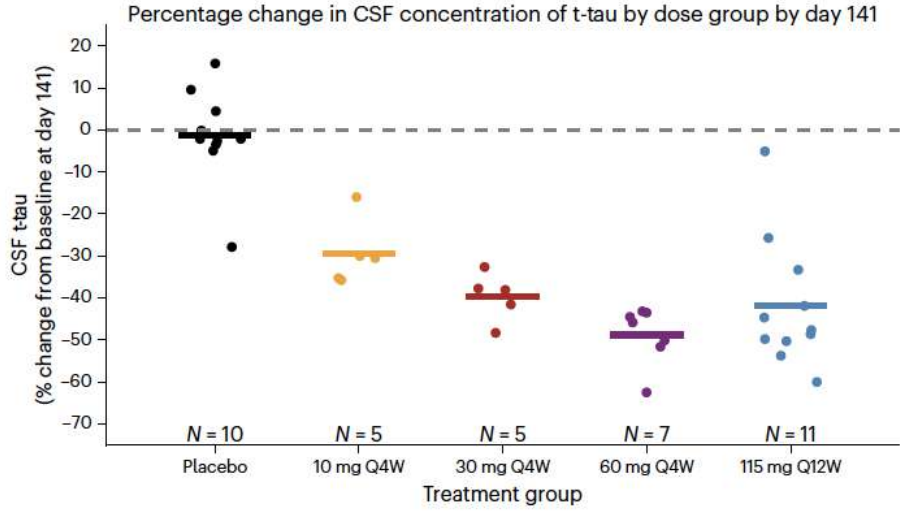
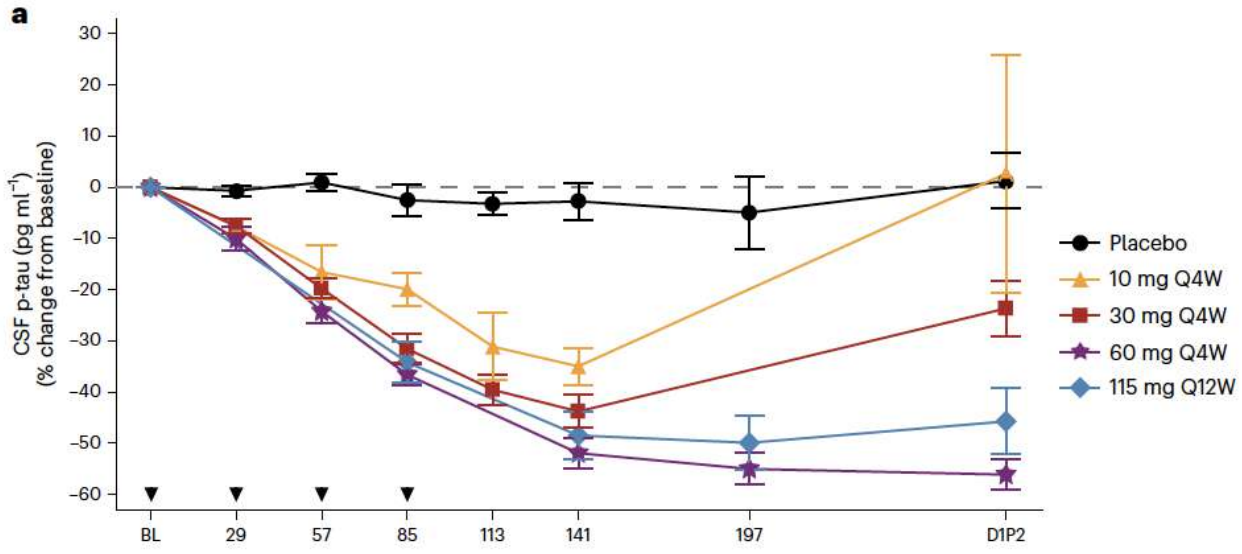


Fig. 2 Immunotherapy strategies targeting tau. Tau immunotherapies, including active vaccines and passive antibodies, are shown based on their target region or site

Tau-targeting antisense oligonucleotide $MAPT_{Rx}$ in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial





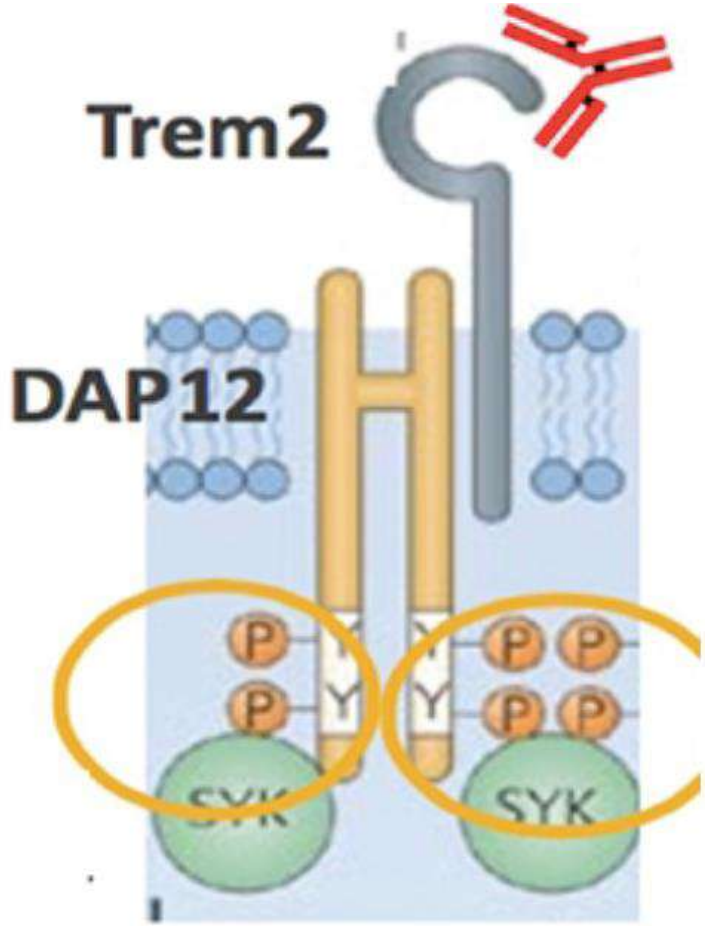
N. 48
IntrathecaL
36 weeks

Mummery CJ, et al. Nature Med 2023

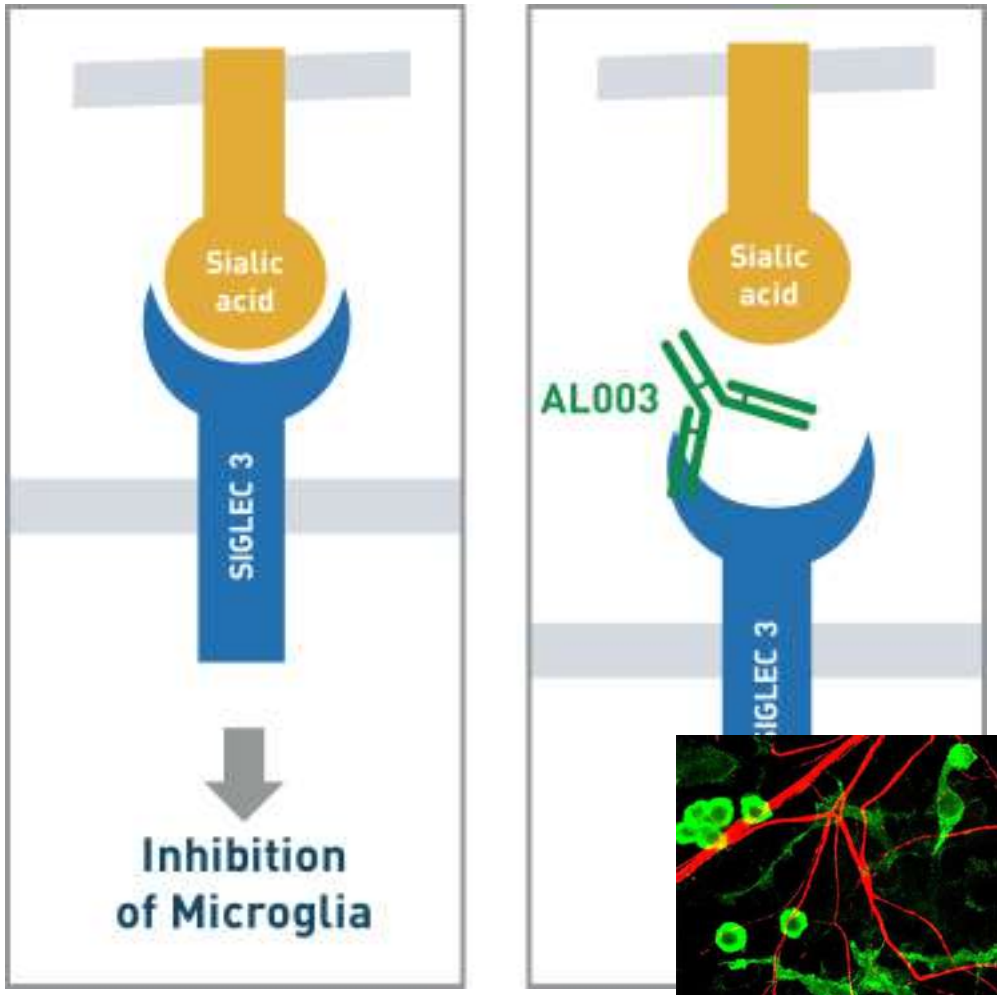
Ensayos clínicos en alzhéimer temprano

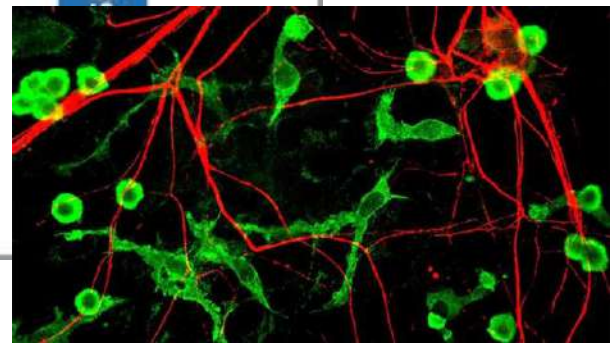
Diana: NeuroInflamación

AL00·3 – CD33



AL002 – TREM2





https://www.alzforum.org/news/research-news/2019-year-hope-alzheimers-research

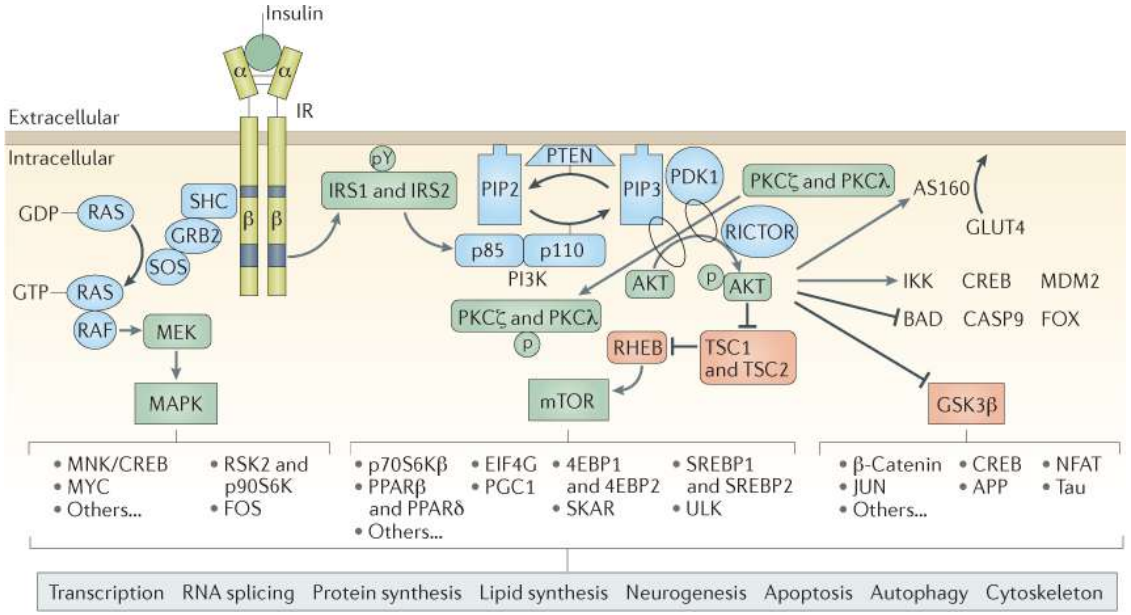
HOSPITAL CLINIC UNIVERSITARI

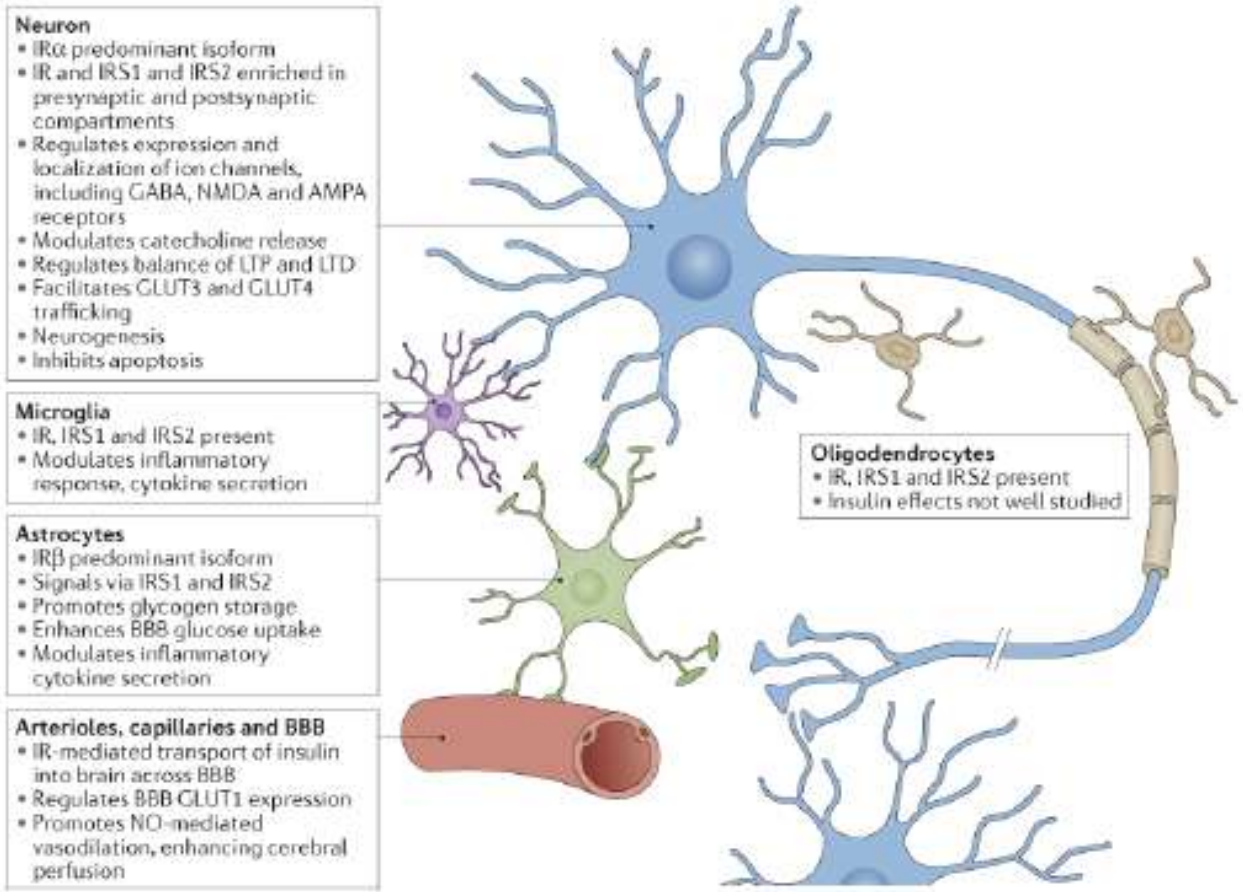
Nat Rev Neurol. 2018 March ; 14(3): 168–181.

Diana: Metabolismo

Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums

Steven E. Arnold[1], Zoe Arvanitakis[2], Shannon L. Macauley-Rambach[3], Aaron M. Koenig[1], Hoau-Yan Wang[4], Rexford S. Ahima[5], Suzanne Craft[6], Sam Gandy[7], Christoph Buettner[8], Luke E. Stoeckel[9], David M. Holtzman[3], and David M. Nathan[10]

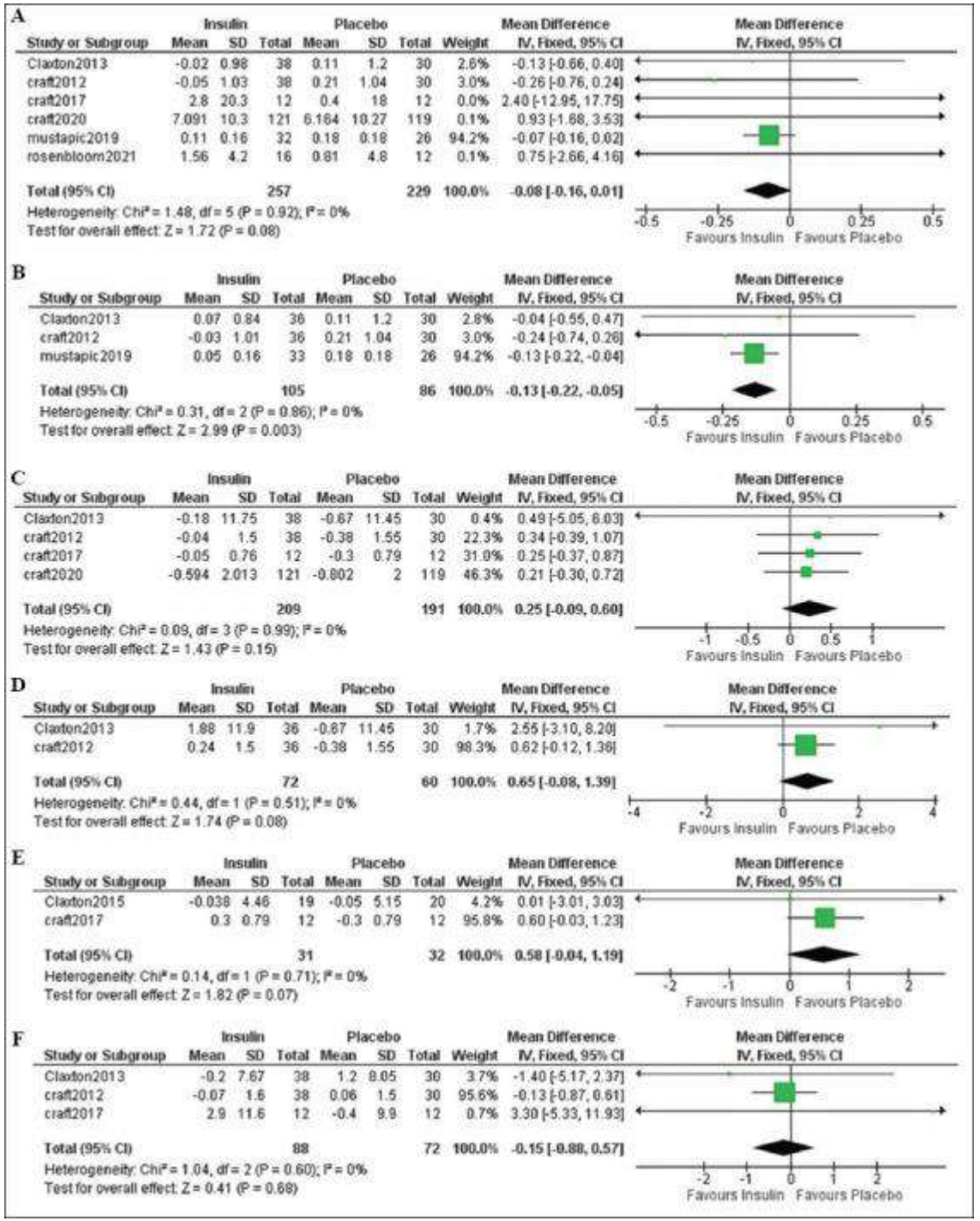




HOSPITAL CLINIC UNIVERSITARI

Universidad Católica de Valencia San Vicente Mártir

Safety and efficacy of intranasal insulin in patients with Alzheimer's disease: a systematic review and meta-analysis

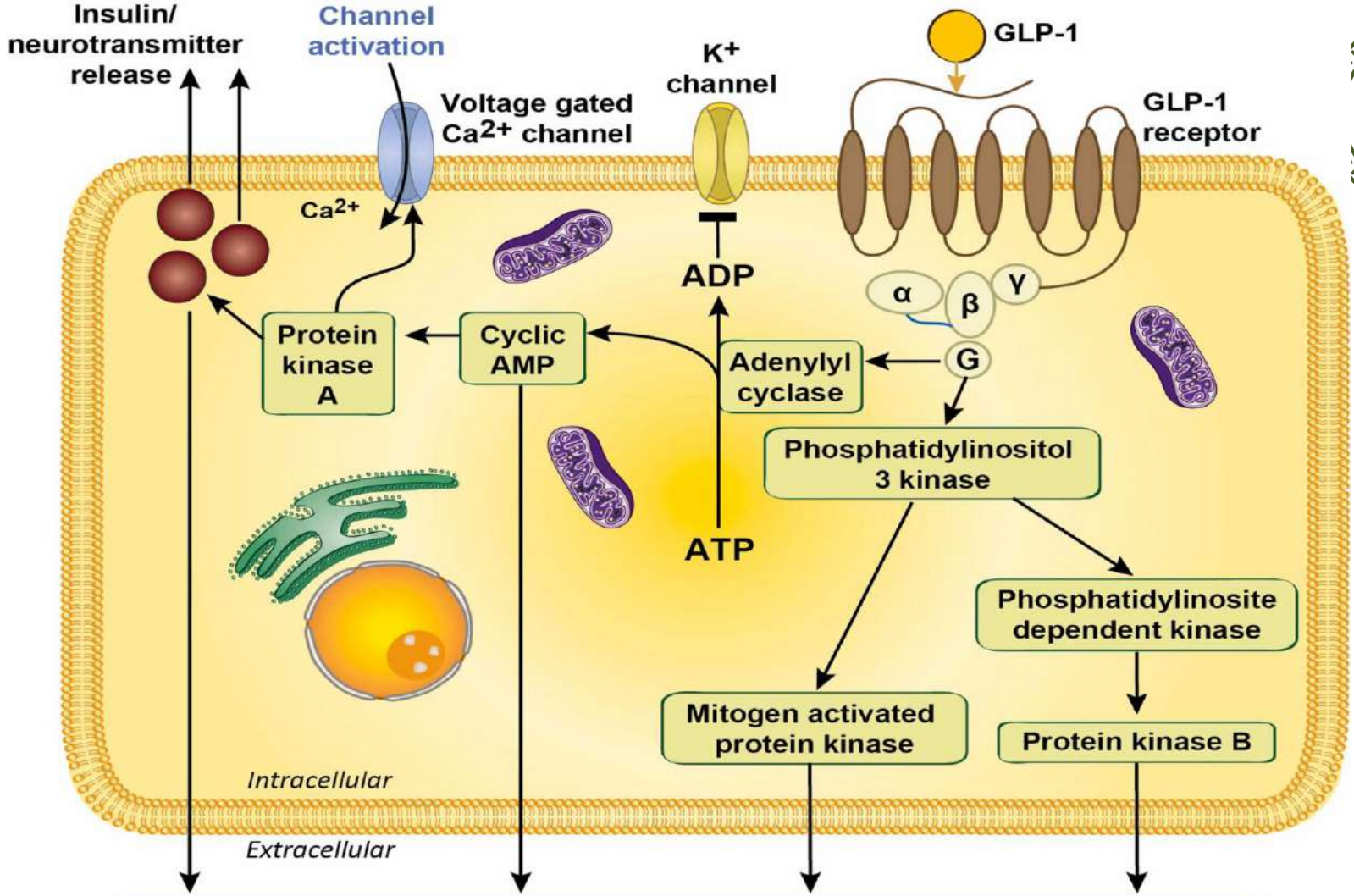


AboEl-Azm YH et al,

J Clin Transl Res. 2023 Jul 12;9(4):222-235.

HOSPITAL CLINIC UNIVERSITARI

Universidad Católica de Valencia San Vicente Mártir



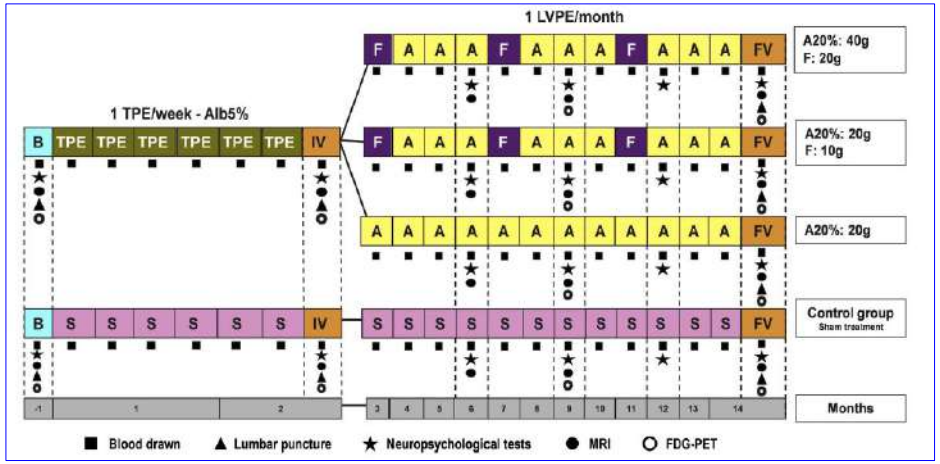
Neuronal development / Neuroprotection / Memory formation

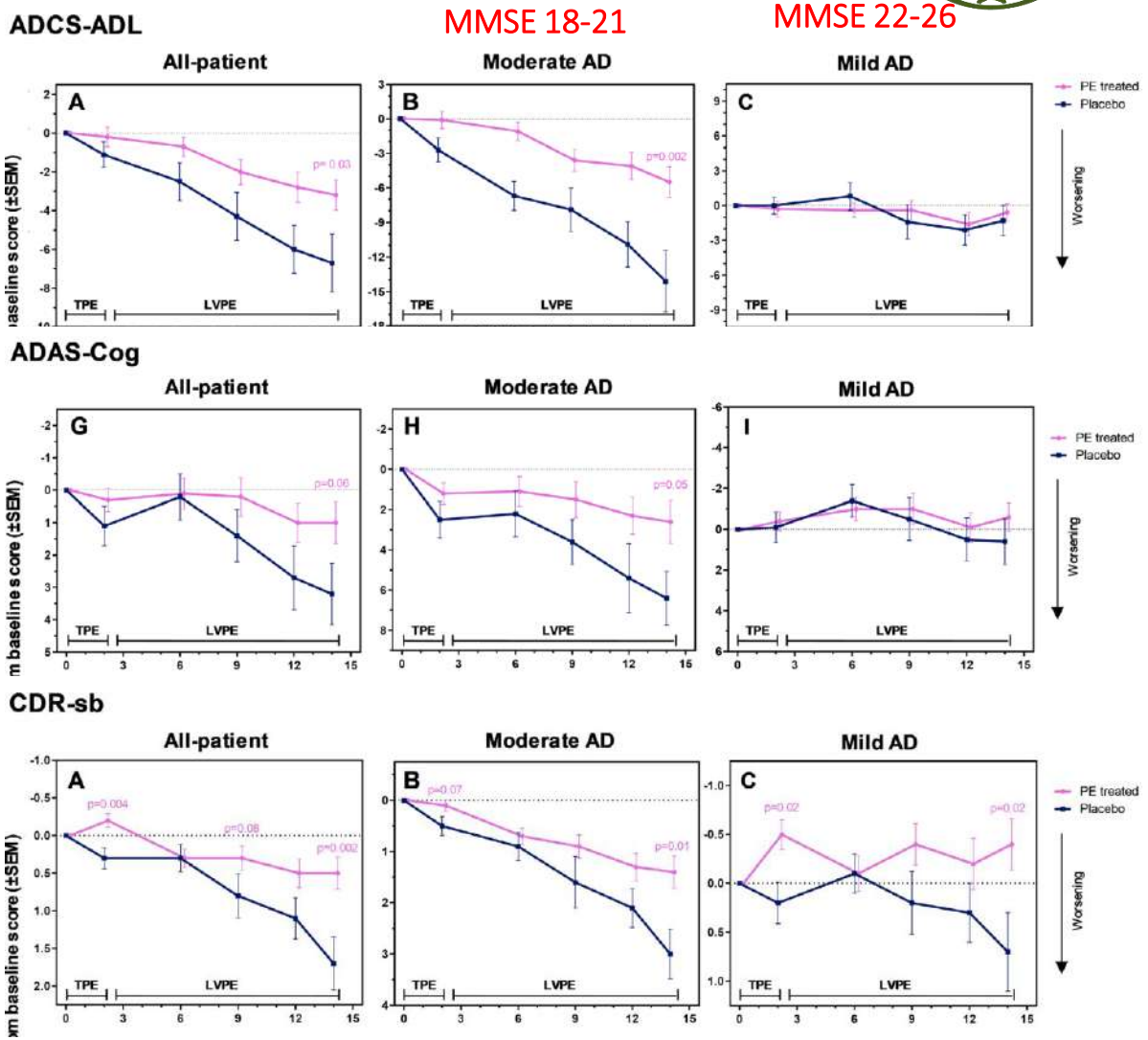
+ Long term potentiation	– Inflammation
+ Memory formation	– Apoptosis
+ Neuronal development	– α-synuclein
+ Cell survival	– Insulin resistance
+ Neurogenesis	– Tau hyperphosphorylation
+ Autophagy	– Amyloid deposition
+ Mitochondrial function	– Oxidative stress

Nowell J et al. Ageing Res Rev. 2023 Aug:89:101979.

Diana: Amiloide (plus?). Recambio de plasma/albúmina, Ig

Estudio AMBAR





Boada M, et al. Alz & Dem 2020, DOI: 10.1002/alz.12137
Boada M, et al Alz & Dem: Transl Res Clin Interv 2019; 5: 61-69

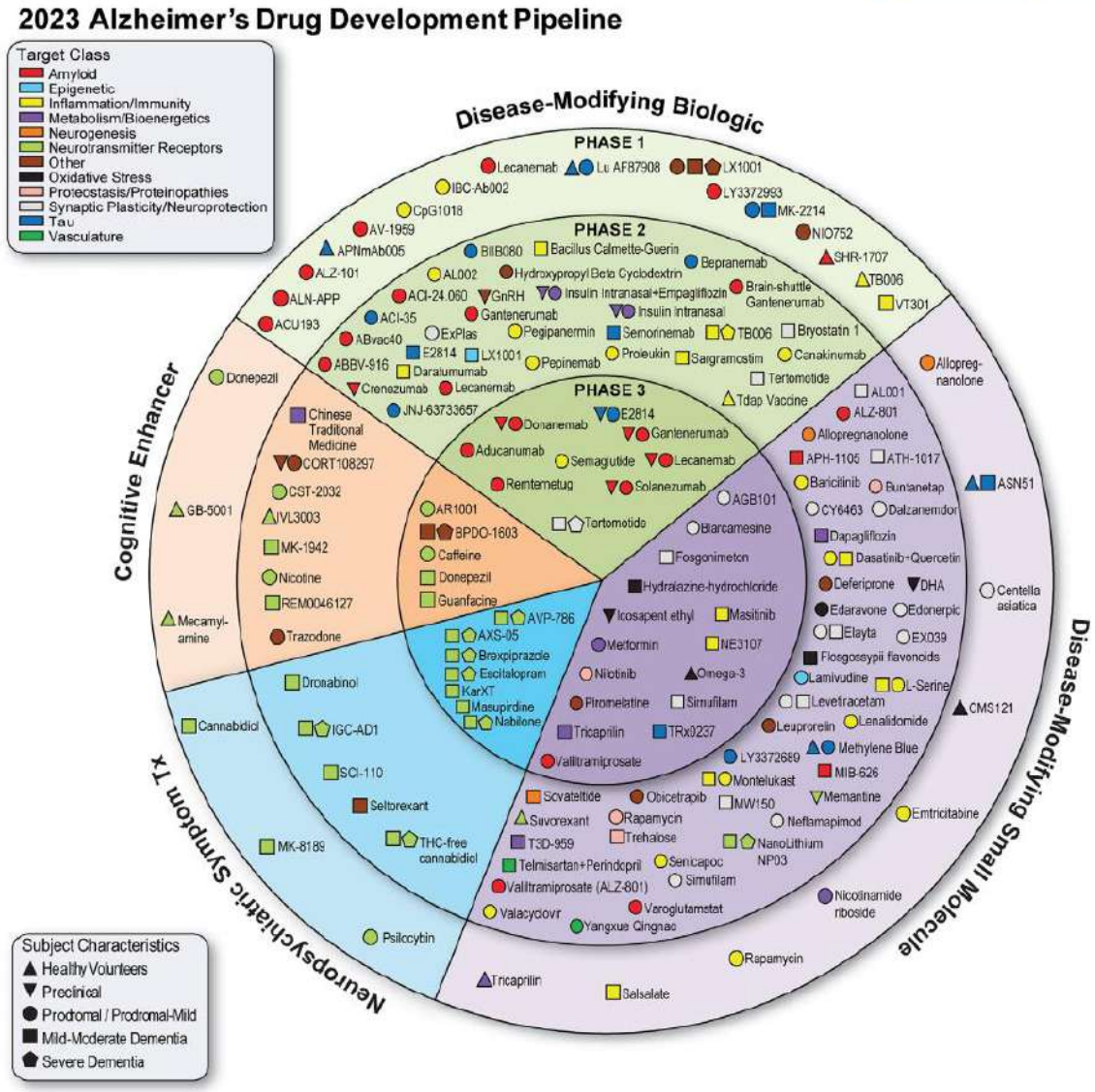
Alzheimer's disease drug development pipeline: 2023

HOSPITAL CLINIC UNIVERSITARI

Alzheimer's & Dementia
Translational Research & Clinical Interventions

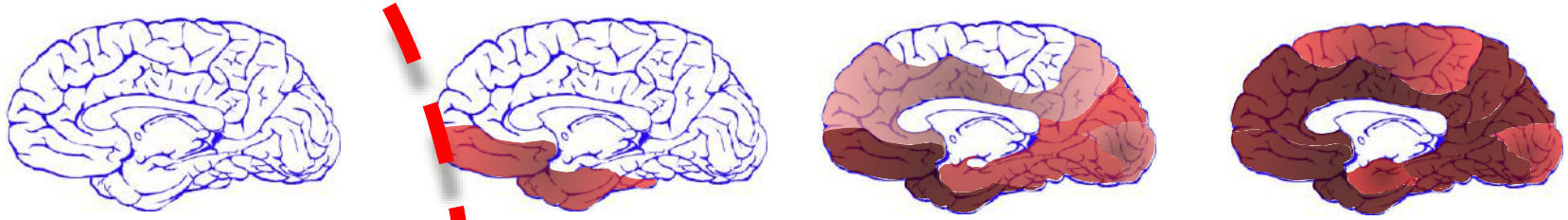
Universidad Católica de Valencia San Vicente Mártir

cita alzheimer



Cummings J, et al. Alz & Dem Trans Res Clin Interv 2023; 9: e12385

PREVENCION



Cerebro sano

PRE-CLINICA

PRODROMICA

“PRIMARIA"

Detección de personas en riesgo / fragilidad
(Índice CAIDE)

Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) Dementia Risk Score,

HOSPITAL CLINIC UNIVERSITARI

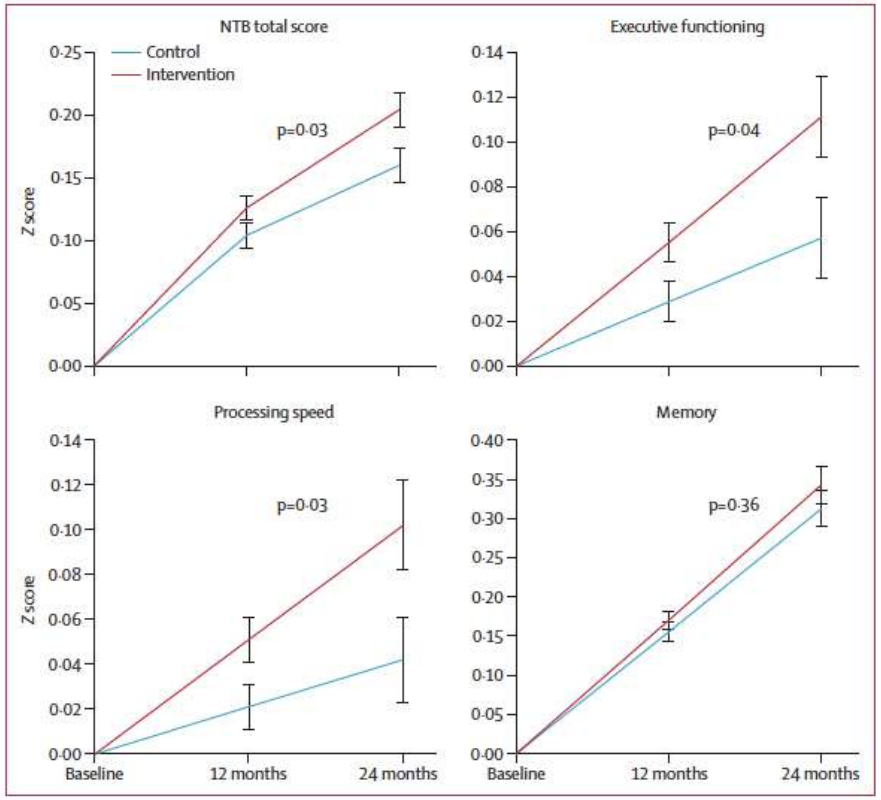
A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälahti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilkka Soininen, Miia Kivipelto

Lancet 2015; 385: 2255–63

Universidad Católica de Valencia San Vicente Mártir

cita alzheimer



Findings from this large, long-term, randomised controlled trial suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population

ESTUDIO FINGER

Intervención:

- **Dieta**
- **Ejercicio físico**
- **Entrenamiento cognitivo**
- **Control de los factores de riesgo**

Control:

- **recomendaciones generales de salud**

Randomized Controlled Trial > Alzheimers Dement. 2023 Apr;19(4):1308-1319.
doi: 10.1002/alz.12767. Epub 2022 Sep 14.

Effects of cocoa extract and a multivitamin on cognitive function: A randomized clinical trial

Laura D Baker [1 2], Joann E Manson [3 4], Stephen R Rapp [5 2], Howard D Sesso [3 4], Sarah A Gaussoin [6], Sally A Shumaker [2], Mark A Espeland [1 6]

Randomized Controlled Trial > Am J Clin Nutr. 2023 Jul;118(1):273-282.
doi: 10.1016/j.ajcnut.2023.05.011. Epub 2023 May 24.

Multivitamin Supplementation Improves Memory in Older Adults: A Randomized Clinical Trial

Lok-Kin Yeung [1], Daniel M Alschuler [2], Melanie Wall [3], Heike Luttmann-Gibson [4], Trisha Copeland [5], Christiane Hale [1], Richard P Sloan [6], Howard D Sesso [7], JoAnn E Manson [8], Adam M Brickman [9]

Decálogo para mantener un

cerebro saludable

SEN
Sociedad Española de Neurología

1

Realiza **actividades que estimulen la actividad cerebral** y te mantengan cognitivamente activo como leer, escribir, participar en juegos de mesa, realizar actividades manuales, completar crucigramas, aprender y practicar un nuevo idioma, etc.

2

Evita el sobrepeso y realiza algún tipo de **actividad física de forma regular**, bien mediante la práctica de algún deporte o realizando uno o dos paseos diarios de al menos 30 minutos.

3

Evita los tóxicos como el alcohol, el tabaco, la contaminación ambiental y cualquier tipo de drogas.

4

Controla otros factores de riesgo vascular, como la tensión arterial, la diabetes o la hiperglucemia. La hipertensión es el principal factor de riesgo de algunas enfermedades neurológicas.

5

Potencia tus relaciones sociales y afectivas evitando la incomunicación y el aislamiento social, pues son factores de riesgo para desarrollar deterioro cognitivo en el futuro.

6

Sigue una **dieta equilibrada** evitando el exceso de grasas animales, azúcar, sal y alimentos procesados y ultraprocesados.
Opta por **alimentos naturales** y potencia el consumo de frutas, legumbres y verduras: la dieta mediterránea es tu mejor aliada.

7

Un **sueño de calidad** es fundamental para la salud de tu cerebro. Trata de dormir unas 8 horas diarias.

8

Ten **moderación en el uso de Internet, pantallas digitales y redes sociales**. Su uso excesivo reduce la capacidad de concentración, atención y aprendizaje y, su uso nocturno, genera mayor dificultad para conciliar y mantener el sueño.

9

Protege tu cerebro contra las agresiones físicas del exterior mediante la utilización sistemática del cinturón de seguridad en vehículos y del casco en cualquier actividad que lo requiera (moto, bicicleta, patinete eléctrico, actividades laborales, etc.).

10

Elimina el estrés en todos los ámbitos de la vida que te sea posible y...

¡Ten una actitud positiva!

El buen humor y la risa fortalecen a tu cerebro.

SEN
Sociedad Española de Neurología

Mantén joven tu cerebro

José Miguel Láinez Andrés
Jesús Porta Etessam

Con objeto de mejorar el bienestar de nuestros pacientes, la Junta Directiva de la Sociedad Española de Neurología desarrolla campañas continuas de promoción de la salud cerebral, entre ellas este manual, que busca ayudar a la población a cuidar su cerebro.

HOSPITAL CLINIC UNIVERSITARI

Universidad Católica de Valencia San Vicente Mártir