

# Regulatory Role of Semaphorin 4D in the Nervous System

**Vaccinex, Inc.**  
**Maurice Zauderer, PhD**  
President & CEO

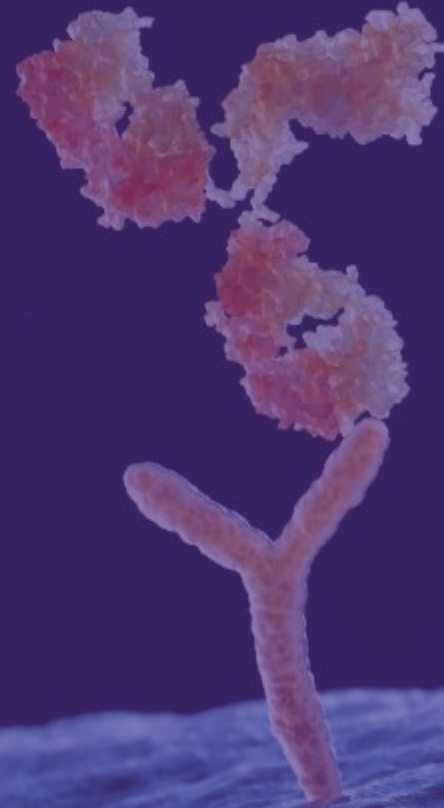


Unique Targets

Novel Mechanisms

New Medicines

December 3, 2025



# Disclosures

## Maurice Zauderer, PhD

Current Employee and  
Stock Shareholder of  
Vaccinex, Inc.

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



## Forward Looking Statements

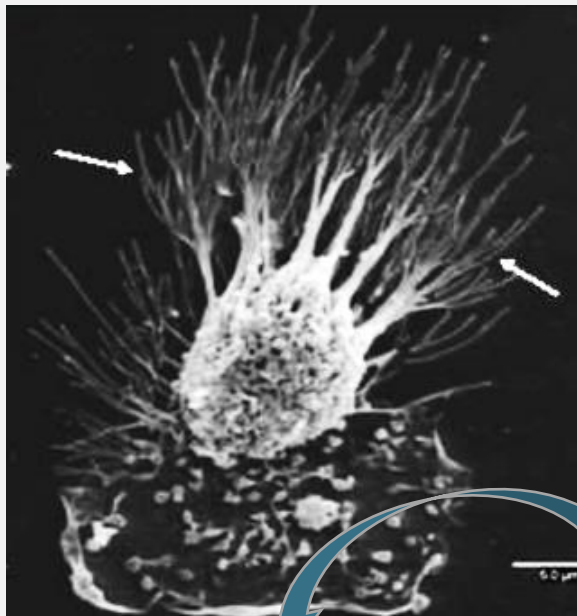
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# SEMA4D signaling pathway regulates cellular morphology, gene expression, and communication in both the immune and nervous systems

Astrocytes in brain and Dendritic Cells in immune tissue express PlexinB1/B2 receptors and *change form and function* in response to SEMA4D signaling, “SEMA4D Reactive Regulators”

## Mature Dendritic Cell

Facilitates interactions with other immune cells:  
T and B lymphocytes, macrophage, endothelial cells

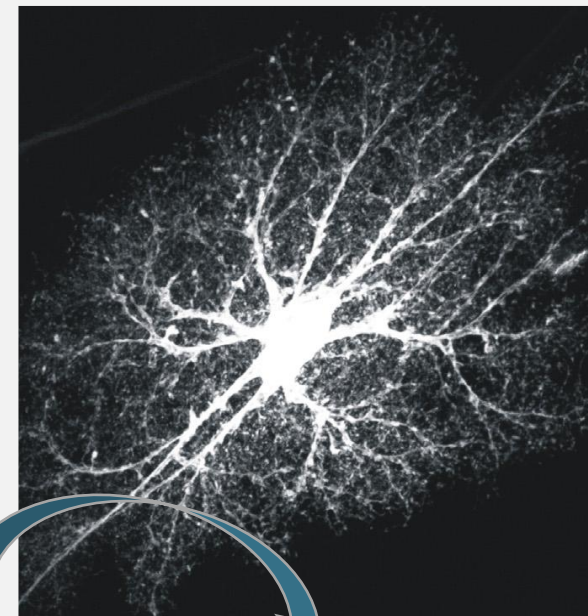


Activated lymphocytes

SEMA4D is  
expressed by

## Healthy Astrocyte

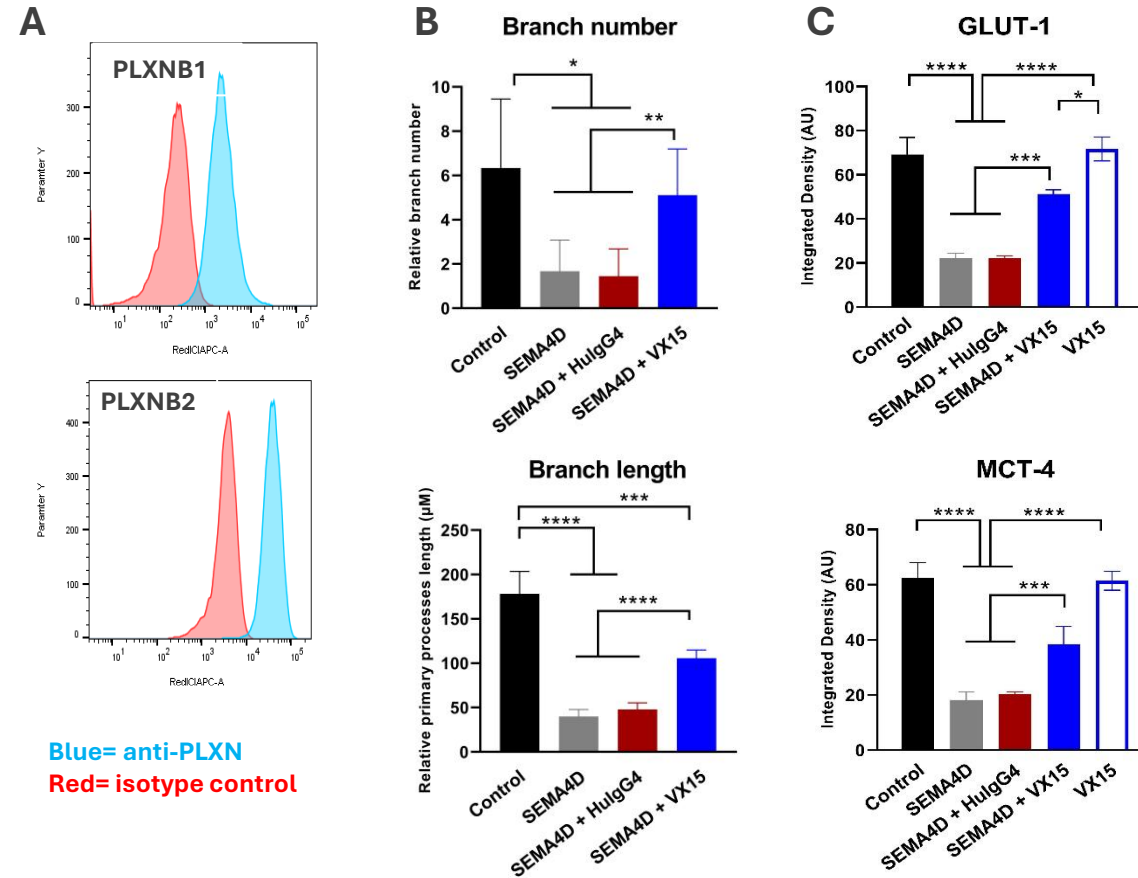
Reaches out to touch and interact with other brain  
cells: neurons, microglia, pericytes, endothelial cells



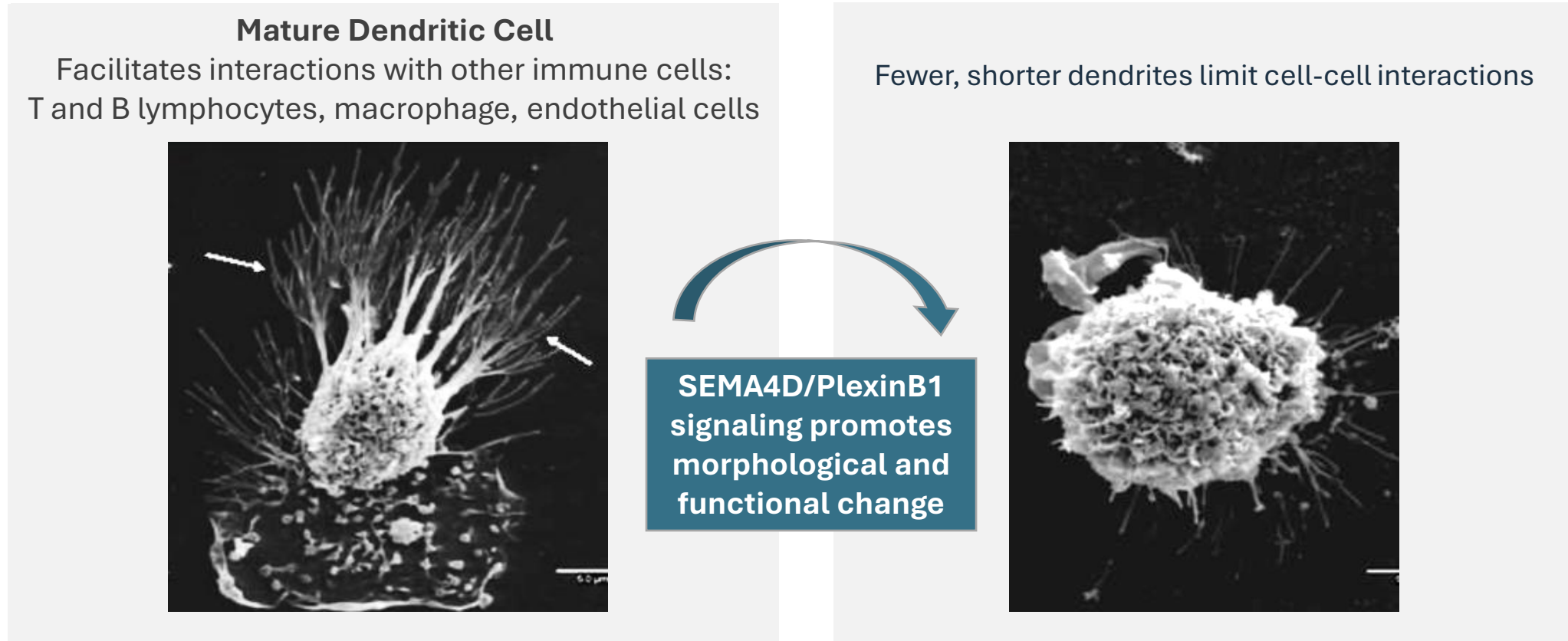
Stressed or Damaged Neurons

# ASTROCYTE FORM and FUNCTION

SEMA4D/PLXN signaling regulates astrocyte morphology and metabolic activity



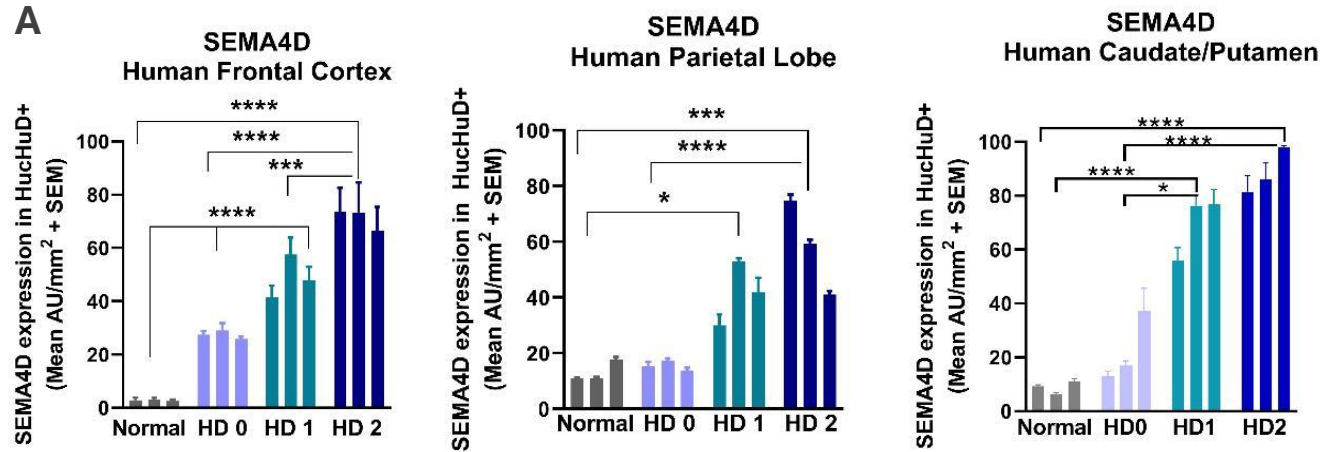
# SEMA4D signaling through PlexinB1/B2 receptors leads to depolymerization of the actin cytoskeleton and collapse of cytoplasmic projections.



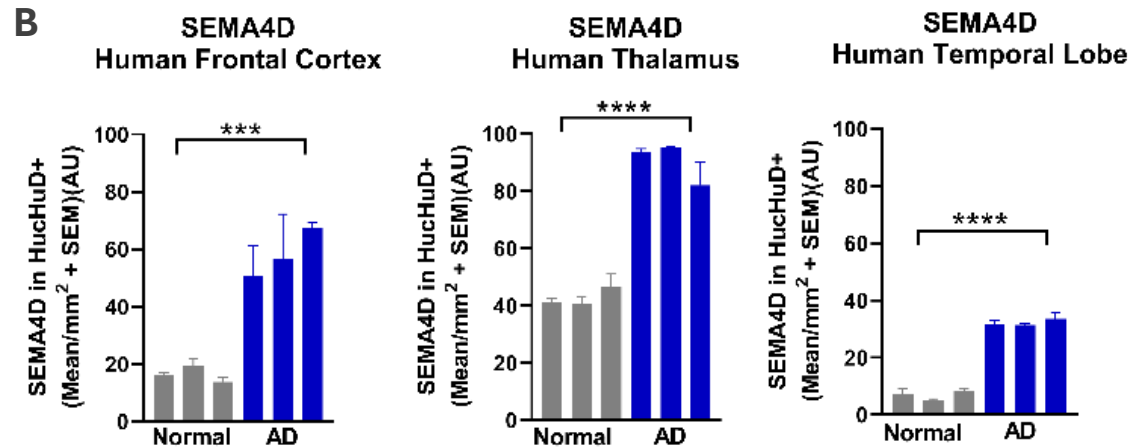
(Courtesy of Rut Olivar and Josep M. Aran. IDIBELL). *U Barcelona Cortadellas N, Fernandez E, Garcia A. Biomedical and Biological Applications of Scanning Electron Microscopy*

# SEMA4D is progressively upregulated with increasing pathologic stage of HD and in AD

SEMA4D in HD neurons



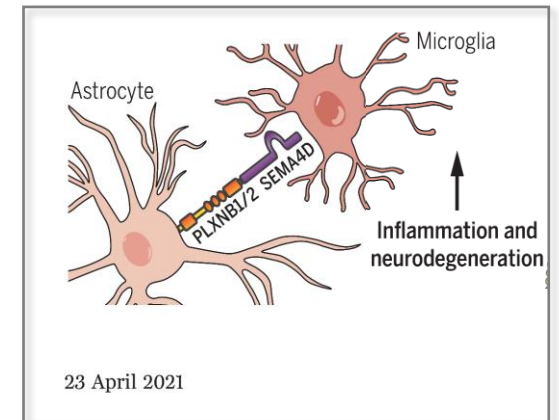
SEMA4D in AD neurons



# Pepinemab treatment prevents a chain of pathogenic events downstream of astrocyte reactivity in AD and HD

**Pepinemab treatment prevents a chain of pathogenic events downstream of astrocyte reactivity that drive disease progression in both AD and HD:**

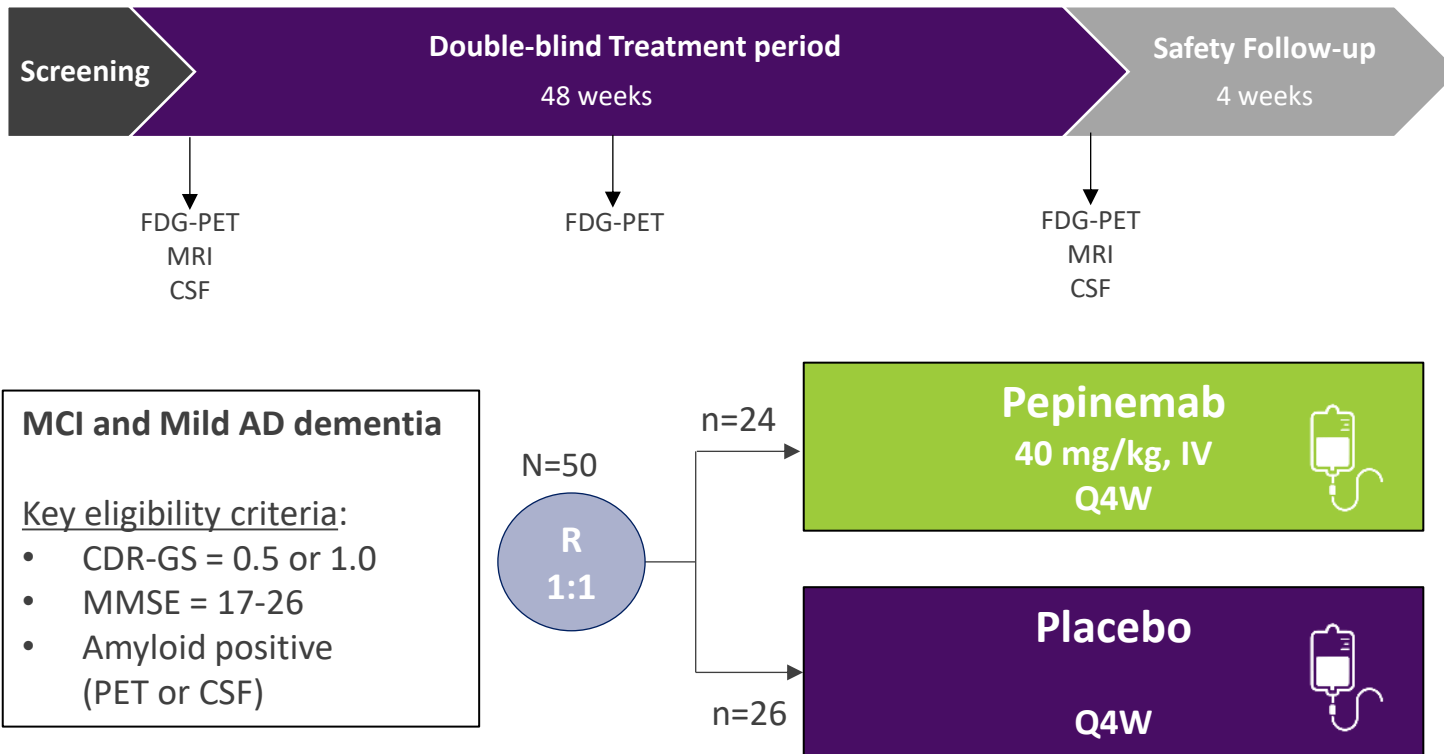
- **Pepinemab** blocks crosstalk between reactive astrocytes and microglia that amplifies glial reactivity leading to inflammation and glial scars.
- **Pepinemab** preserves vascular integrity in brain.
- **Pepinemab** downregulates expression of AD related proteins in CSF: SNAP25 associated with synaptic loss and GAP-43 that promotes tau spreading and accumulation. Synaptic loss and tau spreading are pathologies common to both AD and HD.
- Data from randomized Phase 2 studies in **HD** (n=179) and a recently completed phase 1b/2a study in **MCI and mild AD** (n=49) suggest that early in disease pepinemab treatment has favorable effects on **biomarkers** related to disease progression and appears to **slow cognitive decline**.



Clark ... and Quintana, Barcoded viral tracing of single-cell interactions in central nervous system inflammation Science 372, 360

# ALZHEIMER'S DISEASE

## Phase 1b/2 Trial Design

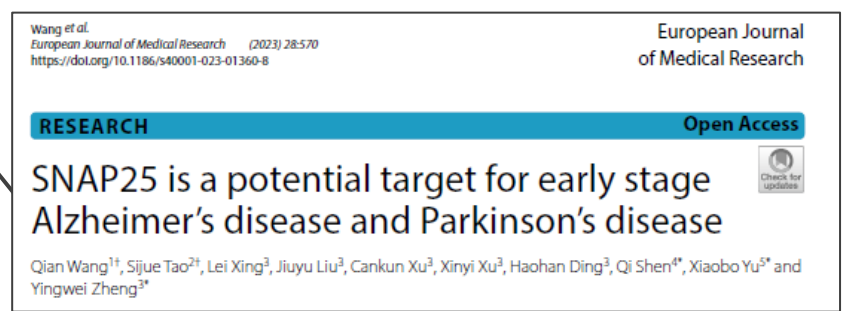
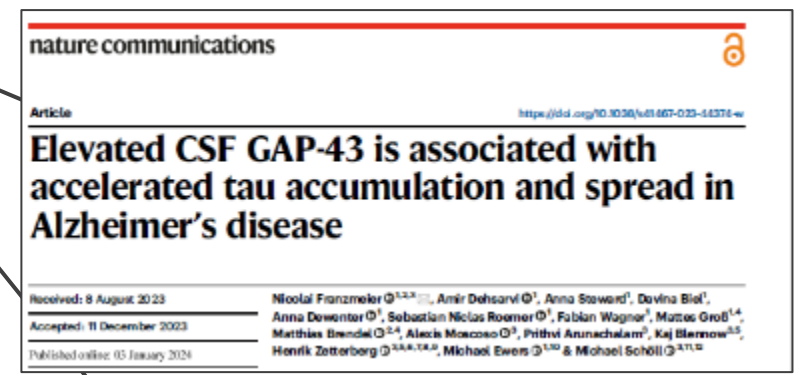
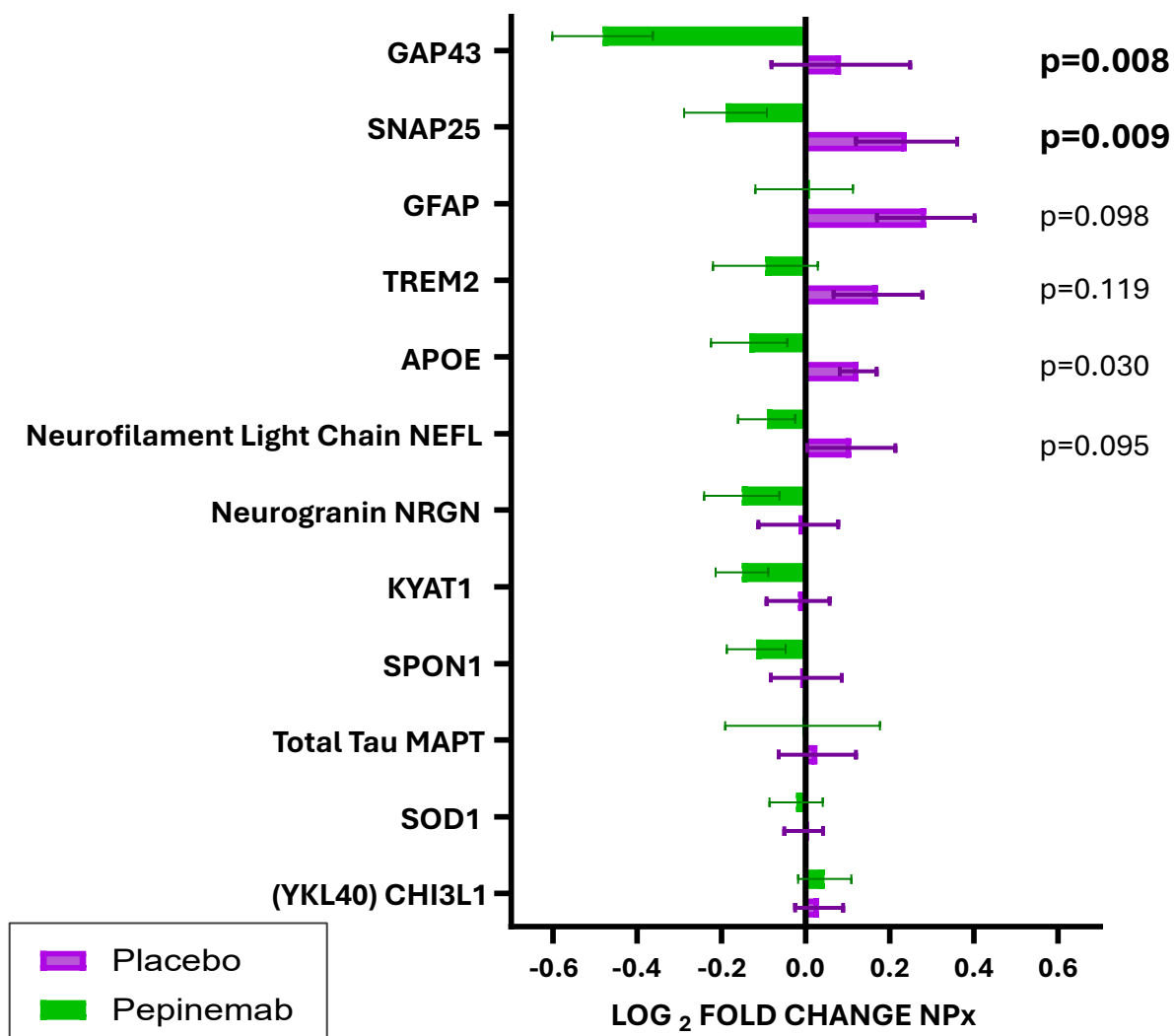


Pepinemab was well-tolerated  
No discontinuations

<u>Objectives:</u>	
<b>Primary</b>	<b>Safety and Tolerability</b>
<b>Secondaries</b>	<ul style="list-style-type: none"> <li>• <b>Biomarkers:</b> <ul style="list-style-type: none"> <li>• Fluid Biomarkers</li> <li>• FDG-PET</li> </ul> </li> <li>• Cognitive and Functional measures: Including change in CDR-SB, iADRS, and ADAS-Cog13</li> </ul>
<b>Exploratory</b>	<ul style="list-style-type: none"> <li>• <b>Subgroup analysis: including MMSE 22-26 and MMSE 17-21 (MCI or mild dementia)</b></li> <li>• PK/PD</li> </ul>

# Pepinemab reduces levels of CSF proteins associated with synaptic loss and tau pathology in patients with AD-related mild dementia

**AD-related Biomarkers MMSE 22-26**  
 Mean Change from Baseline



p-value: PEPI-PBO  
 t-test (adjusted age, sex)

Select AD-related biomarkers reported to be elevated in AD cerebrospinal fluid (CSF) are reduced in patients treated with pepinemab. Olink analysis of CSF, change from baseline at 48 weeks in Baseline MMSE 22-26 prespecified subgroup.

Olink Explore 5000 panel was performed in collaboration with group of Charlotte Teunissen at UMC, Amsterdam.

# SEMA4D/PLXNB1 Pathway Regulates a Key Astrocyte Subset, Ast10, Associated with Cognitive Decline

bioRxiv preprint doi: <https://www.biorxiv.org/content/10.1101/2025.02.24.639868v1>  
QR code below

## **PLXNB1 and other signaling drives a pathologic astrocyte state contributing to cognitive decline in Alzheimer's Disease**

Natacha Comandante-Lou, Tsering Lama, Kevin Chen, Jinglong Zhang, Bin Hu, Shuhui Liu, Sarah Heuer, Kristen J. Brennand, Julie Schneider, Lisa Barnes, Bin Zhang, Minghui Wang, Hongyan Zou, Roland H. Friedel, Yiyi Ma, Tracy Young-Pearse, Aiqun Li, Masashi Fujita, David Bennett, Ya Zhang, Vilas Menon, Hans-Ulrich Klein, Mariko Taga, Philip L. De Jager\*

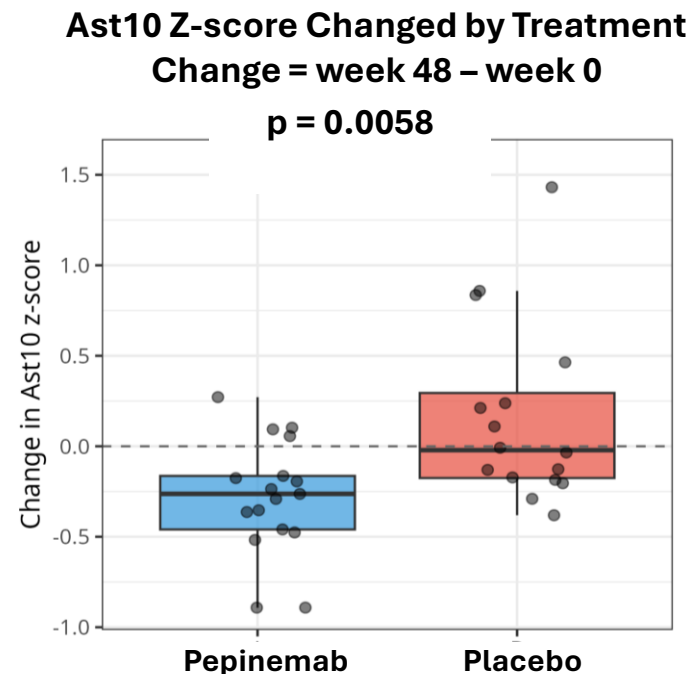
\*Correspondence: Philip L. De Jager, MD PhD  
Professor of Neurology and Chief, Division of Neuroimmunology  
[pld2115@cumc.columbia.edu](mailto:pld2115@cumc.columbia.edu)



# Reactive astrocyte signature driven by PLXNB1 correlates with cognitive decline and is reduced by pepinemab treatment

- Investigators at Columbia/Mount Sinai (NY)/Harvard/Yale, and Rush University identified a genetic signature for an astrocyte subset termed Ast10 that was quantified in 4 sets of single-nucleus transcriptomic data (snRNAseq) derived from a total of 869 brains. Volunteer donors were also characterized as to amyloid and tau burden and slope of cognitive decline late in life.
  - Ast10 cells were found to be significantly associated with rapid AD and aging-related cognitive decline.
- SEMA4D-PLXNB1 was identified as a top ligand-receptor pair that strongly regulates Ast10 representation in brain** increasing frequency from <1% in cognitively normal individuals to as much as 25 to 80% of all astrocytes in AD.

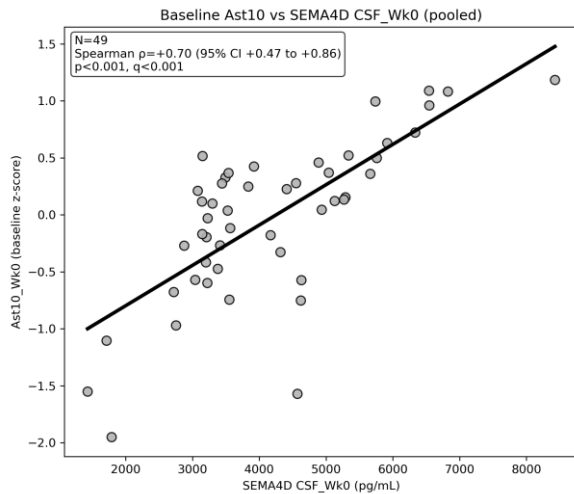
→ Analysis of Ast10 Ligands represented in **SIGNAL-AD** Olink CSF data set showed a significant decline with pepinemab treatment:



# Ast10 correlates with inflammatory and synaptic fluid biomarkers in CSF at Baseline

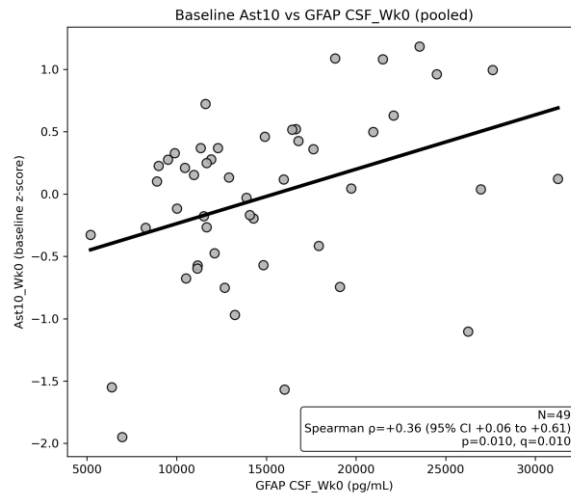
## SEMA4D

$r_s = 0.700$   
 $p < 0.0001$



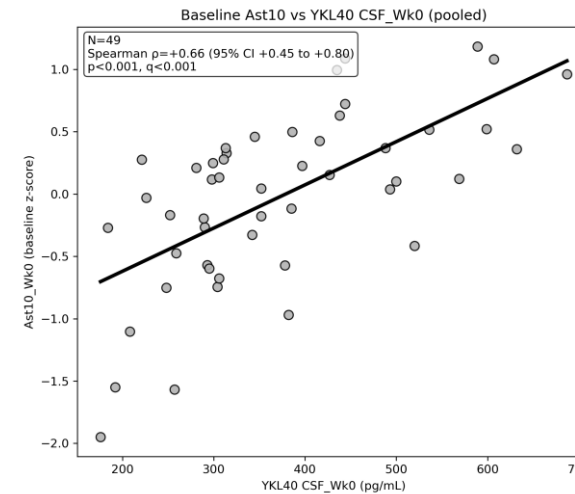
## GFAP

$r_s = 0.364$   
 $p = 0.01$



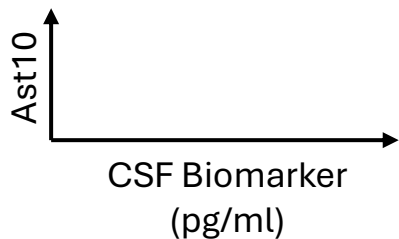
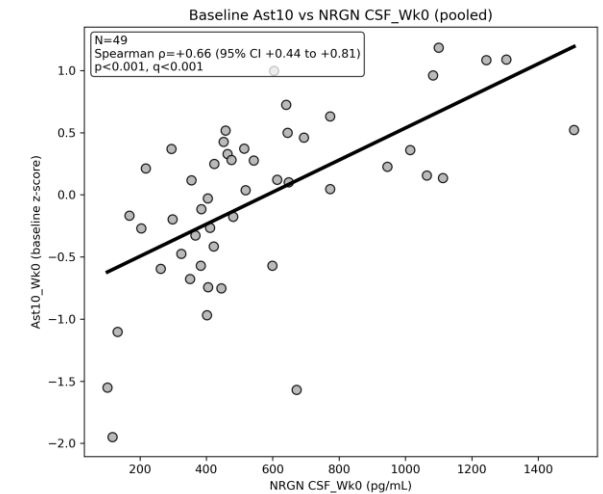
## YKL40

$r_s = 0.663$   
 $p < 0.0001$



## Neurogranin

$r_s = 0.658$   
 $p < 0.0001$

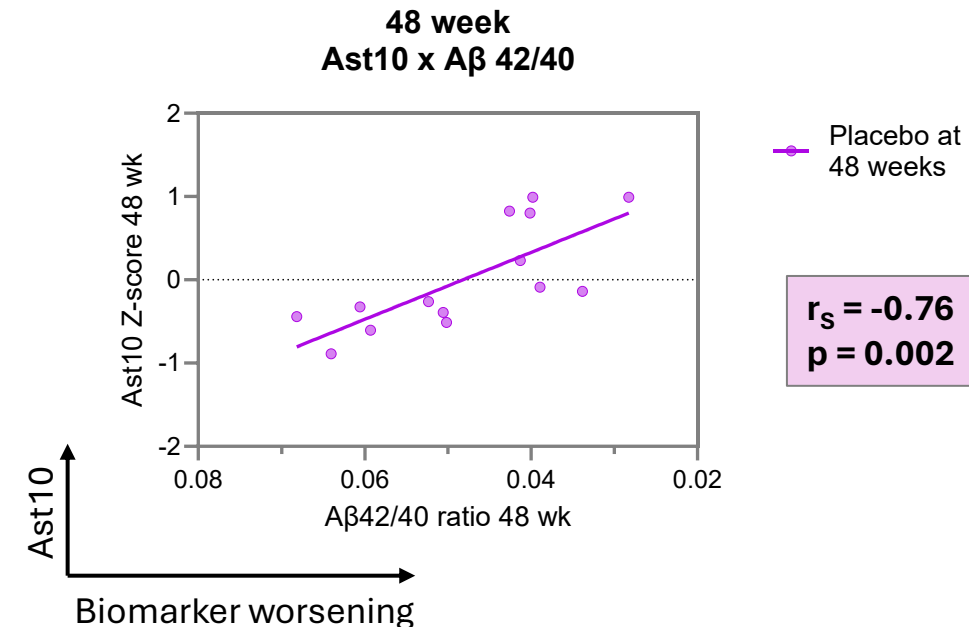
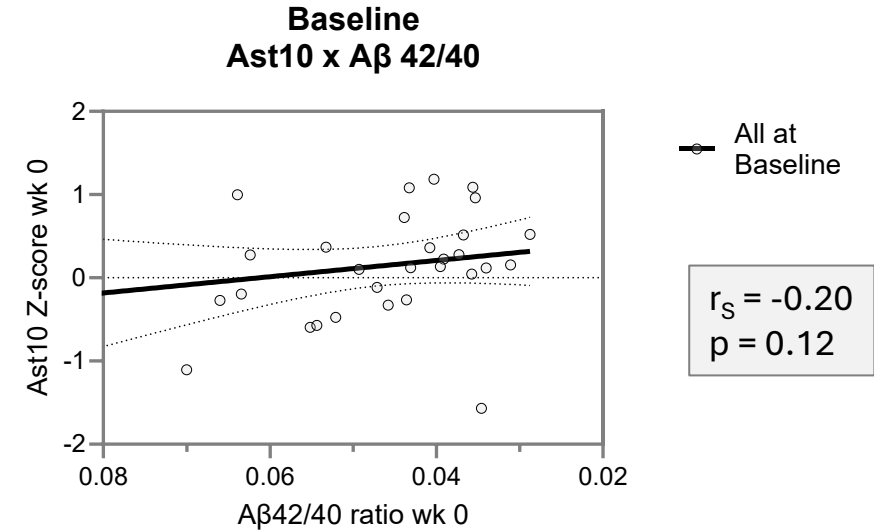


Ast10 Z-score derived from Olink proteomics analysis of CSF, collaboration with group of Philip De Jager, Columbia University. Soluble biomarker concentration determined by SIMOA assay of CSF.

# Ast10 increasingly correlates with NfL, Tau and Aβ during disease progression

**Ast10 Z-score v Biomarker in CSF:**

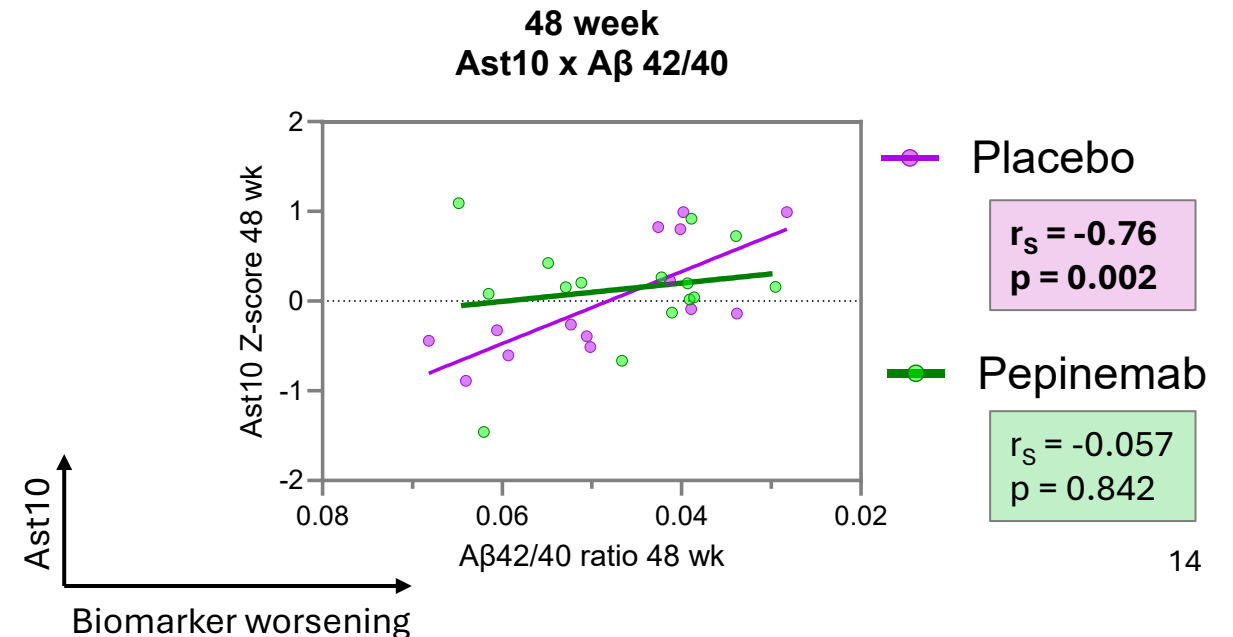
	Baseline			Week 48 PBO		
	Spearman r=	p-value	# pairs	Spearman r=	p-value	# pairs
<b>pTau-181</b>	<b>0.33</b>	<b>*</b>	49	<b>0.83</b>	<b>***</b>	15
<b>tTau</b>	<b>0.42</b>	<b>**</b>	48	<b>0.83</b>	<b>***</b>	15
<b>NfL</b>	0.19	ns	49	<b>0.68</b>	<b>**</b>	16
<b>Aβ 42/40 ratio</b>	-0.29	ns	30	<b>-0.76</b>	<b>**</b>	14



# Pepinemab treatment disrupts the accumulation of Tau, Aβ and NfL

Ast10 Z-score v Biomarker in CSF:	Baseline			Week 48 PBO			Week 48 Pepi		
	Spearman r=	p-value	# pairs	Spearman r=	p-value	# pairs	Spearman r=	p-value	# pairs
<b>pTau-181</b>	<b>0.33</b>	*	49	<b>0.83</b>	***	15	0.44	ns	17
<b>tTau</b>	<b>0.42</b>	**	48	<b>0.83</b>	***	15	0.33	ns	17
<b>NfL</b>	0.19	ns	49	<b>0.68</b>	**	16	0.40	ns	16
<b>Aβ 42/40 ratio</b>	-0.29	ns	30	<b>-0.76</b>	**	14	-0.057	ns	15

**Pepinemab** treatment for 48 weeks reduced correlation with Tau and Aβ suggesting that pepinemab disrupts the accumulation of Aβ, Tau and neurodegeneration biomarkers driven by reactive astrocytes.

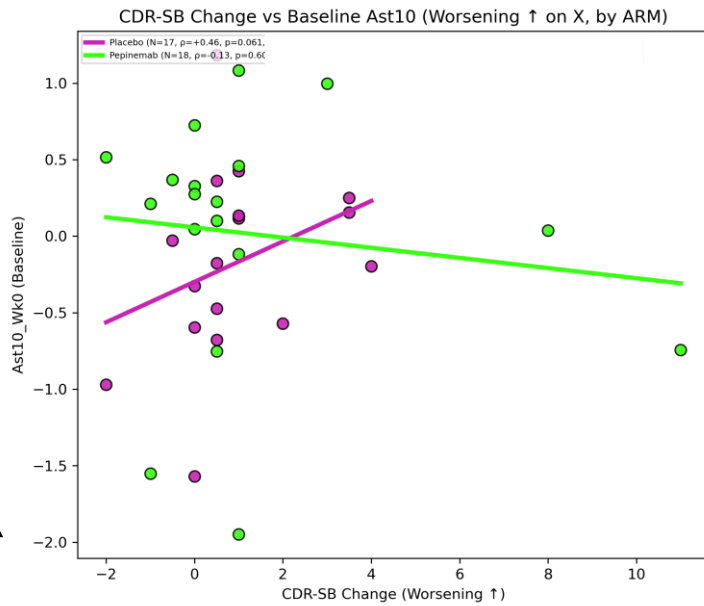


# Baseline Ast10 correlates with Change in Clinical Outcome Assessments

**Pepinemab** treatment appears to alter trajectory of disease progression driven by Ast10 astrocytes

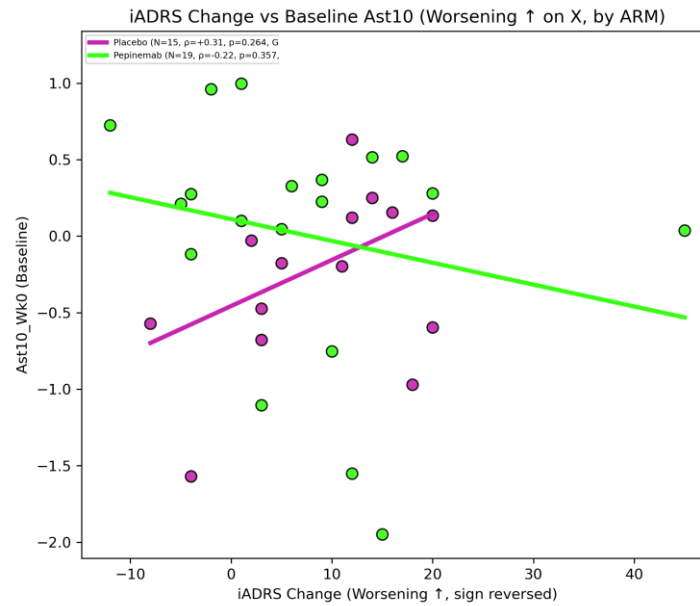
## CDR-SB

●  $r_s = 0.46, p = 0.06$



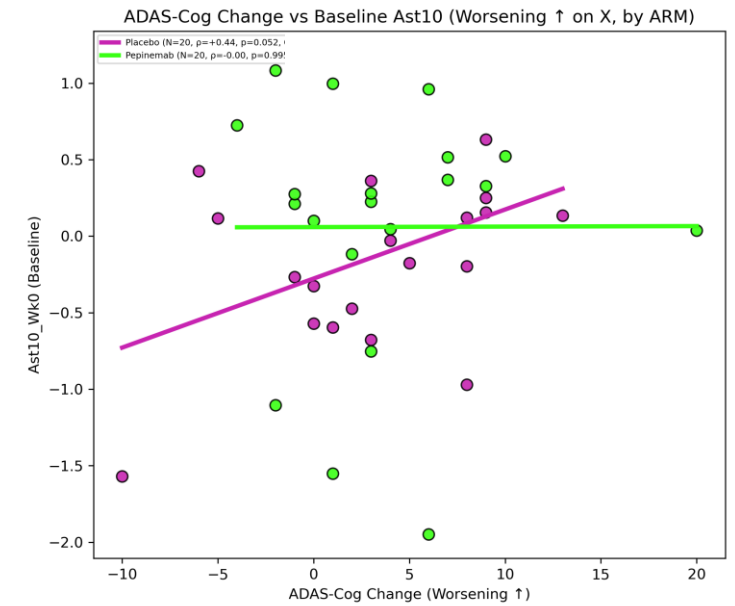
## iADRS

●  $r_s = 0.31, p = 0.26$



## ADAS-Cog13

●  $r_s = 0.44, p = 0.05$



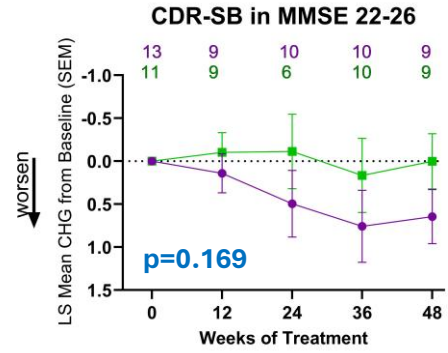
Ast10 BL  
 Δ COA 48 wks, worsening

● Placebo  
 ● Pepinemab

# Pepinemab improved assessments of cognition and function in MMSE 22-26 subgroup

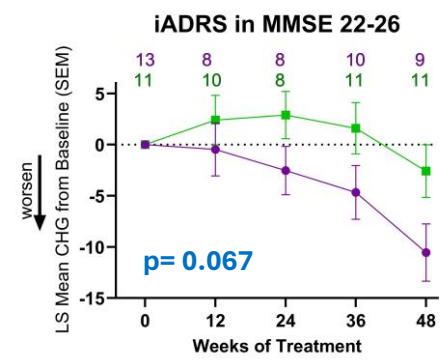
MMSE 22-26 and MMSE 17-21, prespecified subgroup analysis

MMSE 22-26 at baseline

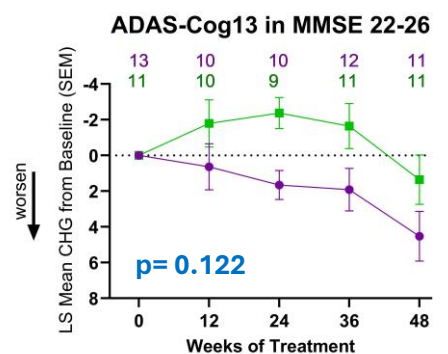


% slowing by pepinemab at week 48

99%

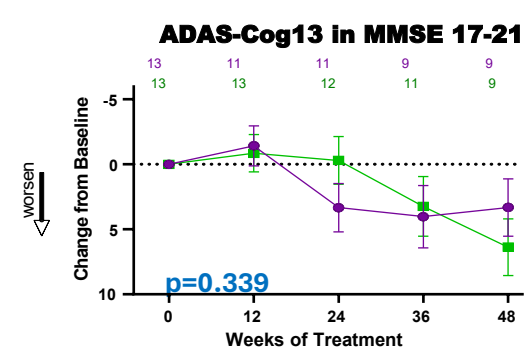
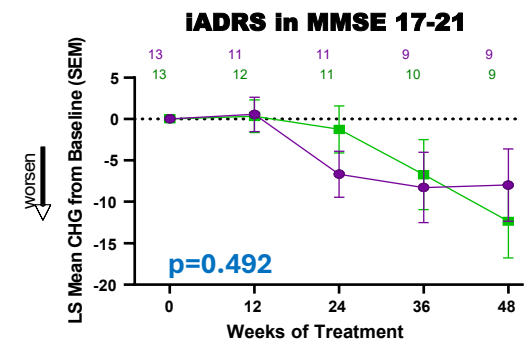
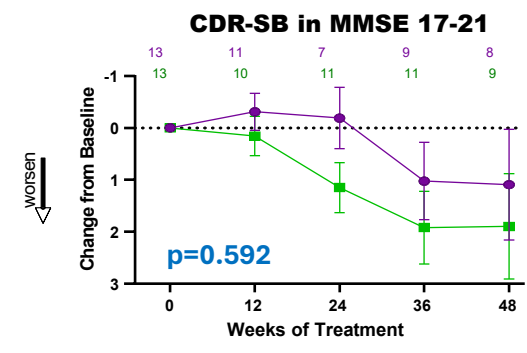




76%



70%

MMSE 17-21 at baseline



 Pepinemab  
 Placebo

# Appreciation and Thanks



**Participants, caregivers and their families!**

Vaccinex Research and Clinical Development Colleagues

**SIGNAL-AD study investigators and staff**

**Philip De Jager, Natacha Comandante-Lou, et al.**



Charlotte Teunissen, et al., UMC, Amsterdam Neuroscience

WCG Clinical Services/Statistics Collaborative Initiative



Alzheimer's  
**Drug Discovery**  
Foundation

