Results of SIGNAL-AD, a randomized, phase 1b/2 trial to evaluate safety and efficacy of pepinemab, anti-SEMA4D antibody believed to block reactive astrogliosis, in patients with Mild Cognitive Impairment (MCI) and mild dementia due to AD

Elizabeth Evans, PhD
Senior VP, Discovery and Translational Medicine
Chief Operating Officer

VACCINEX
Unique Targets
Novel Mechanisms
New Medicines

CTAD
Clinical Trials on Alzheimer's Disease

October 31, 2024

DISCLOSURES

Elizabeth Evans

Full-time employee, officer, and stockholder of Vaccinex, Inc.

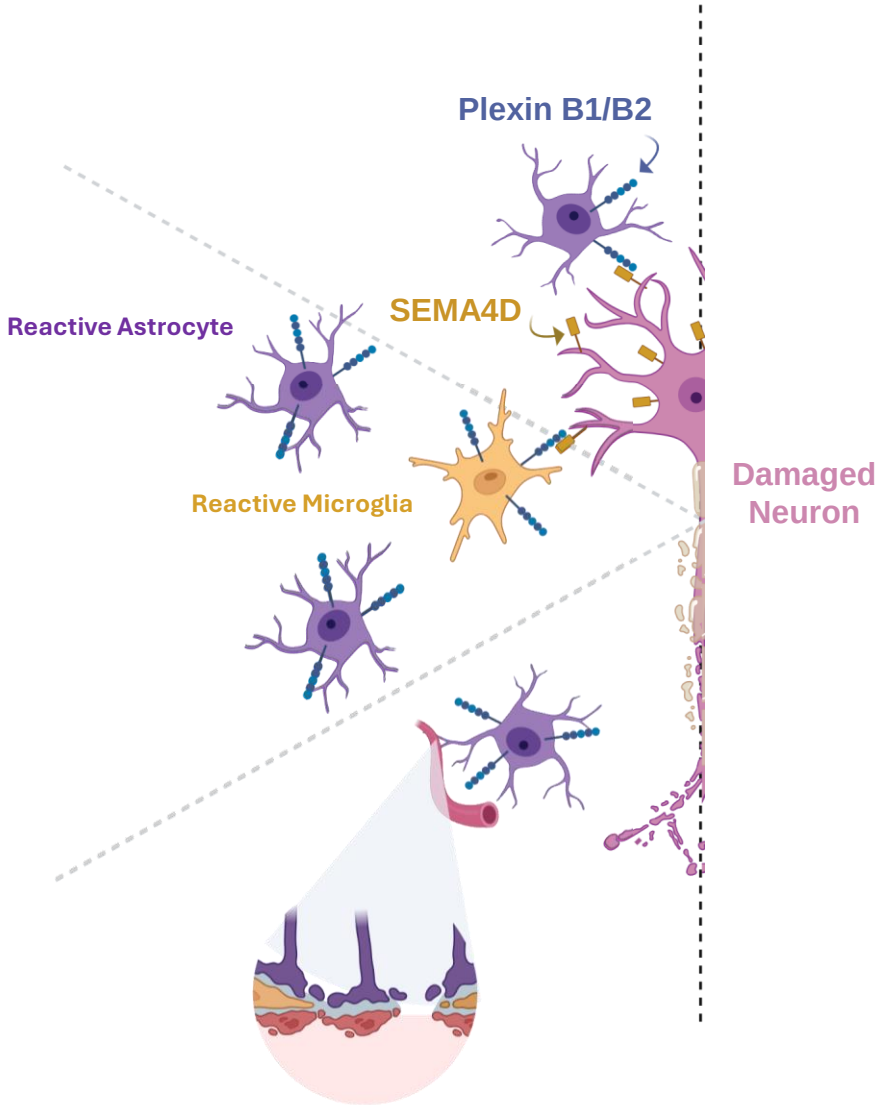
This presentation involves discussion of unapproved, experimental or investigational use of pepinemab.

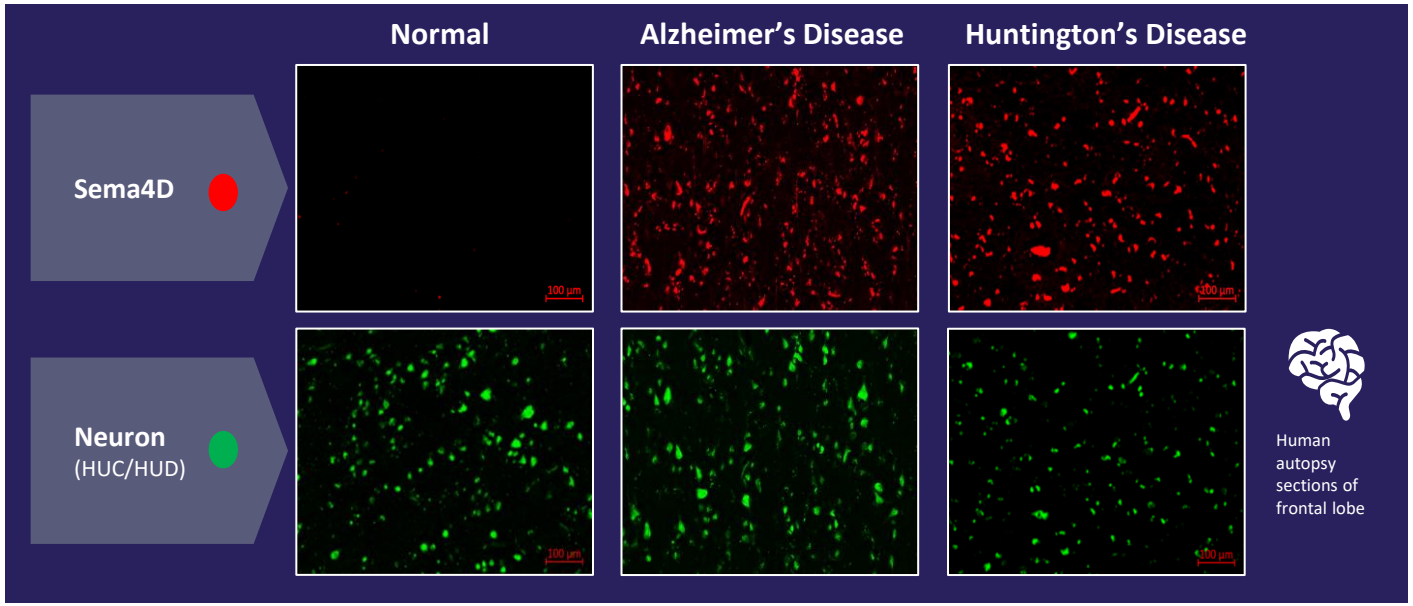
Forward Looking Statements

To the extent that statements contained in this presentation are not descriptions of historical facts regarding Vaccinex, Inc. ("Vaccinex," "we," "us," or "our"), they are forward-looking statements reflecting management's current beliefs and expectations. Such statements include, but are not limited to, statements about the Company's plans, expectations and objectives with respect to the results and timing of clinical trials of pepinemab in various indications, the use and potential benefits of pepinemab in Head and Neck cancer, Huntington's and Alzheimer's disease and other indications, and other statements identified by words such as "may," "will," "appears," "expect," "planned," "anticipate," "estimate," "intend," "hypothesis," "potential," "advance," and similar expressions or their negatives (as well as other words and expressions referencing future events, conditions, or circumstances). Forward-looking statements involve substantial risks and uncertainties that could cause the outcome of the Company's research and pre-clinical development programs, clinical development programs, future results, performance, or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, uncertainties inherent in the execution, cost and completion of preclinical and clinical trials, uncertainties related to regulatory approval, the risks related to the Company's dependence on its lead product candidate pepinemab, the ability to leverage its ActivMAb® platform, the impact of the COVID-19 pandemic, and other matters that could affect the Company's development plans or the commercial potential of its product candidates. Except as required by law, the Company assumes no obligation to update these forward-looking statements. For a further discussion of these and other factors that could cause future results to differ materially from any forward-looking statement, see the section titled "Risk Factors" in the Company's periodic reports filed with the Securities and Exchange Commission ("SEC") and the other risks and uncertainties described in the Company's most recent year end Annual Report on Form 10-K and subsequent filings with the SEC.

Semaphorin 4D

Neuroinflammation /
Neurodegeneration





Loss of glial homeostatic functions

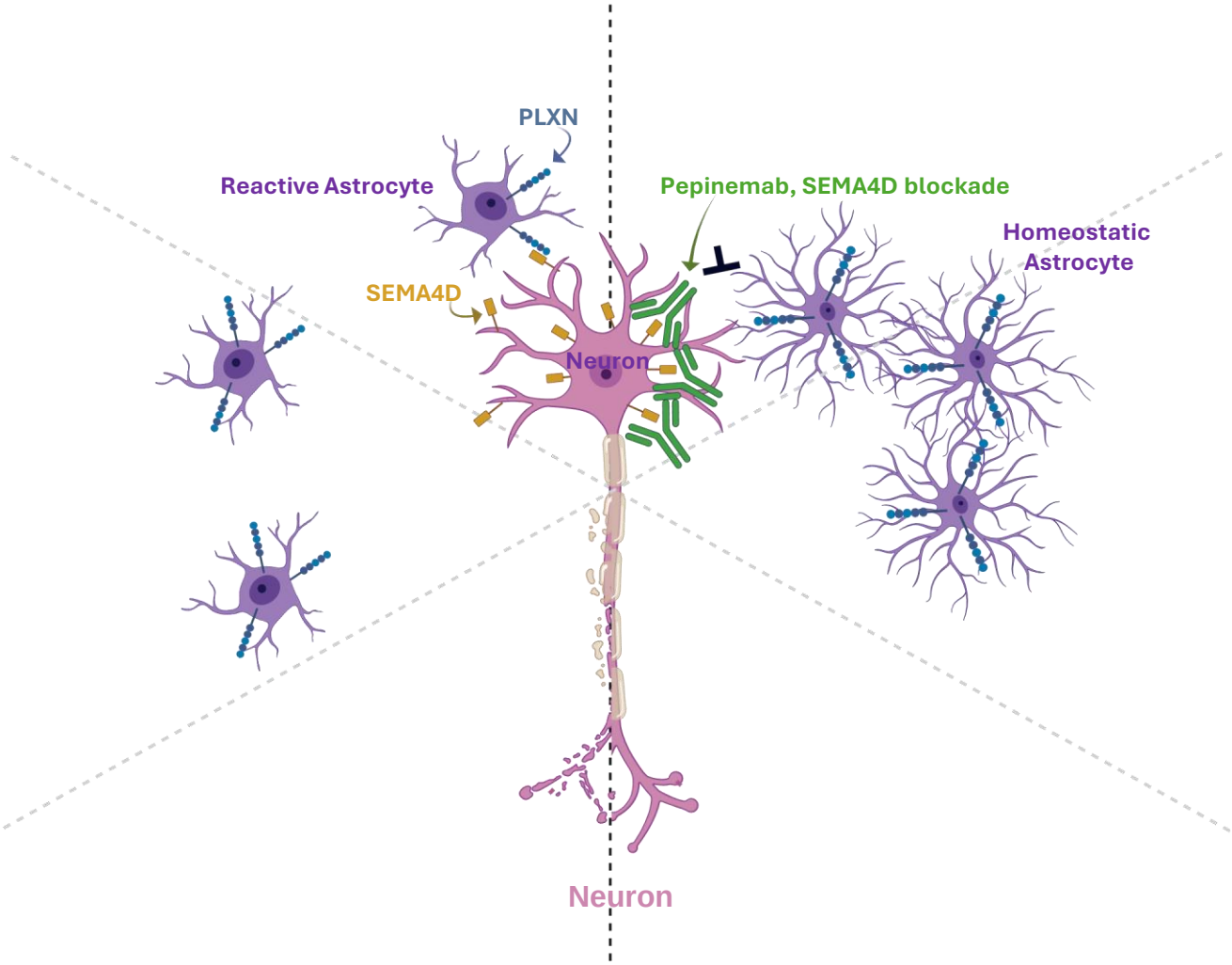
Gain of inflammatory processes

Disruption of vascular integrity

Pepinemab: SEMA4D blocking antibody

Neuroinflammation / Neurodegeneration

Pepinemab to overcome Neuroinflammation / Neurodegeneration

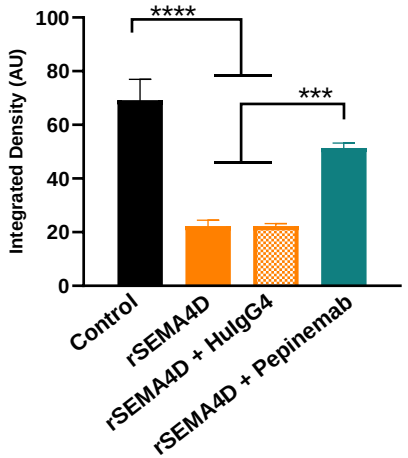


Pepinemab

Restores Astrocyte Function

Glucose Transporter

GLUT-1



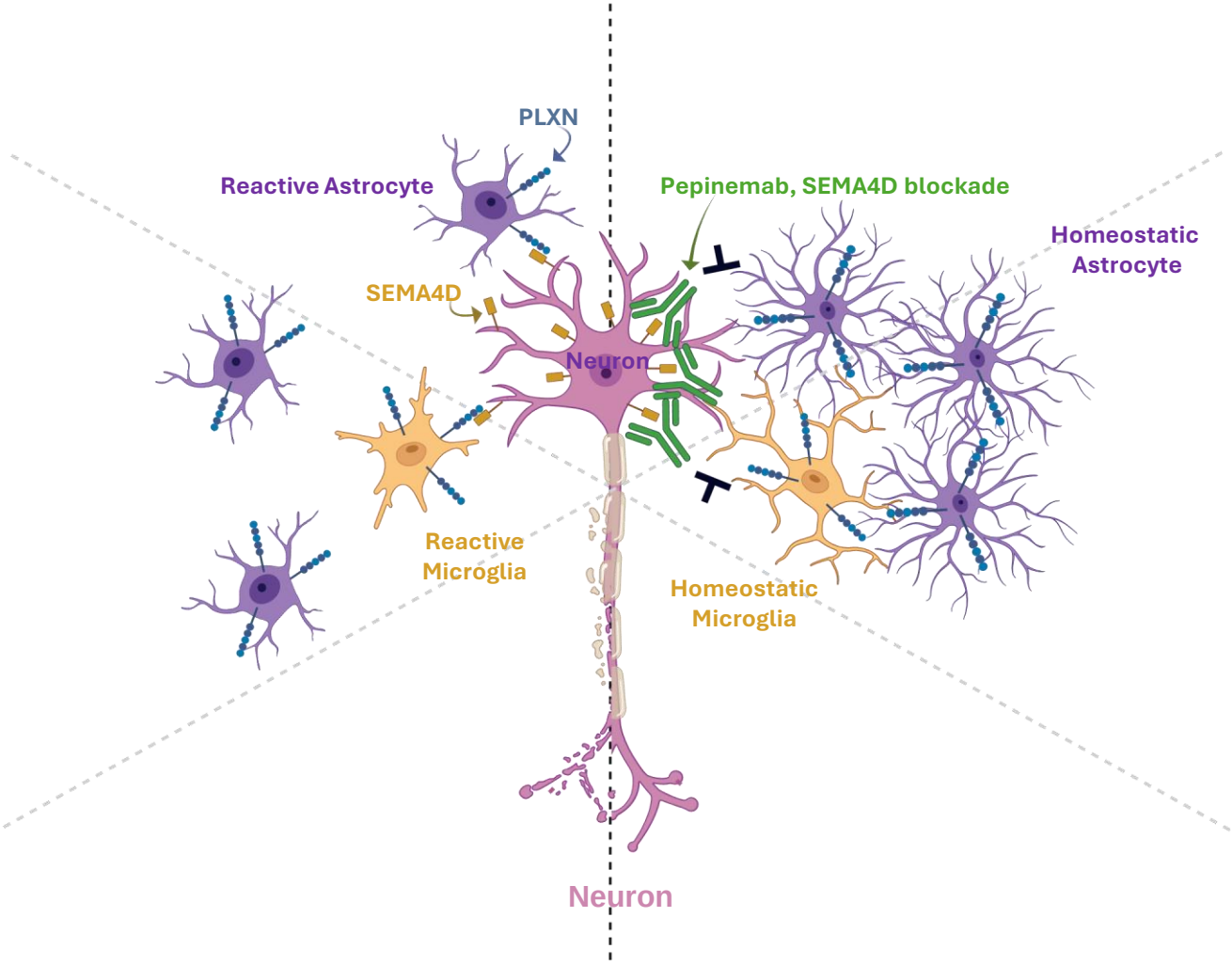
Purified human astrocyte cultures

Evans et al. Journal of Neuroinflammation, 2022

Pepinemab: SEMA4D blocking antibody

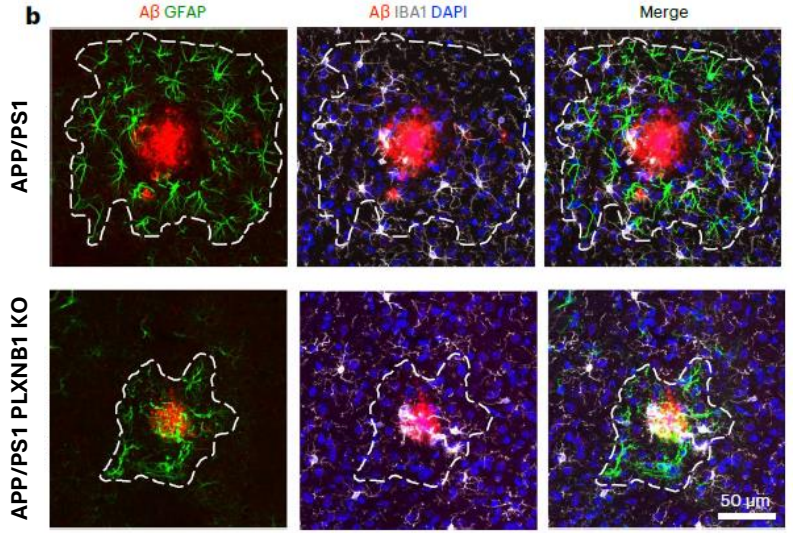
Neuroinflammation / Neurodegeneration

Pepinemab to overcome Neuroinflammation / Neurodegeneration

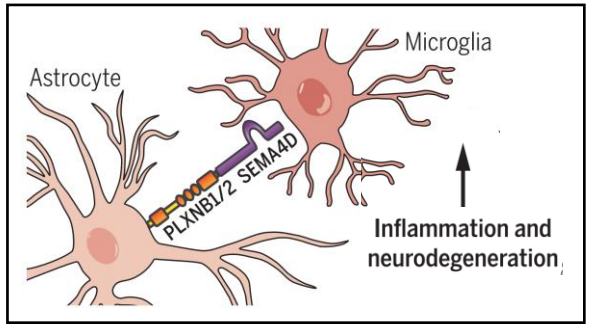


Pepinemab

Regulates Microglia/ Astrocyte Cross talk



Alzheimer's Model:
Huang et al. Nature Neuroscience 2024

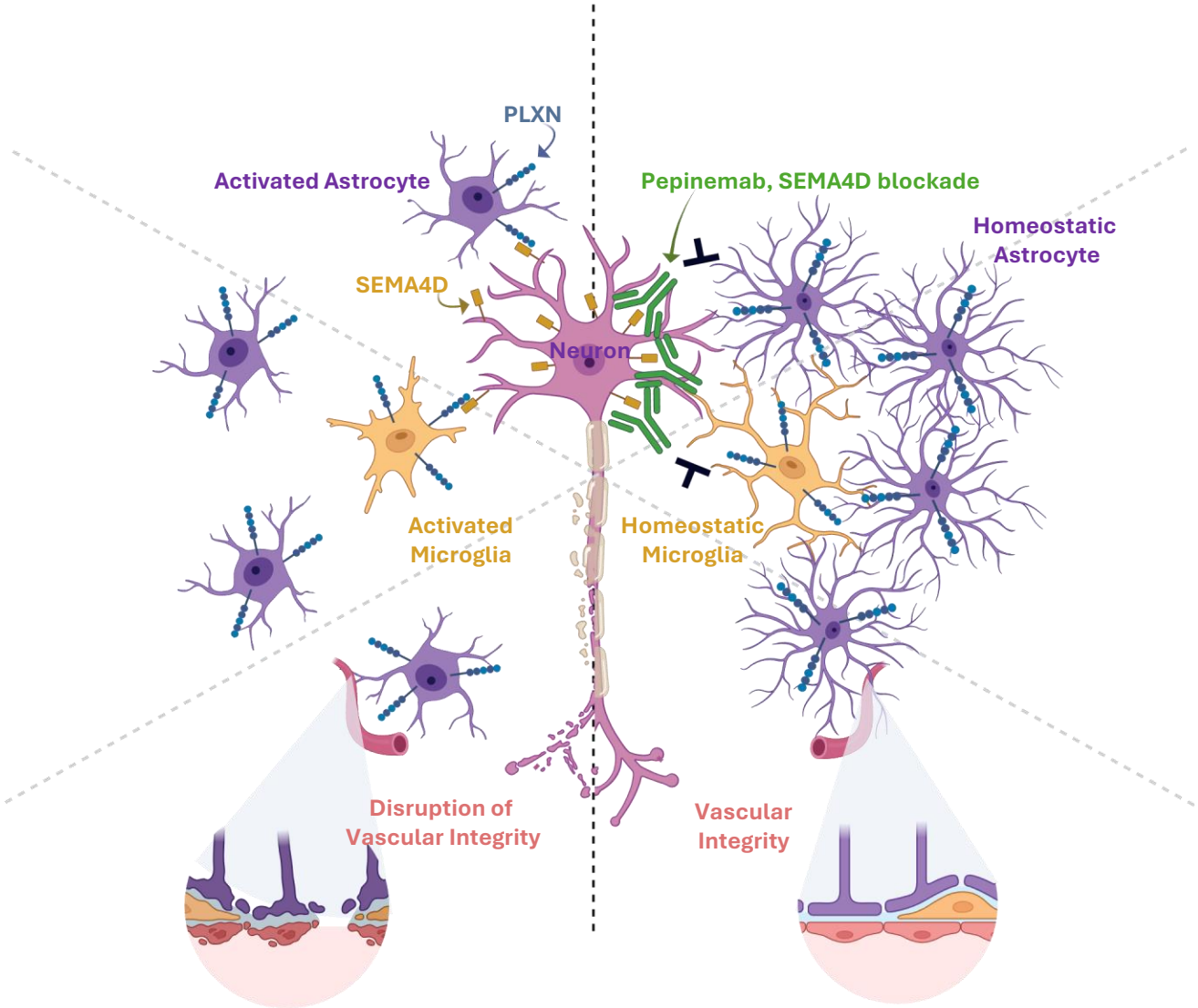


EAE Model of MS:
Clark et al. Science 2021

Pepinemab: SEMA4D blocking antibody

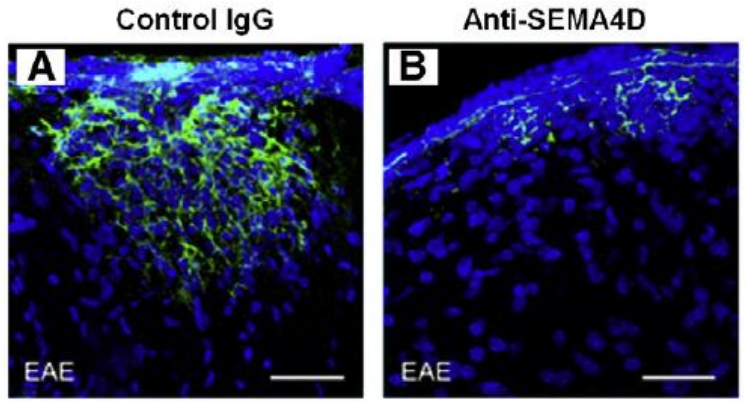
Neuroinflammation / Neurodegeneration

Pepinemab to overcome Neuroinflammation / Neurodegeneration



Pepinemab

Restores Vascular Integrity



Fibrinogen leakage in mouse EAE model of Multiple Sclerosis

Smith et al. Neurobiology of Disease 2015

Huntington's disease Phase 2 trial

NCT02481674

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01919-8

Check for updates

OPEN

Pepinemab antibody blockade of SEMA4D in early Huntington's disease: a randomized, placebo-controlled, phase 2 trial

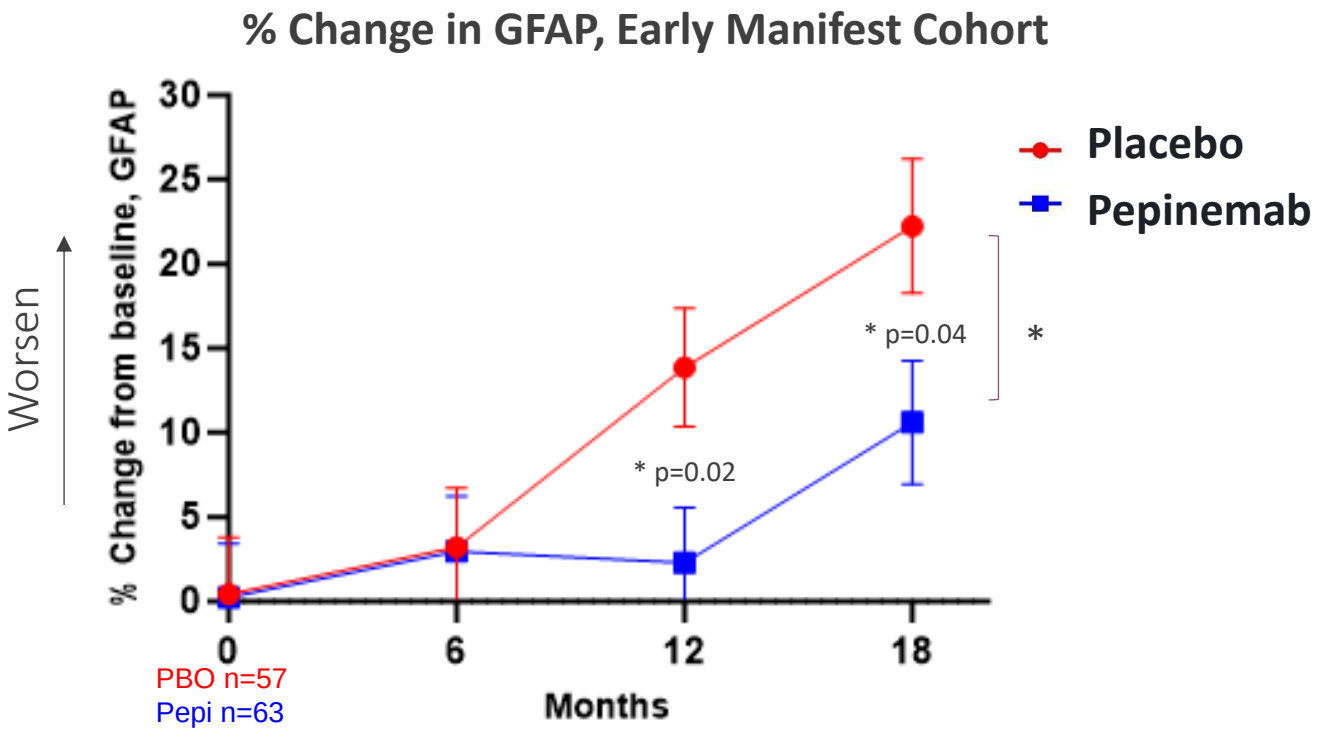
Andrew Feigin[1], Elizabeth E. Evans[2], Terrence L. Fisher[2], John E. Leonard[2], Ernest S. Smith[2], Alisha Reader[2], Vikas Mishra[2], Richard Manber[3], Kimberly A. Walters[4], Lisa Kowarski[4], David Oakes[5], Eric Siemers[6], Karl D. Kieburtz[5], Maurice Zauderer[2]✉ and the Huntington Study Group SIGNAL investigators*

Glial Fibrillary Acidic Protein (GFAP)

Biomarker for astrocyte activation / dysfunction

NCT02481674

SIGNAL



* % change from baseline over time was analyzed via MMRM after adjusting for baseline value and age. P values represent t-tests for significant difference (PEPI-PBO) at each timepoint.

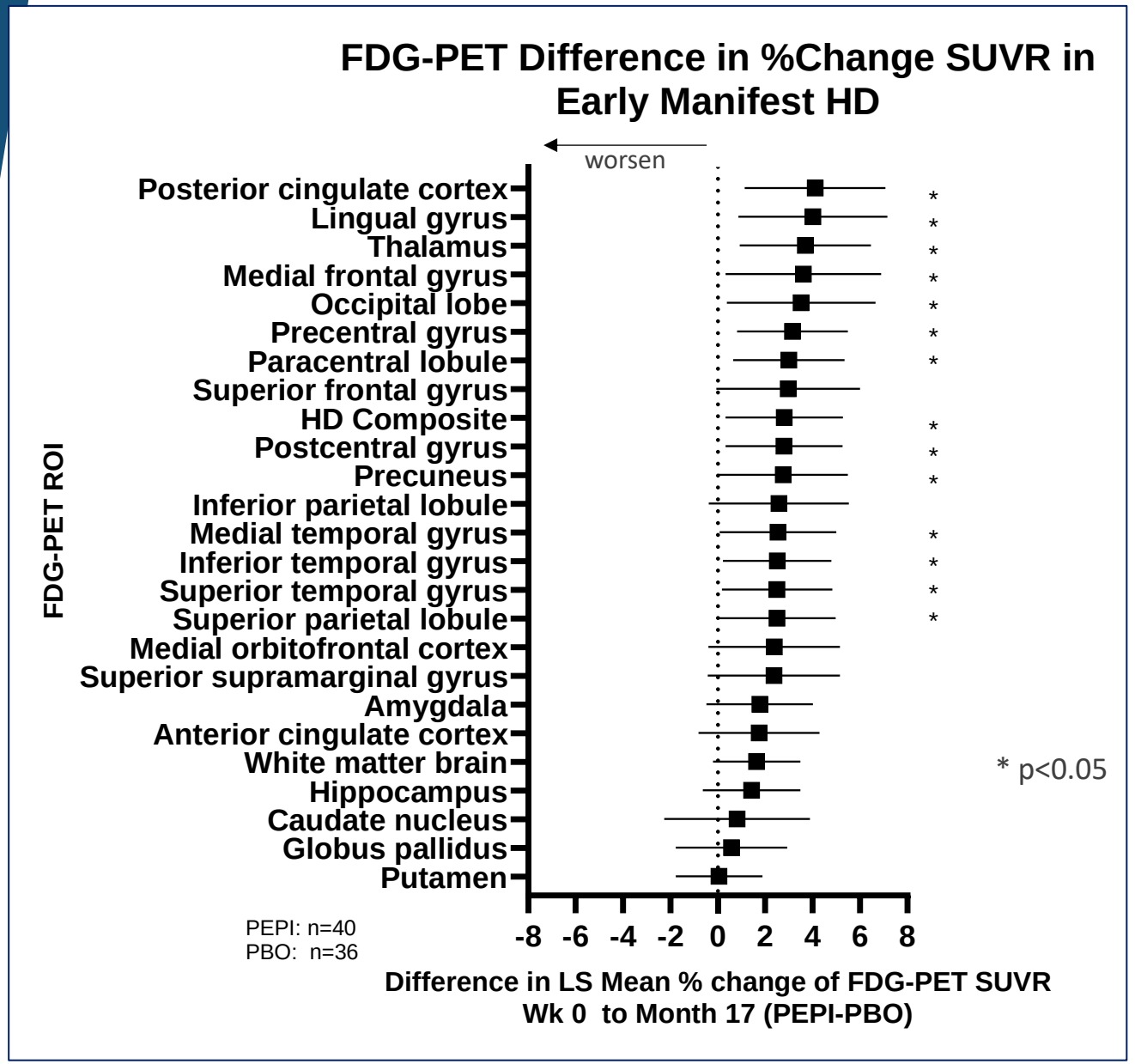
Pepinemab reduced plasma GFAP in SIGNAL-HD

Pepinemab treatment reversed loss of brain metabolic activity

NCT02481674

SIGNAL

Decline in FDG-PET is reported to correlate with cognitive impairment in neurodegenerative diseases.



Feigin, A et al. *Nature Medicine* (2022)
https://doi.org/10.1038/s41591-022-01919-8

HD-COGNITIVE ASSESSMENT BATTERY (HD-CAB)

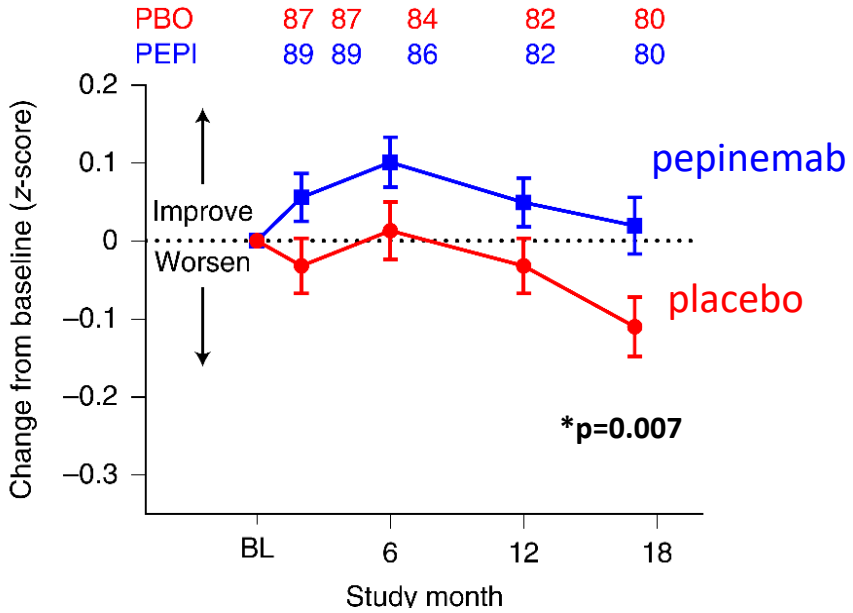
Exploratory and Post-hoc analysis

NCT02481674

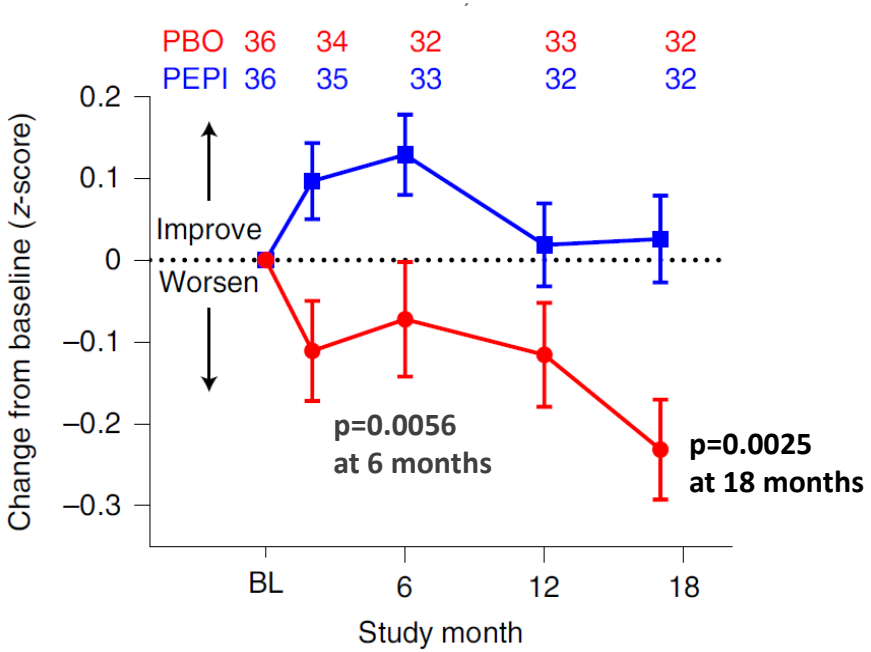
SIGNAL

Treatment effect is most evident in patients with early signs of cognitive deficits (MoCA < 26)

Early Manifest HD:
Intent to treat population (mITT)



MoCA 20-25, Early Manifest
Post-hoc analysis



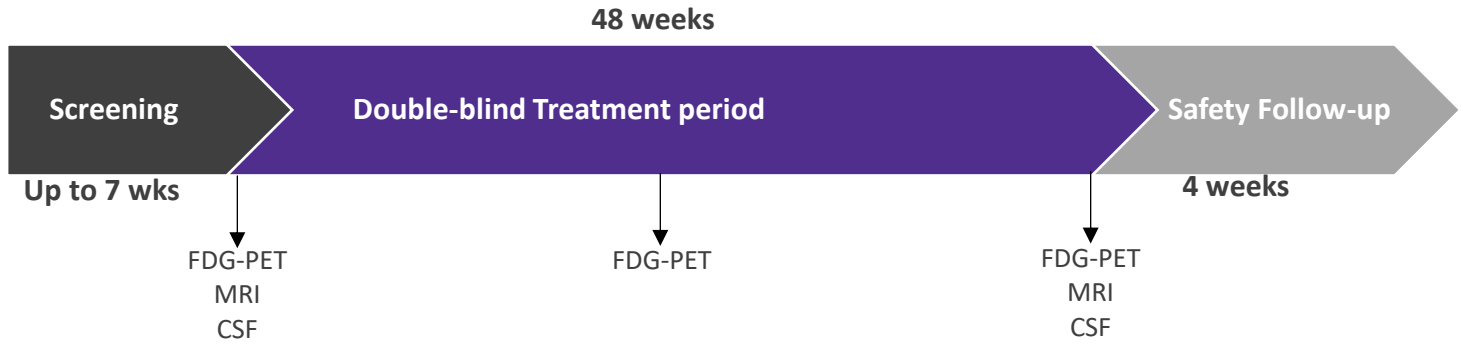
Feigin, A., Evans, E.E., Fisher, T.L. et al.
Nature Medicine (2022), 28: 2183-2193

ALZHEIMER'S DISEASE

Phase 1b/2 Trial Design

NCT04381468
SIGNAL-AD

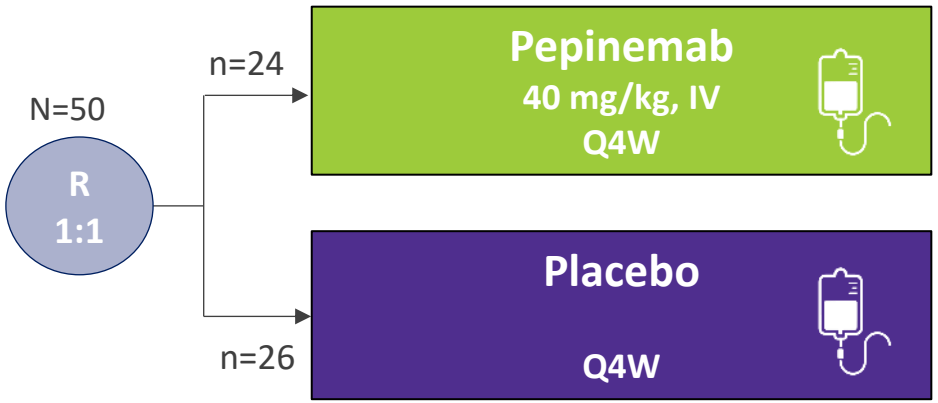
Funding by alzheimer's association® Alzheimer's Drug Discovery Foundation



MCI and Mild AD dementia

Key eligibility criteria:

- CDR-GS = 0.5 or 1.0
- MMSE = 17-26
- Amyloid positive (PET or CSF)



Objectives:

Primary	**Safety and Tolerability**
Secondaries	• **Change in FDG-PET SUVR at Week 48** • Plasma GFAP and pTau-217 • Cognitive and Functional measures: Change in CDR-SB, iADRS, ADAS-Cog13, MMSE, ADCS-ADL (basic, instrumental, total), and ADCS-CGIC
Exploratory	• **Subgroup analysis: including CDR-GS 0.5/1 and MMSE 22-26/17-21 (MCI or mild dementia)** • PK/PD

Pepinemab-induced Cognitive and Fluid Biomarker Changes Diverge with Stage of AD Disease

NCT04381468
SIGNAL-AD

“MCI” **“Mild Dementia”**

Disease Progression

Very early

- CDR-GS 0.5 *and* Low GFAP (plasma GFAP levels <225 pg/ml)
- **Pepinemab treatment blocks or reduces increase in plasma GFAP and pTau-217, biomarkers of disease progression**

Early

- MMSE 22-26
- **Pepinemab treatment prevents or limits cognitive decline without significant effects on GFAP or pTau**

More advanced

- CDR-GS 1, MMSE 17-21
- **Little or no treatment effect evident on cognitive decline by CDR-SB or iADRS.**

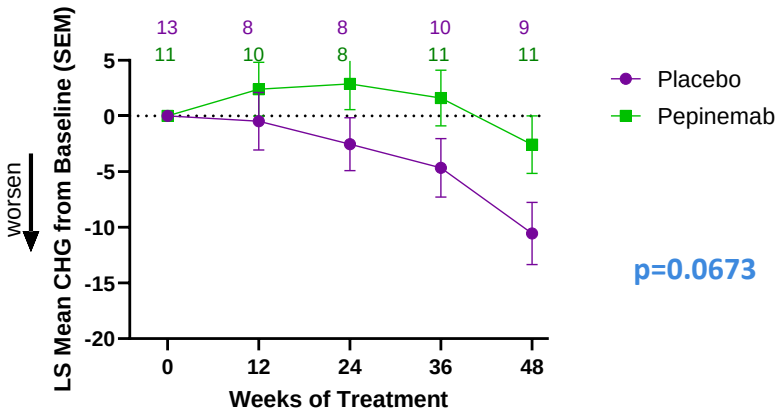
Clinical Outcome Assessments

Pepinemab-induced Cognitive Changes Diverge with Stage of AD

NCT04381468
SIGNAL-AD

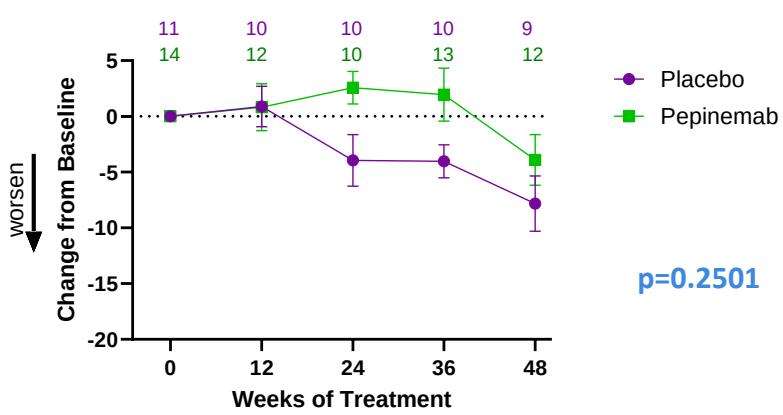
Placebo
Pepinemab

iADRS in MMSE 22-26 subgroup



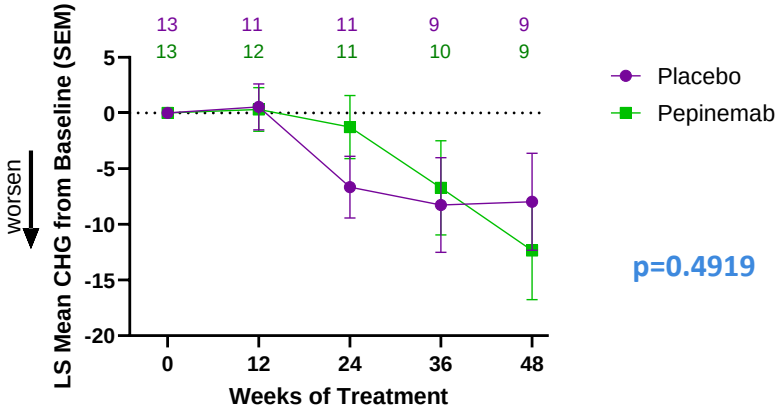
p=0.0673

iADRS in CDR-GS 0.5 subgroup



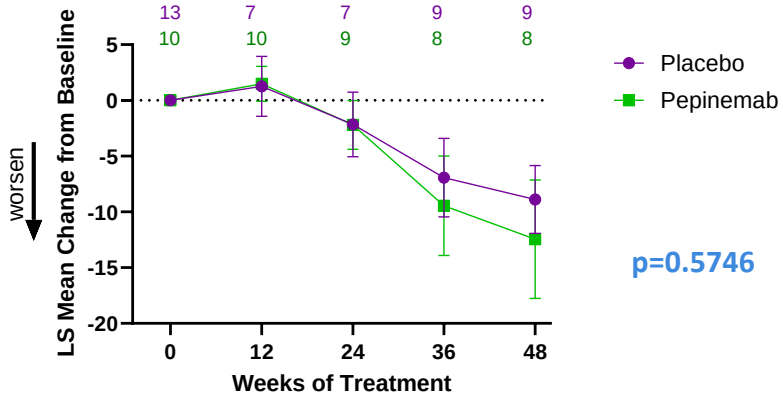
p=0.2501

iADRS in MMSE 17-21 subgroup



p=0.4919

iADRS in CDR-GS 1 subgroup



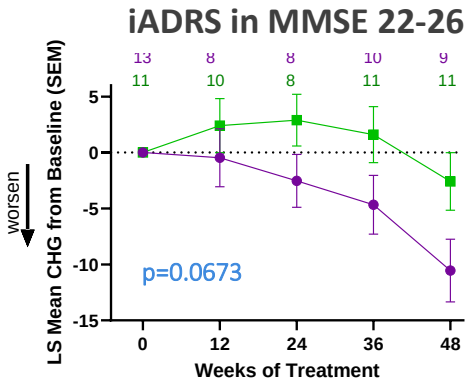
p=0.5746

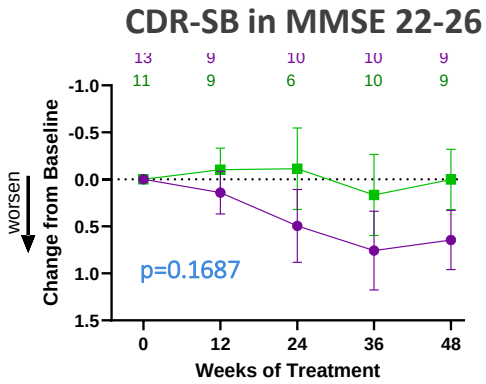
Disease Progression

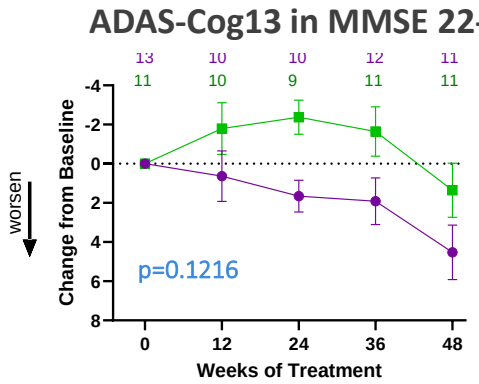
Cognitive effects for MMSE 22-26 (63% CDR-GS 0.5, 36% GS 1) overlap but do not coincide with CDR-GS 0.5

NCT04381468
SIGNAL-AD

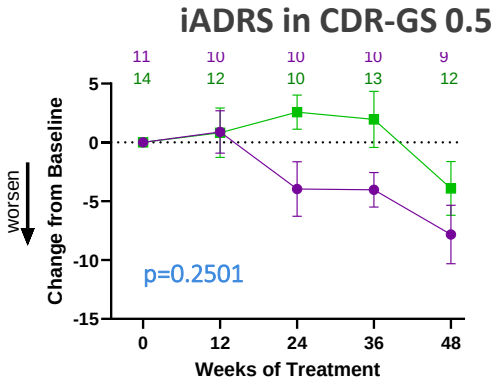
Subgroup: Baseline MMSE 22-26

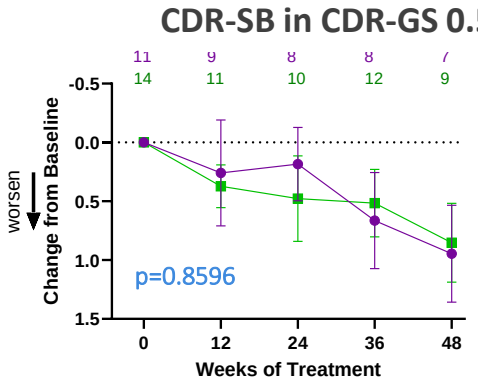


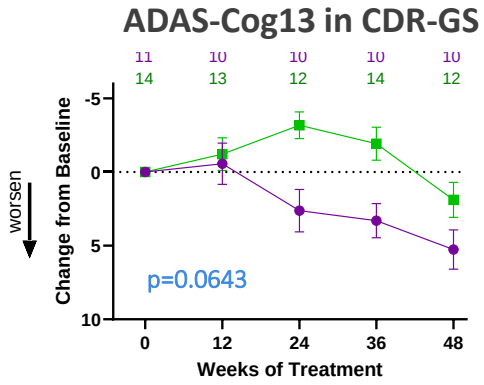




Subgroup: Baseline CDR-GS 0.5







Placebo
Pepinemab

Disease Progression

Plasma Biomarkers

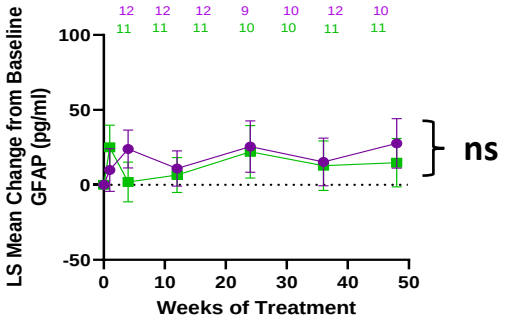
Pre-specified early AD subgroups (MMSE 22-26 or CDR 0.5)

NCT04381468

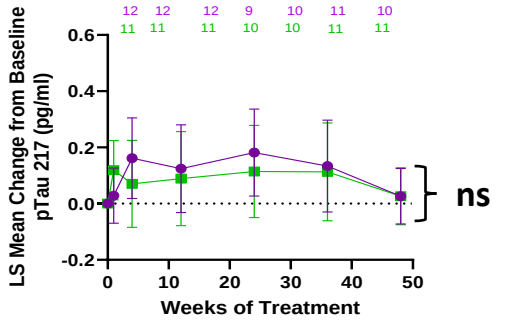
SIGNAL-AD

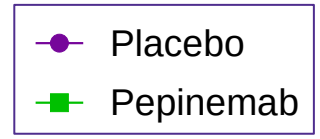
Subgroup: Baseline MMSE 22-26

Plasma GFAP in MMSE22-26



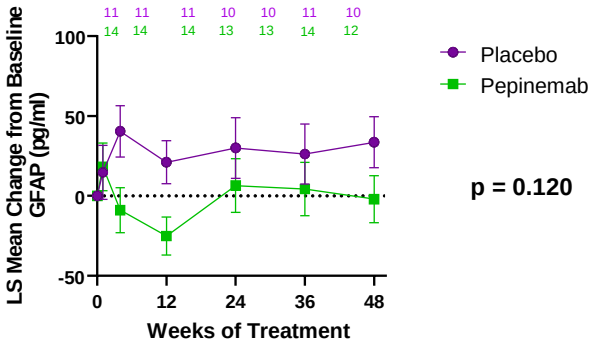
Plasma pTau-217 in MMSE22-26



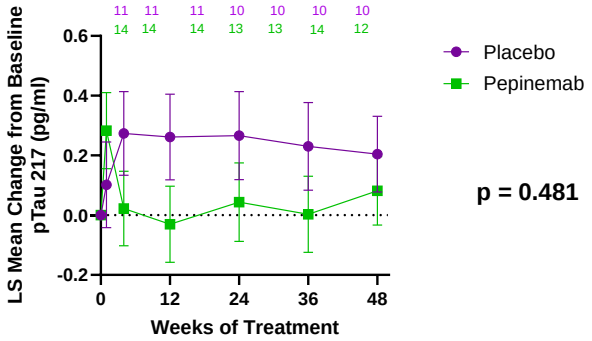


Subgroup: Baseline CDR-GS 0.5

Plasma GFAP



Plasma pTau-217

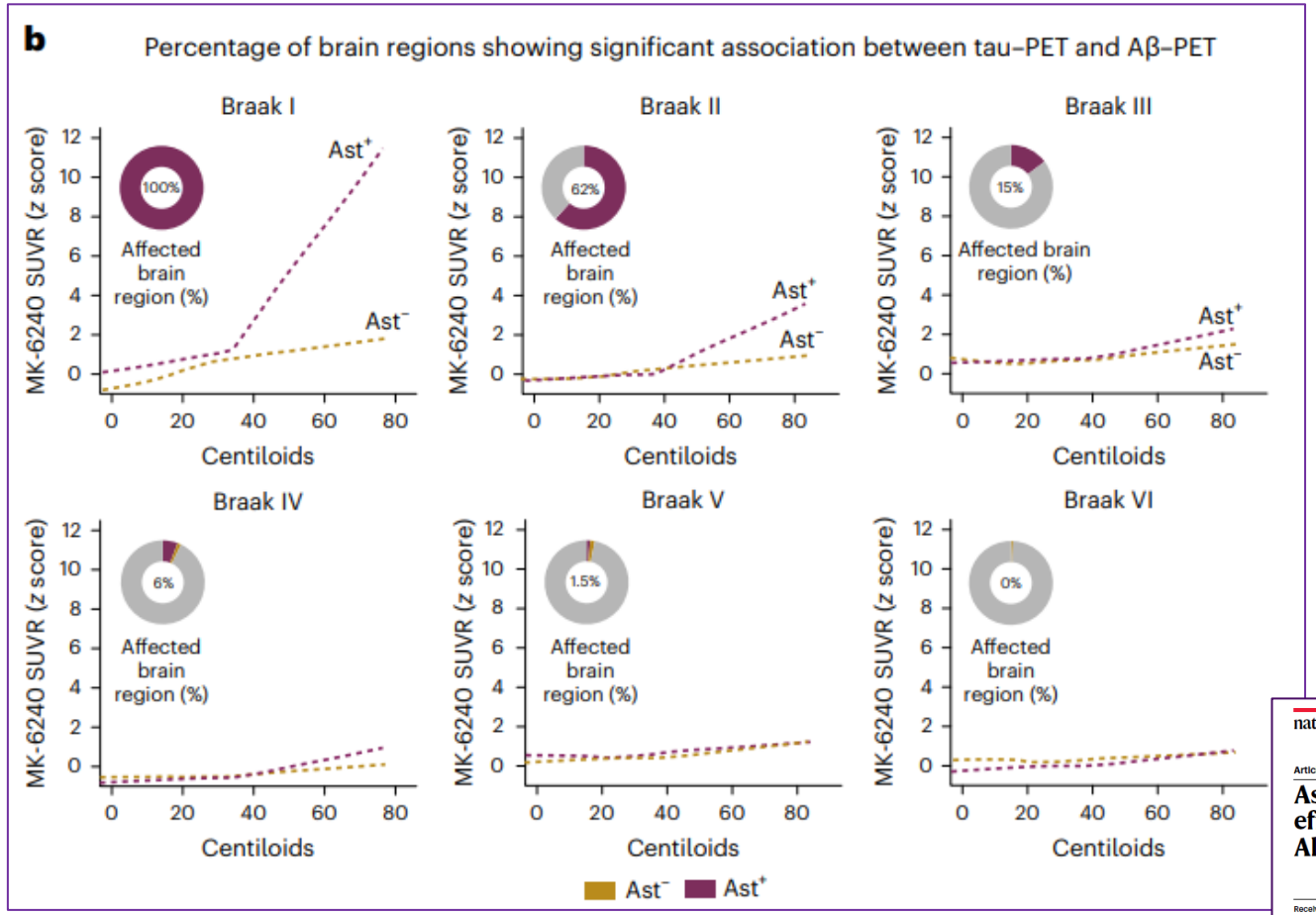


Reactive astrocytes are impactful in early stages of AD

Contribution of reactive astrocytes diverges with Stage of AD

Reactive astrocytes appear to be most effectual at earliest Braak stages.

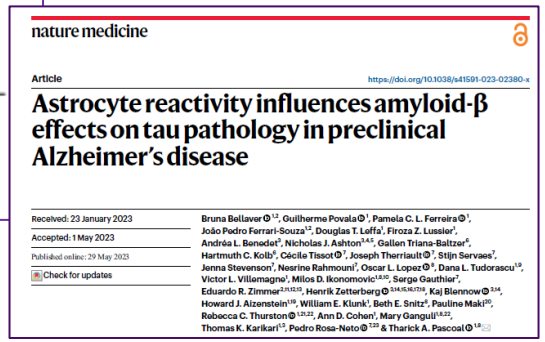
Can we leverage fluid biomarkers to detect treatment effects even before cognitive impairment is evident?



Tau PET

Amyloid PET

Disease Progression



nature medicine

Article

https://doi.org/10.1038/s41591-023-02380-x

Astrocyte reactivity influences amyloid-β effects on tau pathology in preclinical Alzheimer's disease

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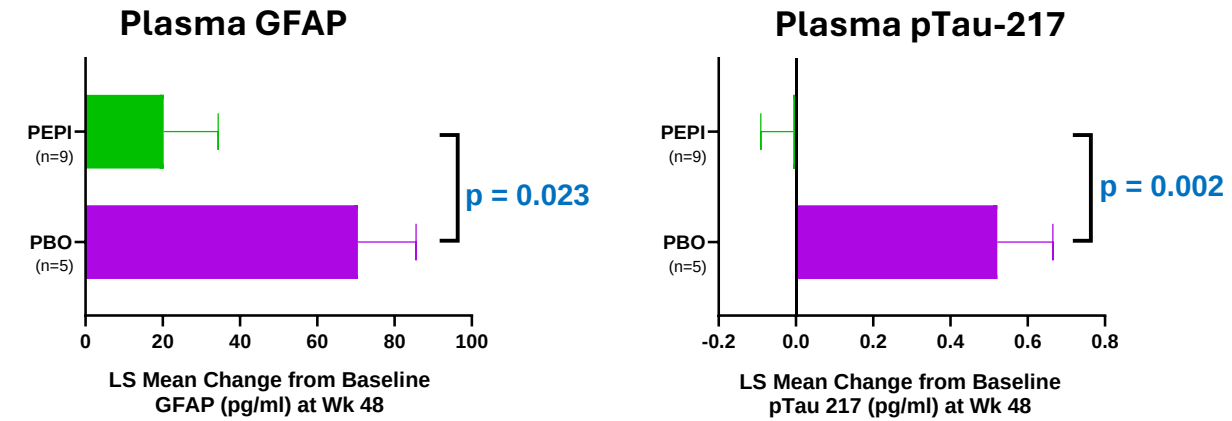
Check for updates

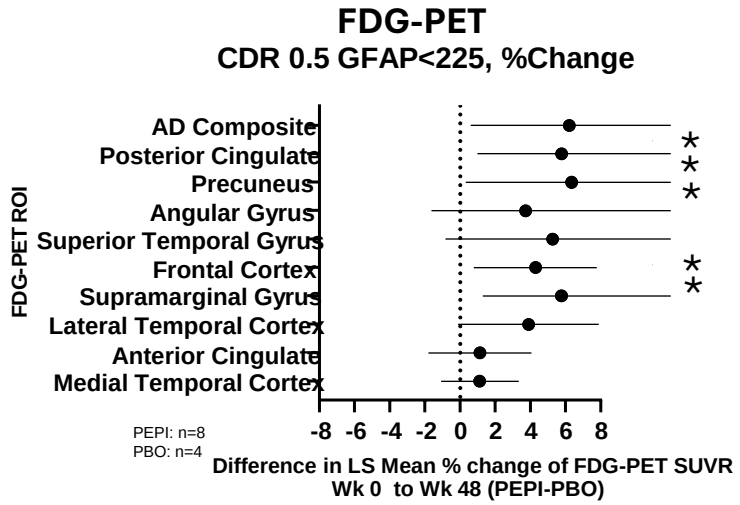
Bruna Bellaver[1,2], Guilherme Povala[1], Pamela C. L. Ferreira[1], João Pedro Ferrari-Souza[1,2], Douglas T. Leffa[3], Firoza Z. Lussier[1], Andréa L. Benedet[1], Nicholas J. Ashton[1,4,5], Gallen Triana-Baltzer[6], Hartmuth C. Kolb[6], Cécile Tissot[7], Joseph Therriault[7], Stijn Servaes[7], Jenna Stevenson[7], Nesrine Rahmouni[7], Oscar L. Lopez[8], Dana L. Tudorascu[1,9], Victor L. Villemagne[1], Milos D. Ikonomovic[1,8,10], Serge Gauthier[7], Eduardo R. Zimmer[2,11,12], Henrik Zetterberg[13,14,15,16,17], Kaj Blennow[13,14], Howard J. Aizenstein[1,18], William E. Klunk[1], Beth E. Snitz[8], Pauline Maki[20], Rebecca C. Thurston[1,21,22], Ann D. Cohen[1], Mary Ganguli[1,8,23], Thomas K. Karikari[1,2], Pedro Rosa-Neto[2,7] & Tharick A. Pascoal[1,8]

Biomarkers of reactive astrocytes at early stage of disease

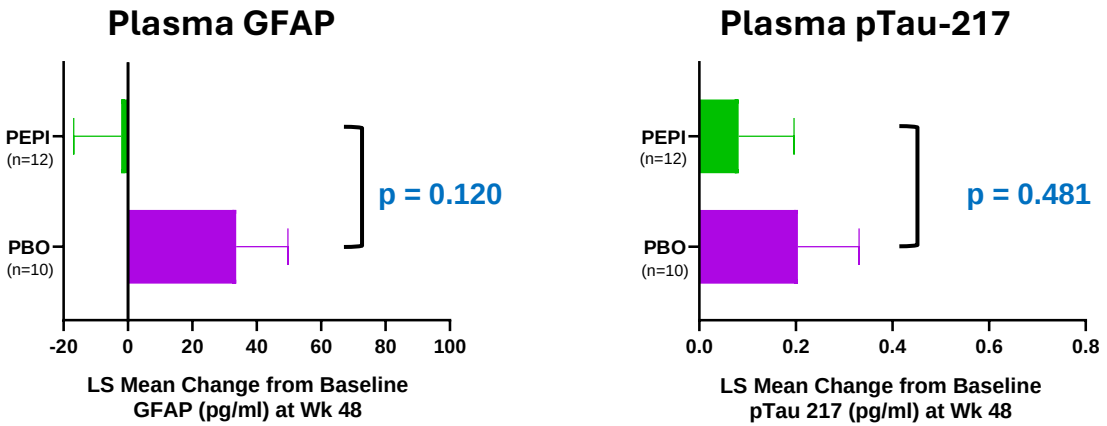
NCT04381468
SIGNAL-AD

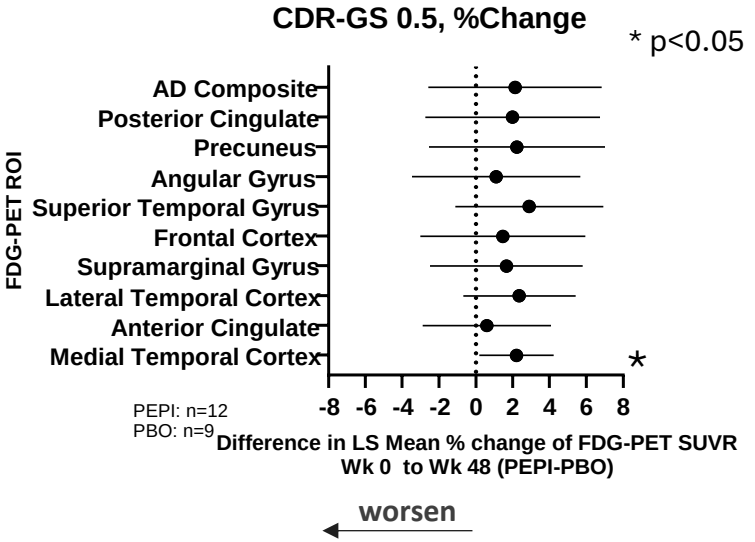
Post-hoc subgroup: Baseline CDR 0.5 and Low GFAP (<225 pg/ml)





Pre-specified subgroup: Baseline CDR-GS 0.5





Placebo
Pepinemab

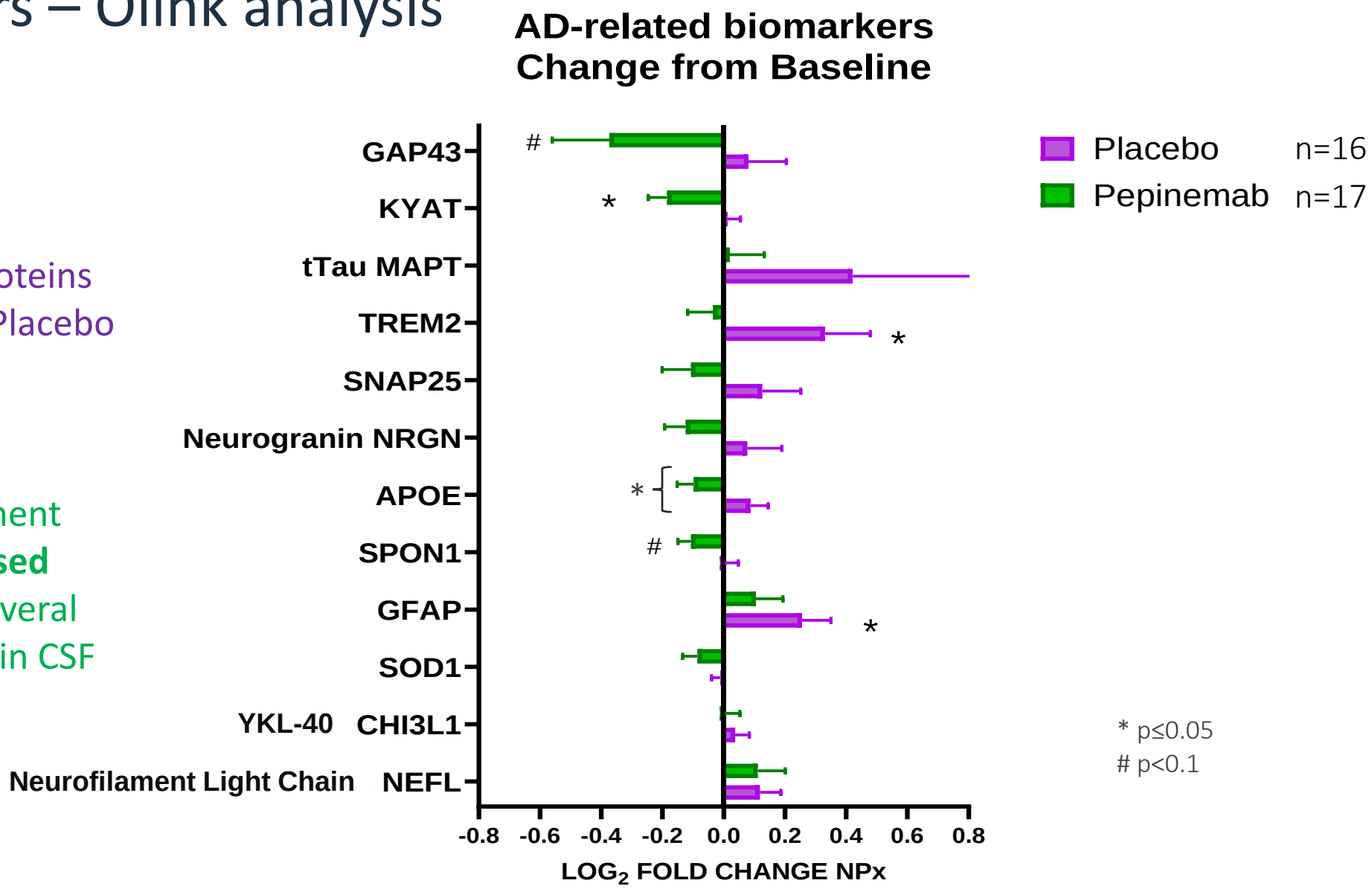
Disease Progression

ALZHEIMER'S DISEASE

CSF Biomarkers – Olink analysis

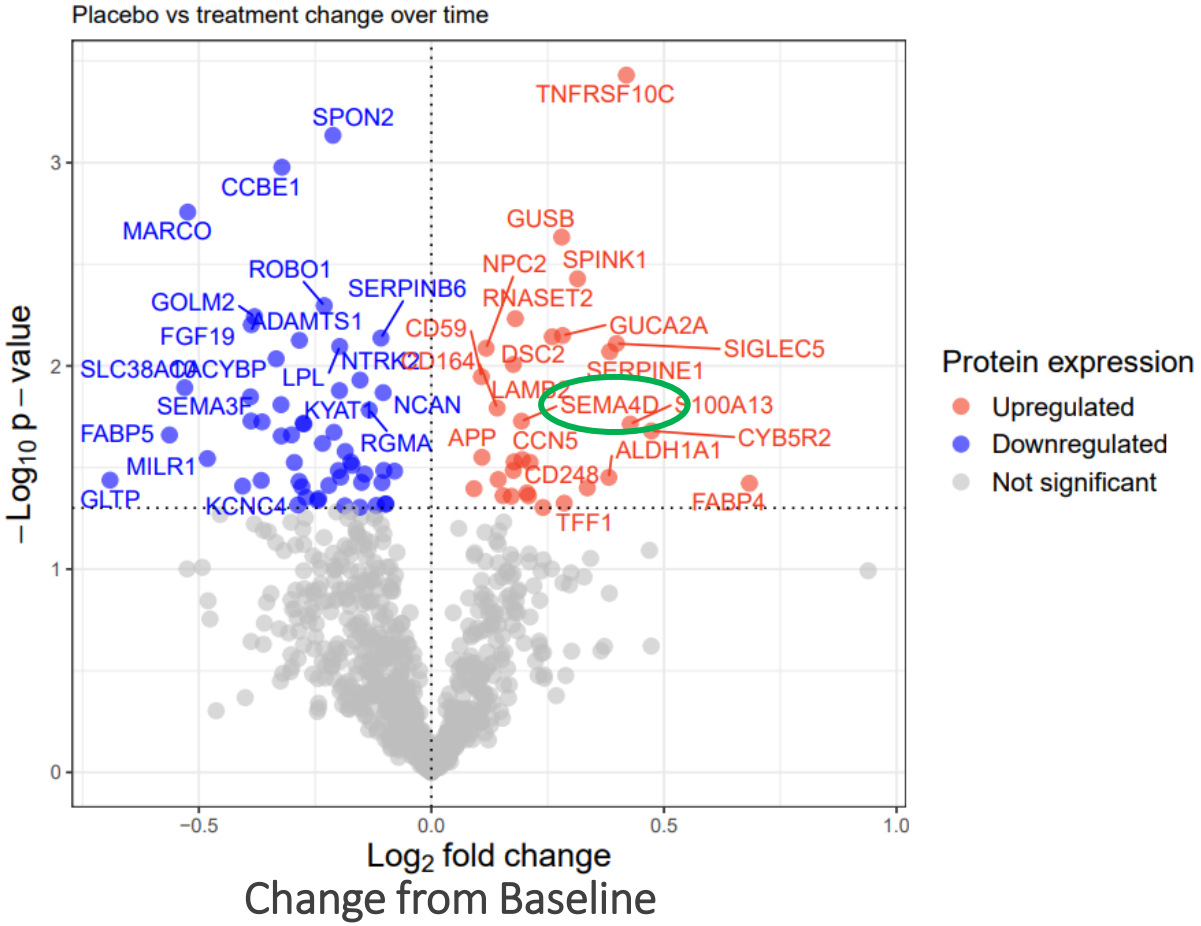
Many AD-related proteins increase (worsen) in Placebo

Pepinemab treatment **reduced or reversed accumulation** of several AD-related proteins in CSF



ALZHEIMER'S DISEASE

CSF Biomarkers – Olink analysis



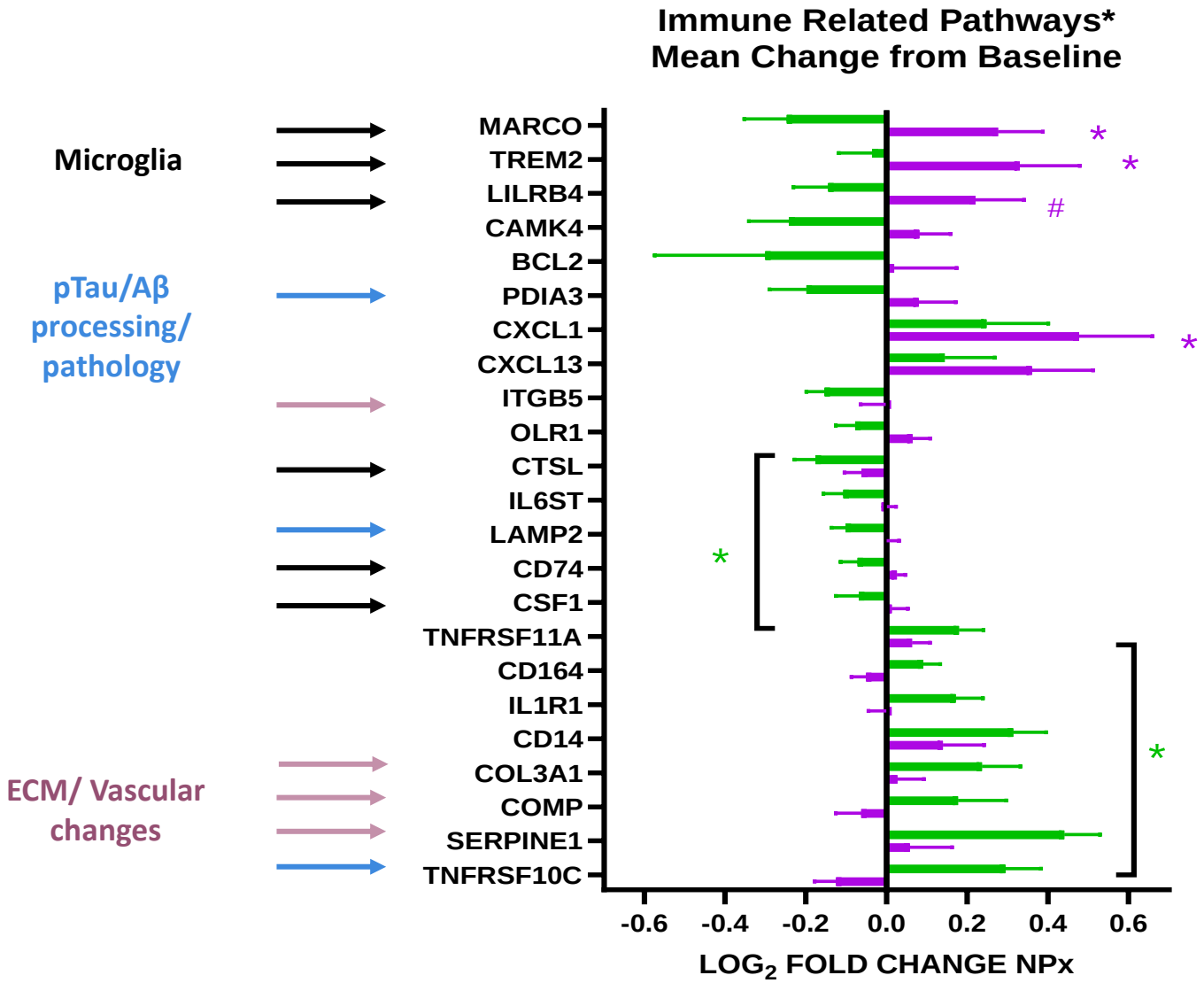
→ KEGG Pathway Analysis

Immune related	Antigen processing and presentation	**
	Viral protein interaction with cytokine and cytokine receptor	*
	Osteoclast differentiation	
	Phagosome	
Lipid & metabolic pathways	PPAR signaling pathway	*
	Cholesterol metabolism	*
	Regulation of lipolysis in adipocytes	*
	Glycosaminoglycan biosynthesis	*
	Ether lipid metabolism	
	Pentose phosphate pathway	
Vascular/ ECM	Apelin signaling pathway	*
	Vascular smooth muscle contraction	
Aging	Longevity regulating pathway	

* p≤0.05
** p<0.01

ALZHEIMER'S DISEASE

Significant Changes in proteins identified in Immune-Related pathways



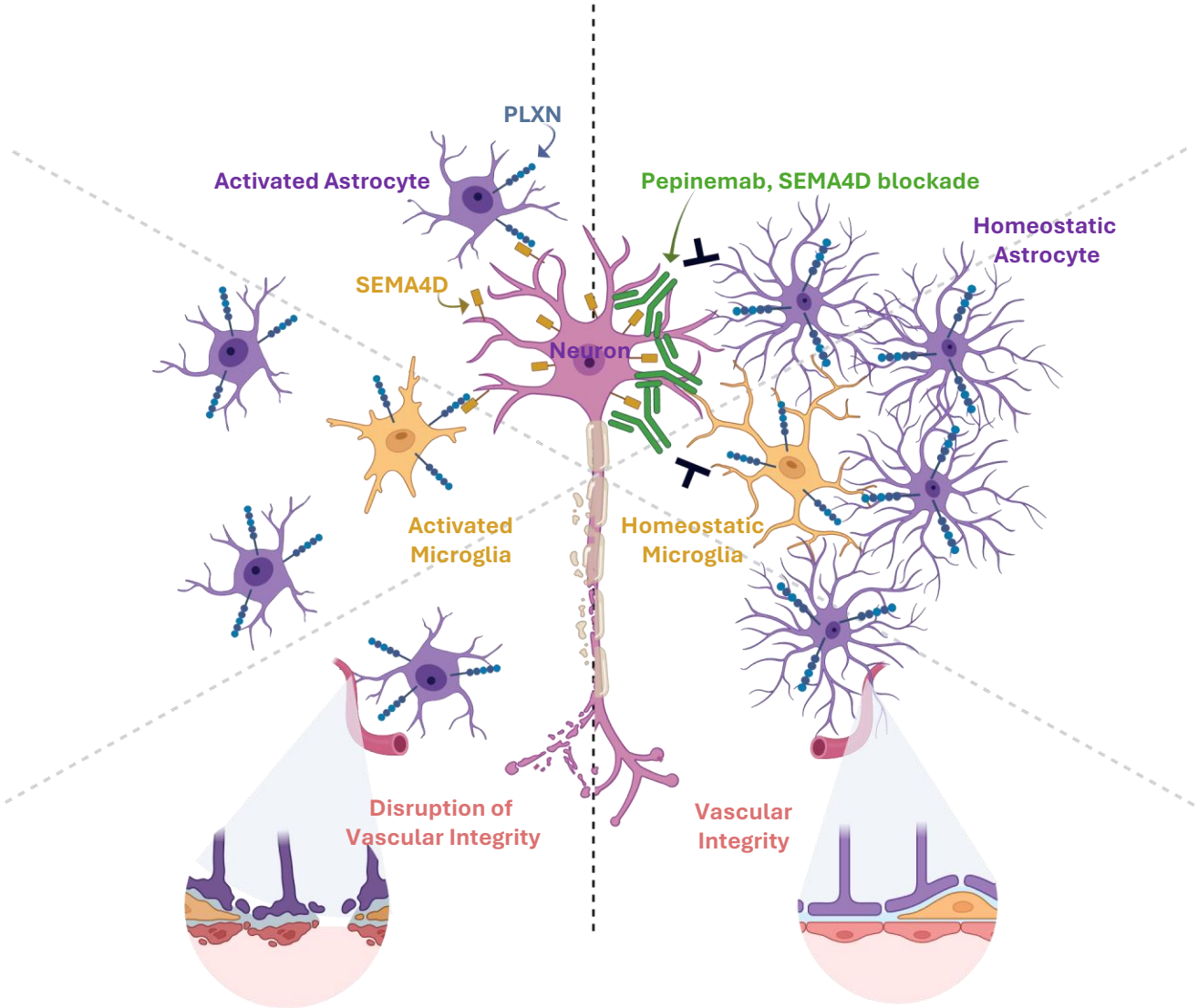
- Immune-related pathways contribute to multiple aspects of AD pathology
- **Pepinemab** treatment affects multiple downstream mechanisms of pathology

* p≤0.05
# p<0.1

Pepinemab: SEMA4D blocking antibody

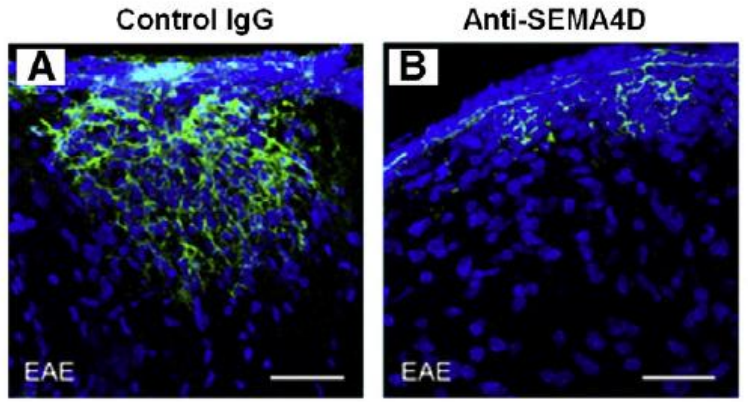
Neuroinflammation / Neurodegeneration

Pepinemab to overcome Neuroinflammation / Neurodegeneration



Pepinemab

Restores Vascular Integrity

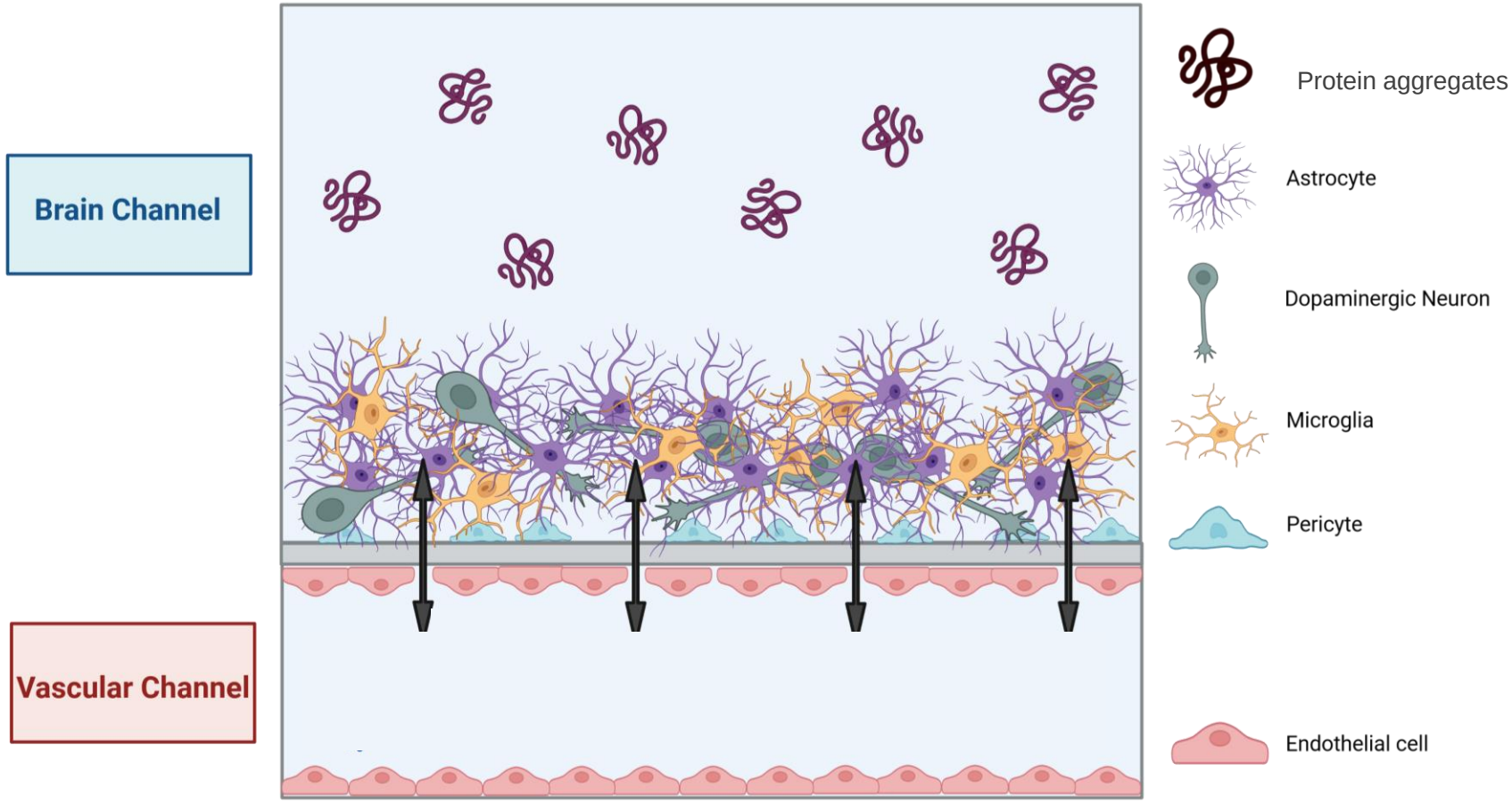


Fibrinogen leakage in mouse EAE model of Multiple Sclerosis

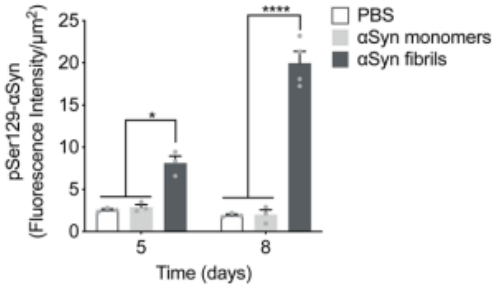
Smith et al. Neurobiology of Disease 2015

3D “Brain chip” model

Brain protein aggregates induce inflammation and disrupt vascular integrity



α-Synuclein aggregates, but not monomers induced inflammation and disrupted vascular integrity

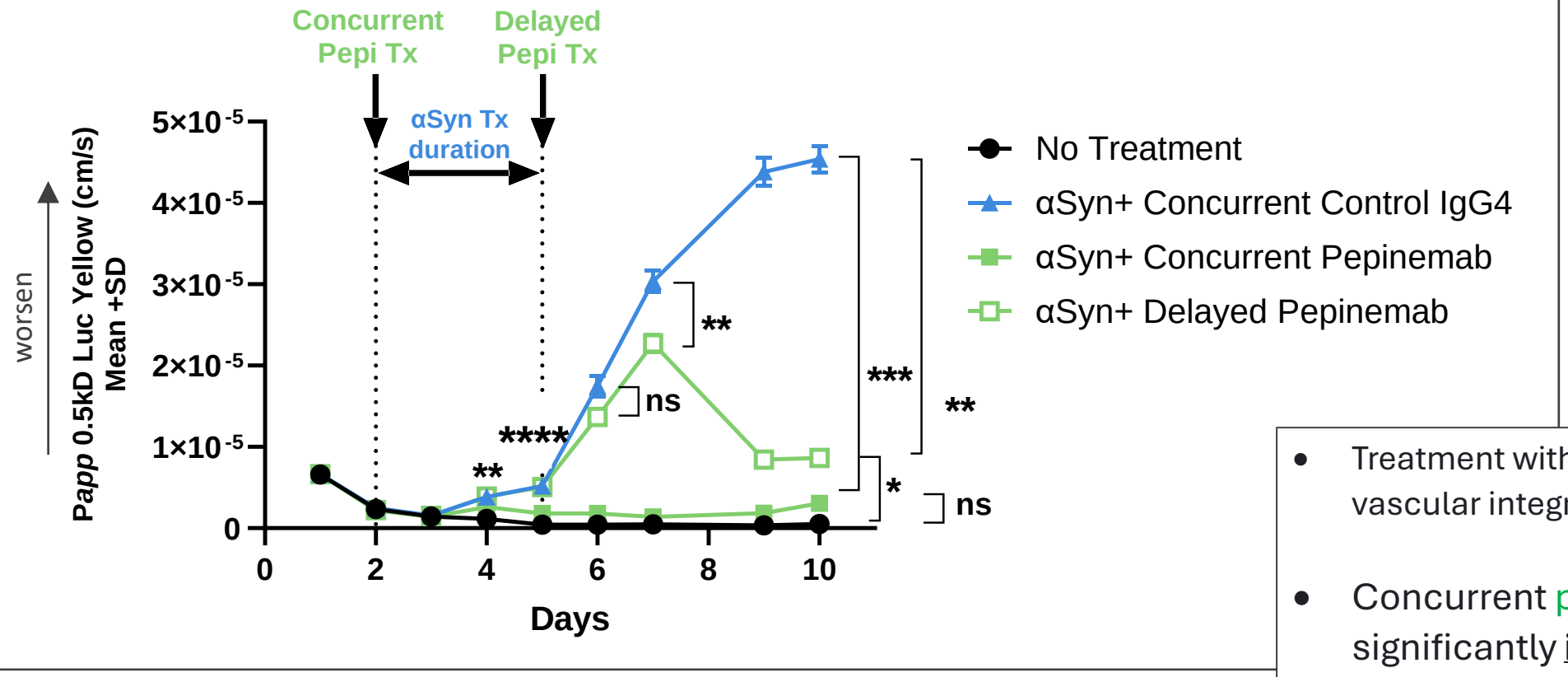


Pediatikis et al.
NATURE COMM. 2021. 12:5907

Brain and vascular channels are seeded at physiologically relevant ratios and maintained under continuous physiologic flow.

Pepinemab reversed damaging effects of toxic protein aggregates

3D "Brain chip" model



aSyn fibrils added to parenchymal channel
Pepinemab and Control Ig added to vascular channel

- Treatment with **aSyn fibrils** disrupted vascular integrity of brain chip
- Concurrent pepinemab treatment significantly **inhibited** effects of aSyn
- Delayed pepinemab treatment significantly **reversed** effects of aSyn

Pepinemab

Summary of Clinical Findings

- **SIGNAL HD** was a larger randomized Ph2 study, ~ 90 patients/group with Early manifest disease and ~42 pre-symptomatic
  - Pepinemab inhibited biomarkers of reactive astrocytes: GFAP and FDG-PET
  - Pepinemab significantly improved cognition, using HD-CAB (cognitive assessment battery), particularly in patients with baseline mild cognitive impairment (MoCA <26)

- **SIGNAL-AD** enrolled 50 patients, including both MCI and mild dementia
  - Pepinemab was well-tolerated and treatment effects (ns) were observed in clinical outcome assessments (COAs) at early stages of disease progression
  - Biomarker analysis supports benefit of pepinemab treatment
    - Biomarkers of reactive astrocytes are most evident very early in disease
    - Multiplex proteomics analysis suggest treatment induced reduction of AD-related biomarkers in CSF and regulation of immune related and metabolic pathways, consistent with mechanism of action
- Evidence from clinical and preclinical studies suggest pepinemab treatment appears to inhibit or reverse damaging effects of neuroinflammation and the loss of metabolic functions, as well as vascular integrity that contribute to disease progression.

Thanks and Gratitude

Participants, caregivers and their families!

SIGNAL-AD study investigators and staff

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SIGNAL-AD

alzheimer's association®

Alzheimer's Drug Discovery Foundation

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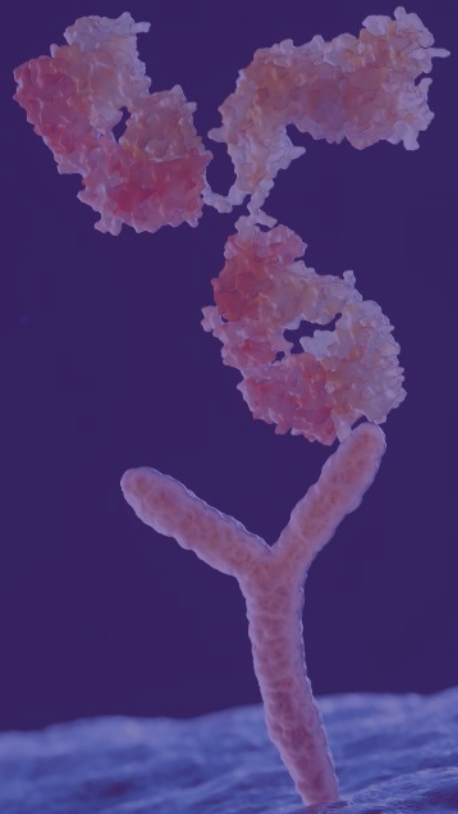
APPENDIX



VACCINEX

Unique Targets
Novel Mechanisms
New Medicines

CTAD
Clinical Trials on Alzheimer's Disease

October 31, 2024

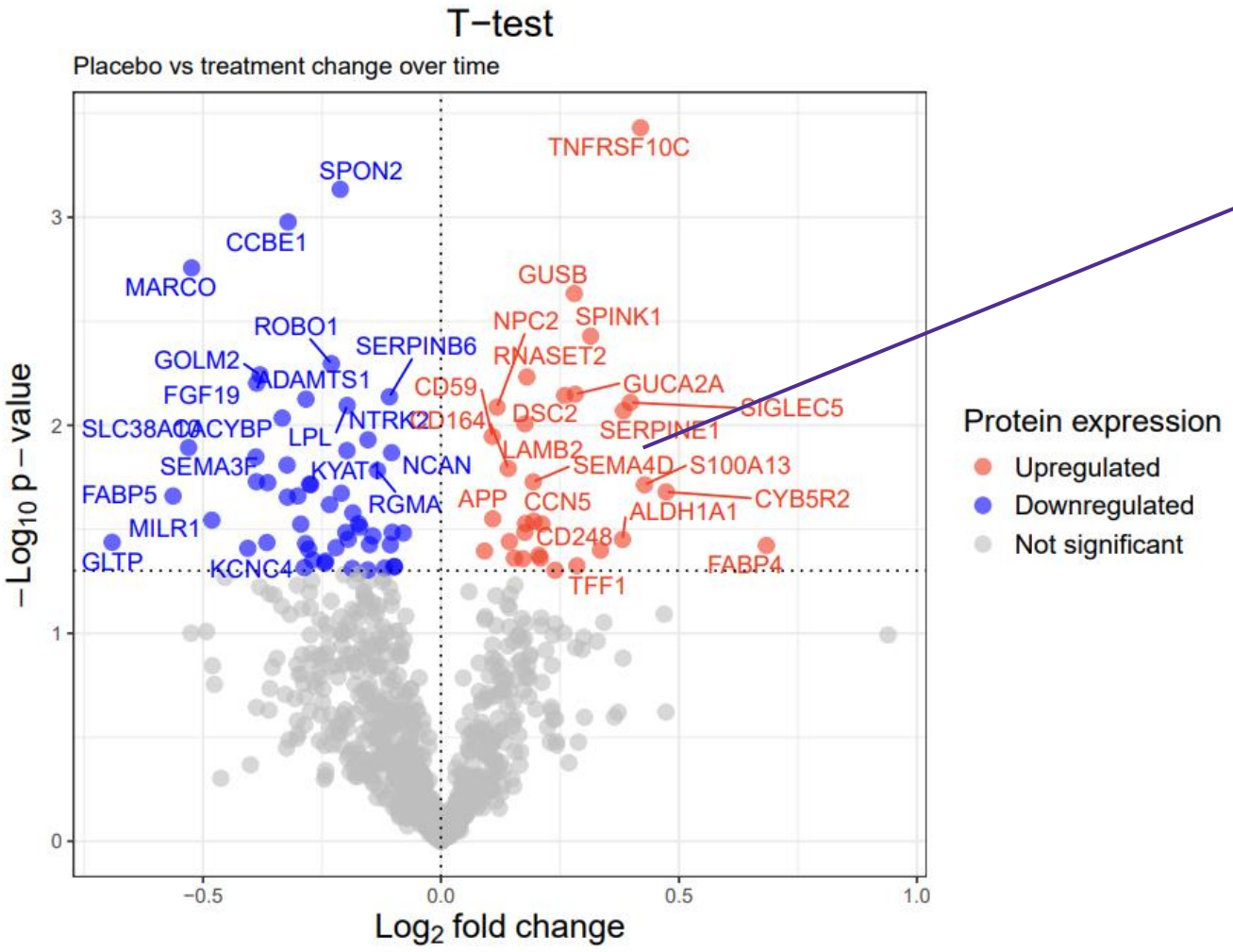
ALZHEIMER'S DISEASE

Safety and Tolerability

Topline Safety Results, Number (%) of Patients	Pepinemab 40 mg/kg (N=24)	Placebo (N=26)	All Patients (N=50)
	n (%)	n (%)	n (%)
TEAE	21 (87.5)	23 (88.5)	44 (88.0)
Serious TEAE	1 (4.2)	7 (26.9)	8 (16.0)
TEAE with CTCAE Grade ≥ 3	2 (8.3)	4 (15.4)	6 (12.0)
TEAE Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAE Related to Treatment	0 (0.0)	0 (0.0)	0 (0.0)
TEAE Related to Treatment	12 (50.0)	5 (19.2)	17 (34.0)
TEAE Leading to Treatment Discontinuation	0 (0.0)	1 (3.8)	1 (2.0)
TEAE of Special Interest (TEAESI)	3 (12.5)	0 (0.0)	3 (6.0)
Amyloid-related imaging abnormalities			
ARIA-E	0 (0.0)	0 (0.0)	0 (0.0)
ARIA-H	2 (8.3)	0 (0.0)	2 (4.0)
Any abnormal post-baseline value(s)			
Laboratory: Hematology	19 (79.2)	22 (84.6)	41 (82.0)
Laboratory: Chemistry	24 (100.0)	26 (100.0)	50 (100.0)

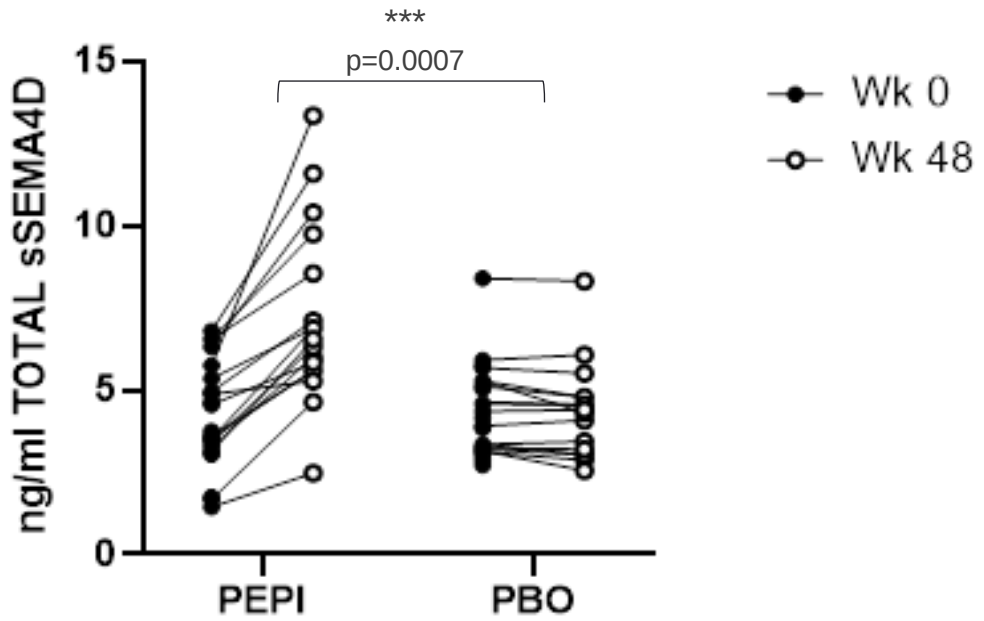
ALZHEIMER'S DISEASE

CSF Biomarkers – Olink analysis



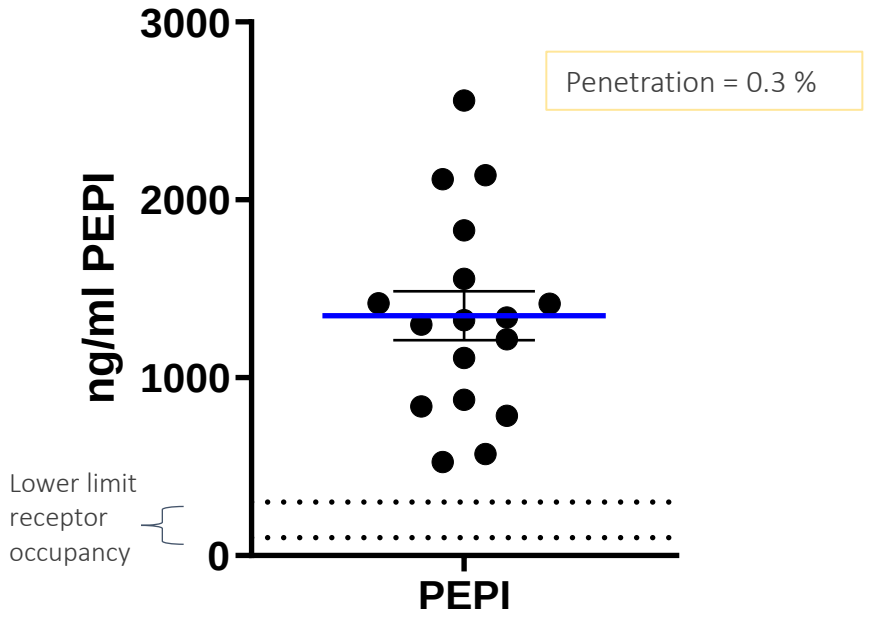
Change from Baseline

sSEMA4D: PEPI complexes in CSF of subjects dosed with pepinemab – suggesting target engagement

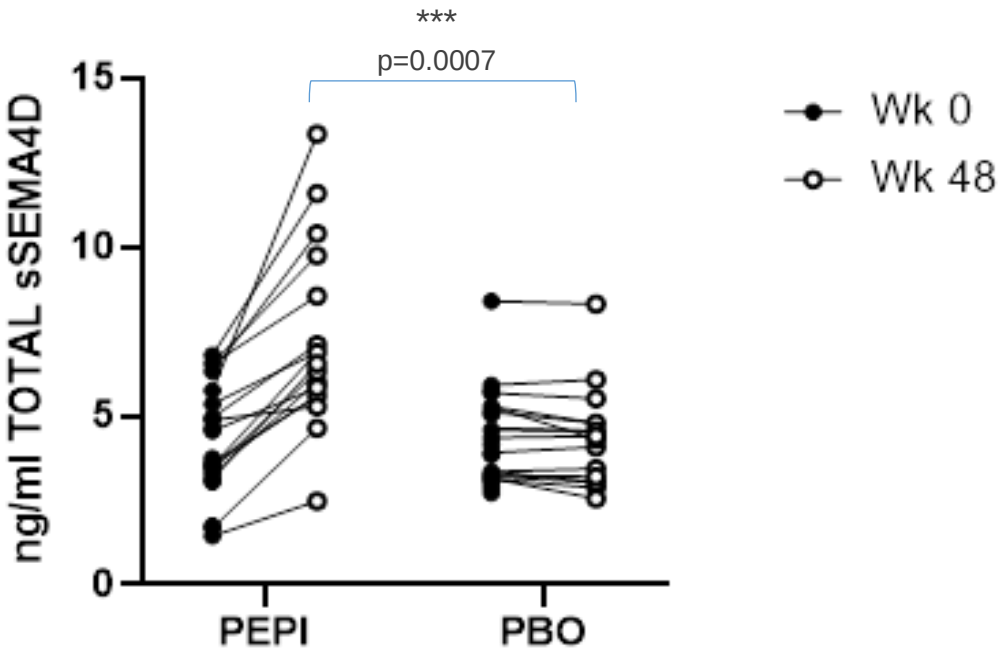


Pepinemab is detected at expected levels in CSF and binds to target (SEMA4D)

Subjects dosed with pepinemab contain ≥ saturating levels of drug (100-300 ng/ml) in CSF



sSEMA4D: PEPI complexes in CSF of subjects dosed with pepinemab – suggesting target engagement

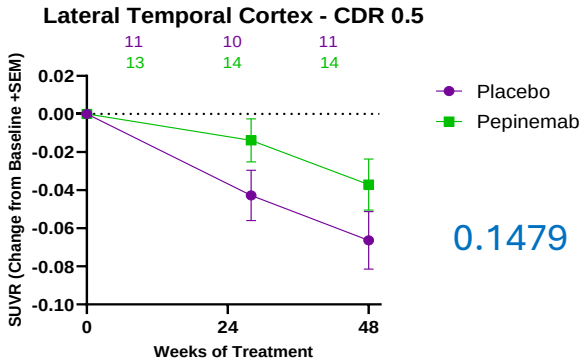


FDG-PET Imaging Biomarker

MCI Subgroup: CDR-GS = 0.5 Subgroup, Pons Reference

NCT04381468

SIGNAL-AD



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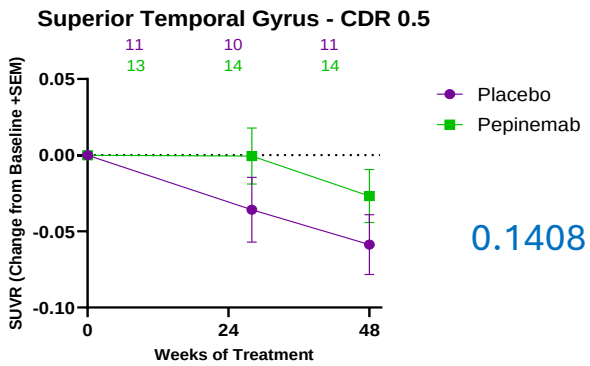

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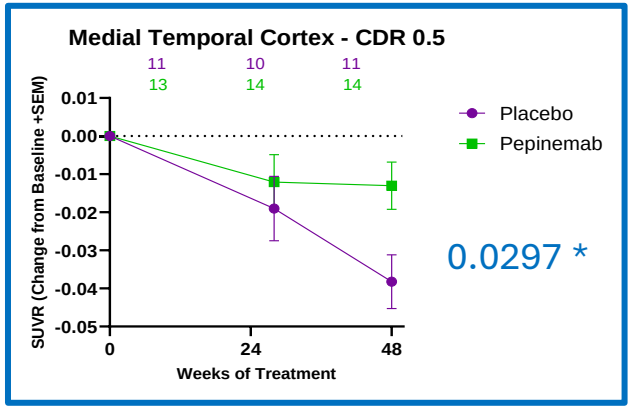

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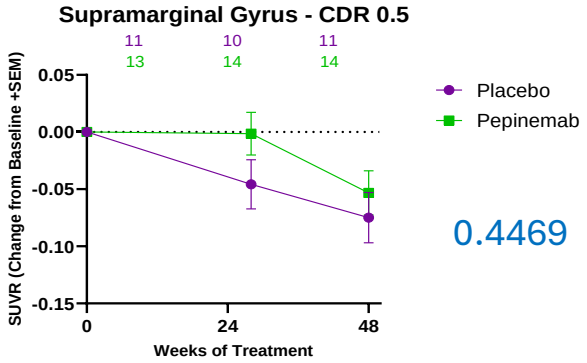

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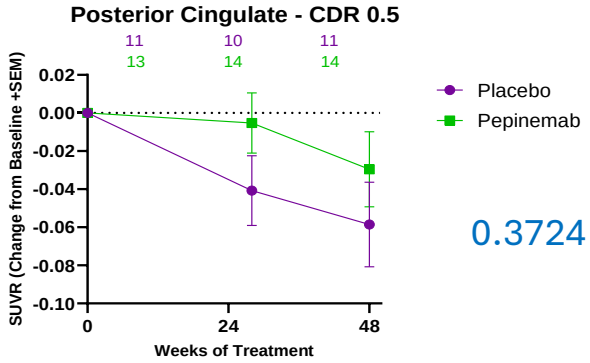

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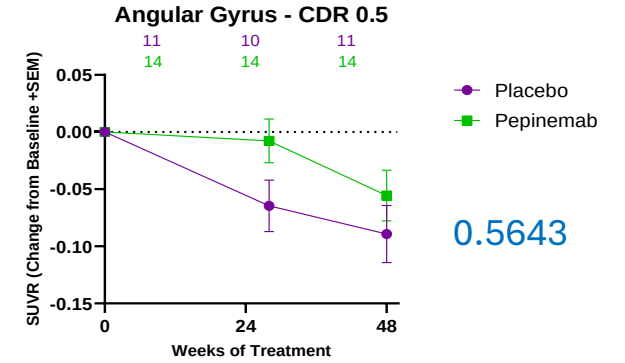

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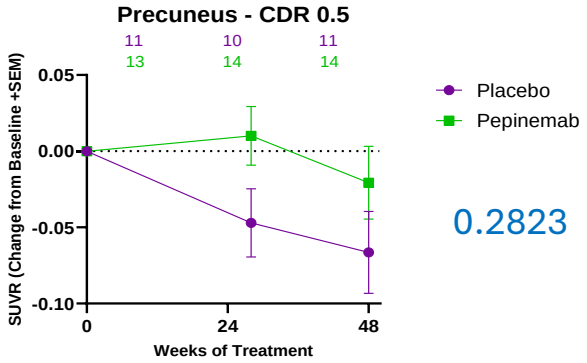

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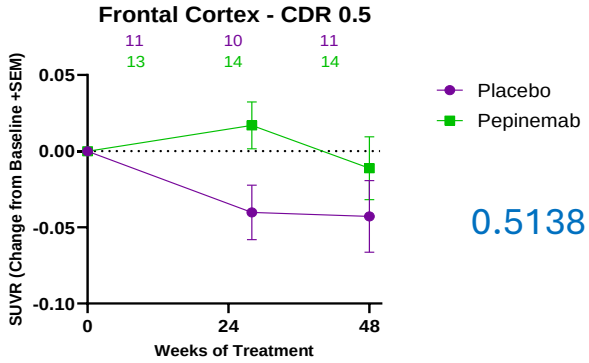

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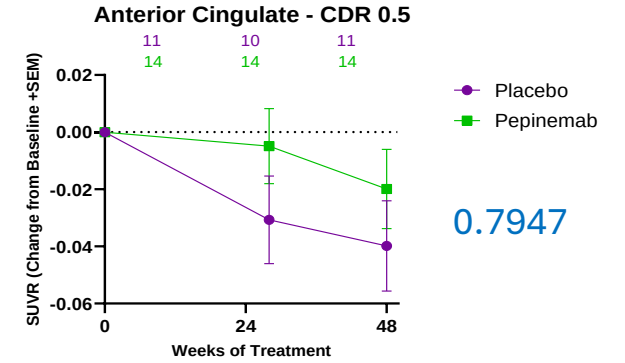

0.7947

Worsen

Figures display LS mean (SE) estimated from a fitted MMRM model. p values are indicated in blue