Pepinemab, a SEMA4D blocking antibody, is a novel potential treatment for neurodegenerative disease: clinical proof of concept in Phase 2 HD study supports clinical development in and ongoing Phase 1/2 AD study

SIGNAL

SIGNAL-AD

Terrence Fisher, PhD
SVP, Clinical Development

tfisher@vaccinex.com

VACCINEX
Rochester, New York

CTAD 2023
Clinical Trials on Alzheimer's Disease

October 24-27 Boston, MA

Disclosures

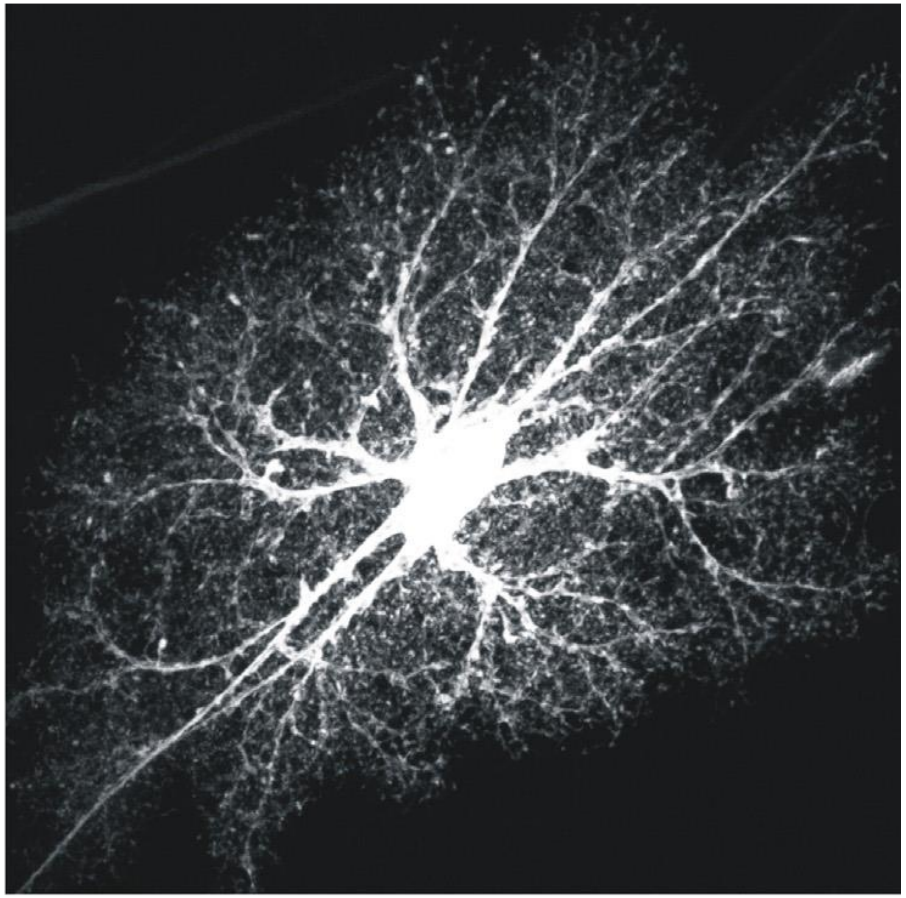
Terrence Fisher is a full-time employee, officer and shareholder at Vaccinex, Inc.

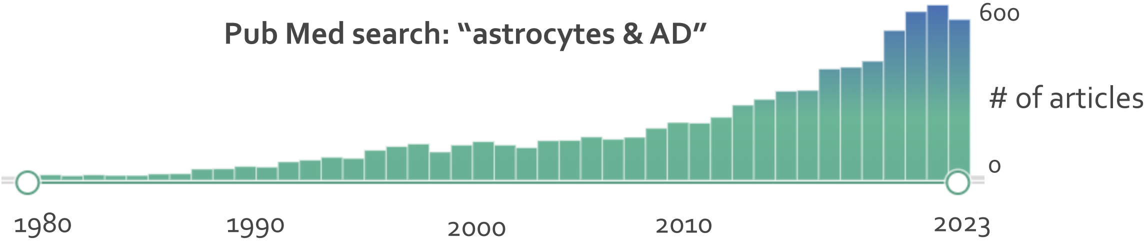
I will be discussing investigational drug and ongoing clinical trials.

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.

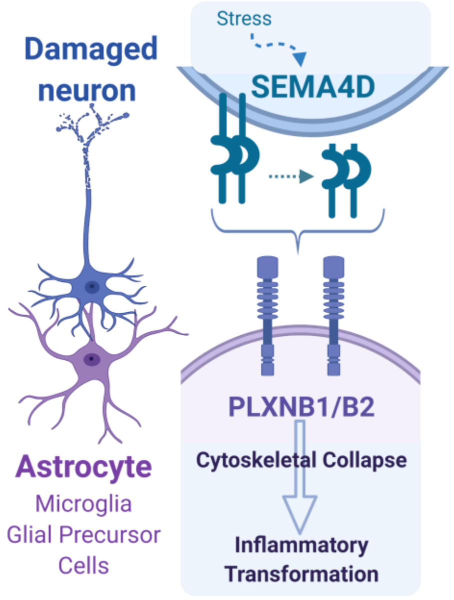
Astrocytes reach out to touch and interact with other brain cells



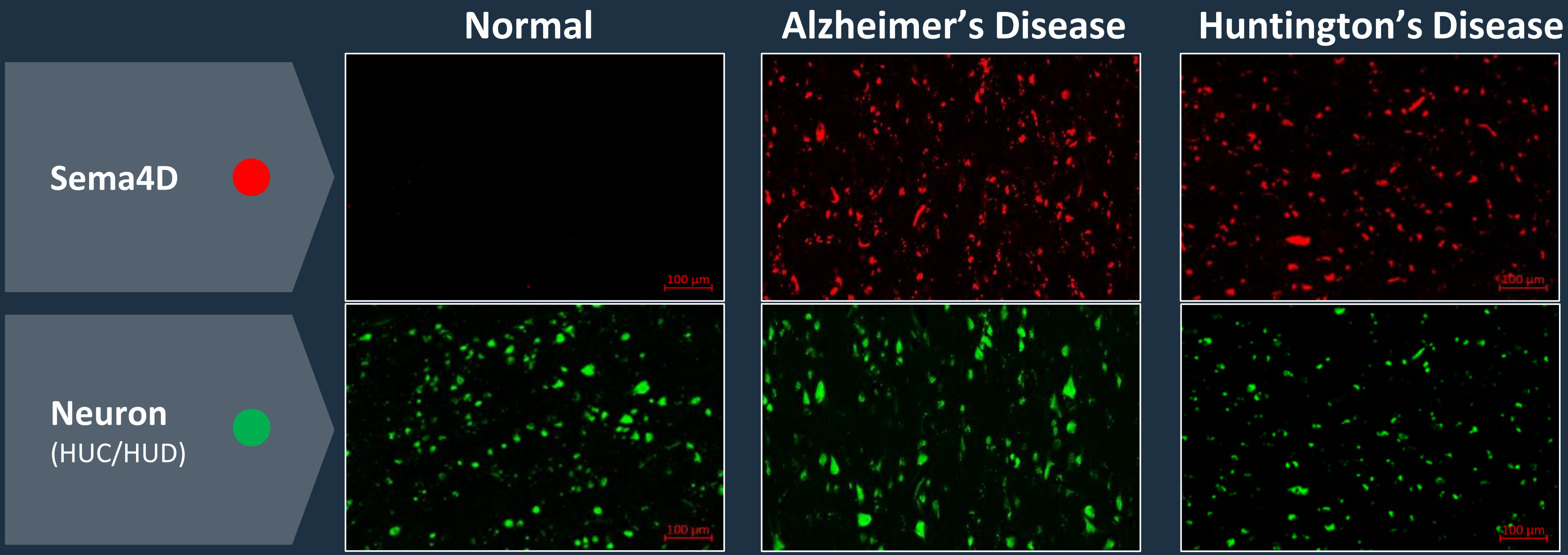


Astrocyte "arms" provide essential functional support to neurons.

- Fully cover capillaries and facilitate glucose uptake from circulation
- Cradle synapses and recycle glutamate
- Positioned to couple energy metabolism with neuronal activity



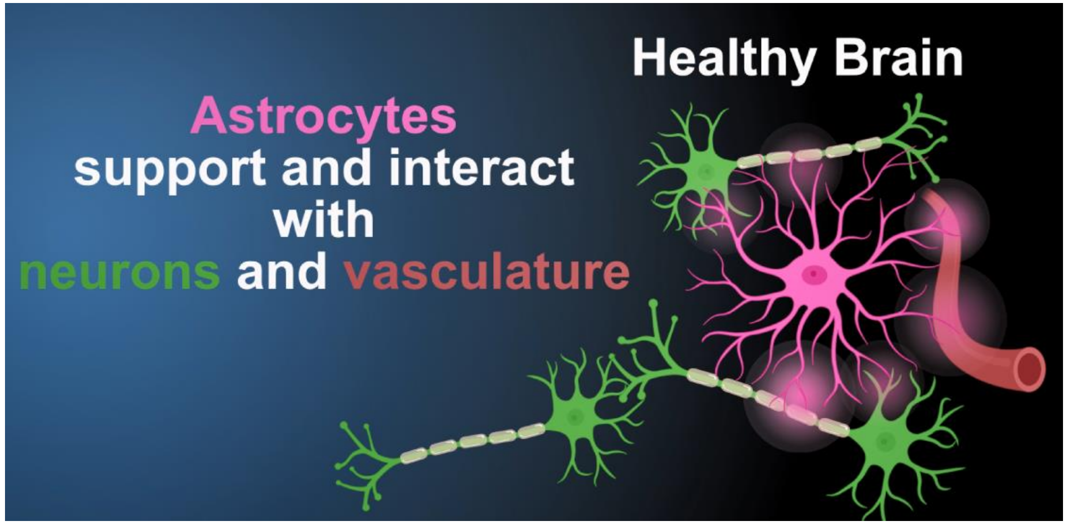
SEMA4D IS OBSERVED TO BE UPREGULATED IN NEURONS DURING DISEASE PROGRESSION

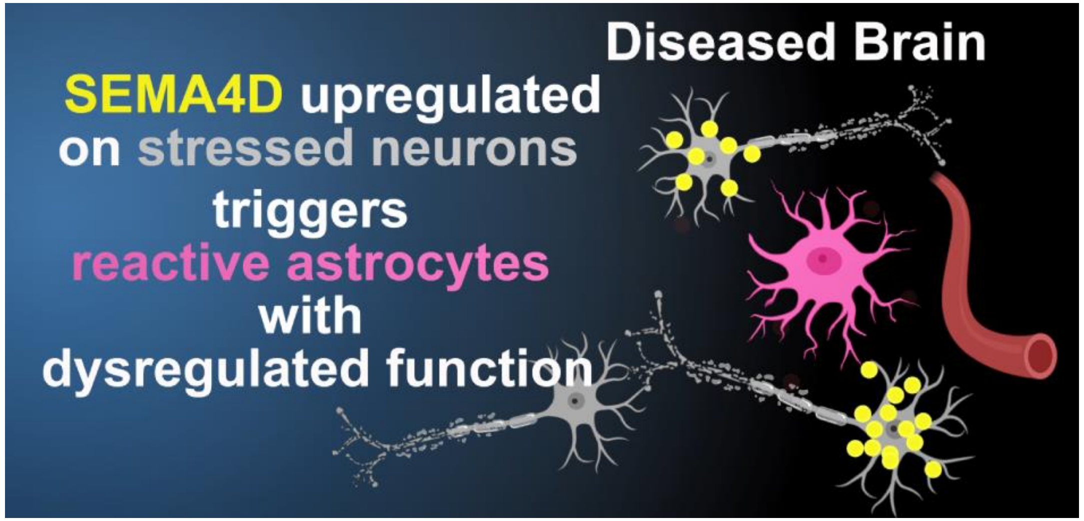


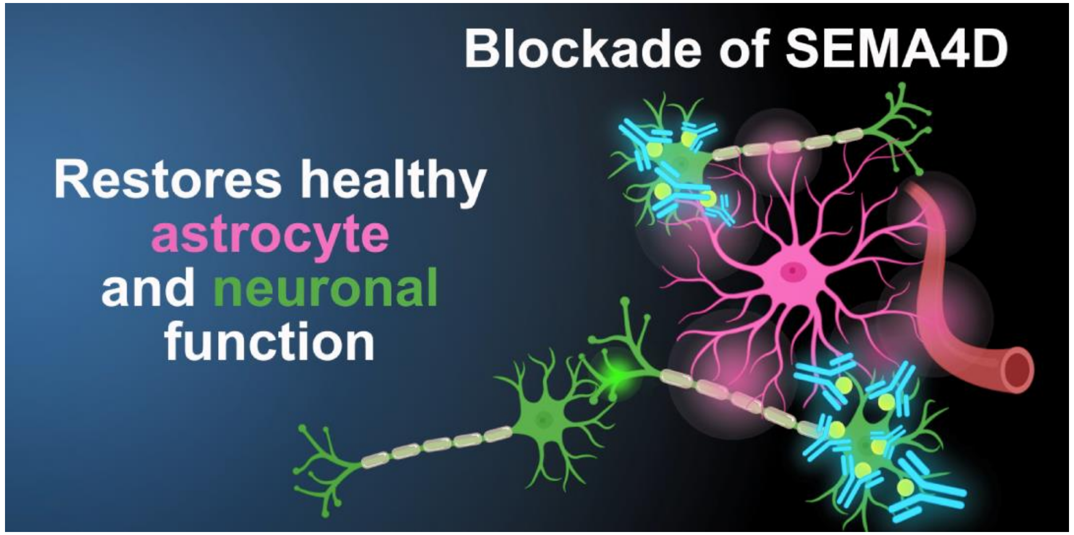
Human autopsy sections of frontal lobe

Semaphorin 4D is upregulated in neurons of diseased brains and triggers astrocyte reactivity
Elizabeth E Evans, Vikas Mishra, Crystal Mallow, Elaine Gersz, Leslie Balch, Alan Howell, Ernest S. Smith, Terrence L. Fisher, Maurice Zauderer*
Journal of Neuroinflammation, 2022.

SEMA4D regulates neuron-astrocyte communication and inflammation in diseased brain







Evans et al. Journal of Neuroinflammation (2022) 19:200
https://doi.org/10.1186/s12974-022-02509-8
Journal of Neuroinflammation

RESEARCH Open Access

Semaphorin 4D is upregulated in neurons of diseased brains and triggers astrocyte reactivity

Elizabeth E. Evans[1], Vikas Mishra[1], Crystal Mallow[1], Elaine M. Gersz[1], Leslie Balch[1], Alan Howell[1], Christine Reilly[1], Ernest S. Smith[1], Terrence L. Fisher[1] and Maurice Zauderer[1,2*]

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

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*

HUNTINGTON'S DISEASE

Clinical Trial Design

SIGNAL

Orphan Disease and Fast Track Designations

Cohort B1
Early Manifest ("Mild") HD

n=179

CAG repeat ≥36
TFC 11-13, DCL 4

randomized 1:1 double-blind

pepinemab or placebo

Monthly X18 months

Safety Follow-up 1 month

Cohort B2
Prodromal HD

n=86

CAG repeat ≥36
DCL 2 or 3

randomized 1:1 double-blind

pepinemab or placebo

Monthly X18 months

Safety Follow-up 1 month

Data Analysis and Study Objectives

Safety and tolerability

Primary Efficacy Outcomes (mITT)
Cognitive Function
CGIC

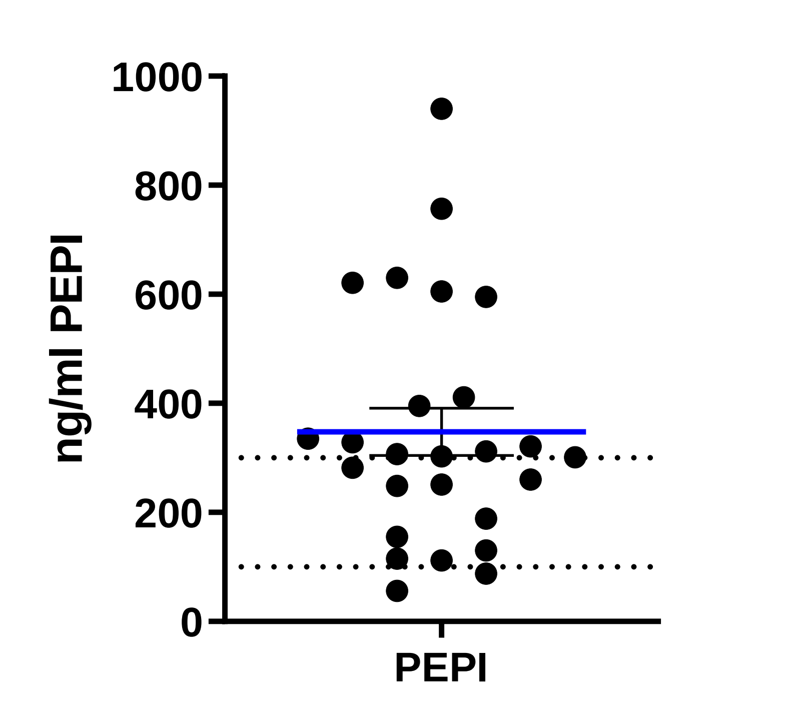
Key Exploratory and Biomarker Outcomes
Metabolic imaging (FDG-PET)
Brain Volume (vMRI)
GFAP

NCT02481674

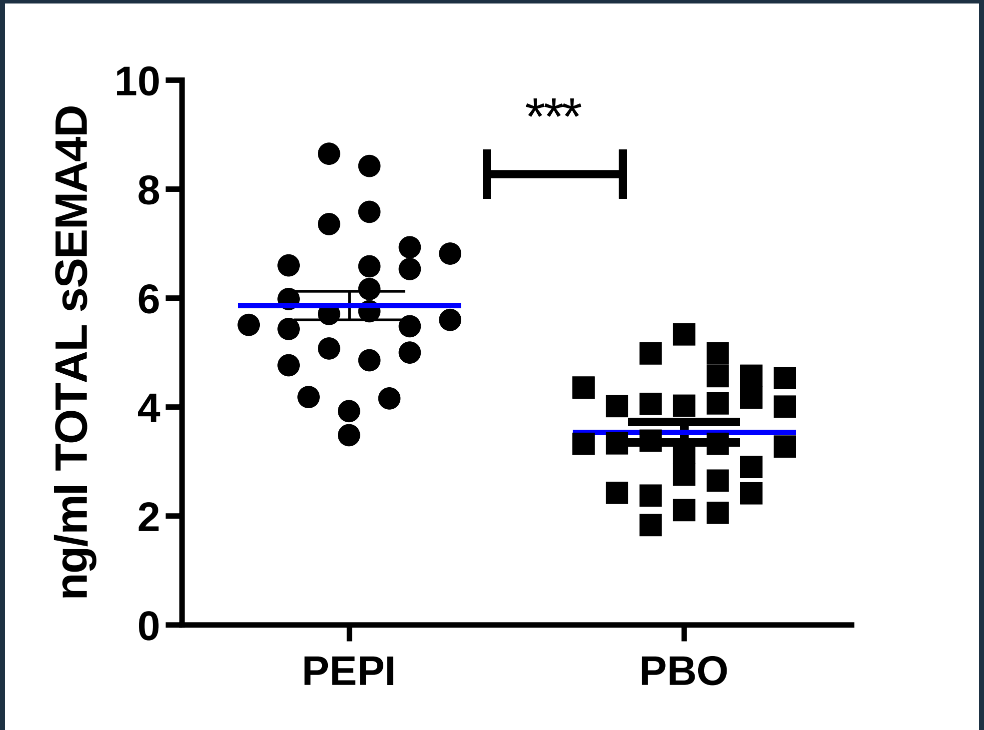
Pepinemab is detected at expected levels in CSF

PK/PD

Most subjects dosed with pepinemab have at least saturating levels (100-300 ng/ml) in CSF



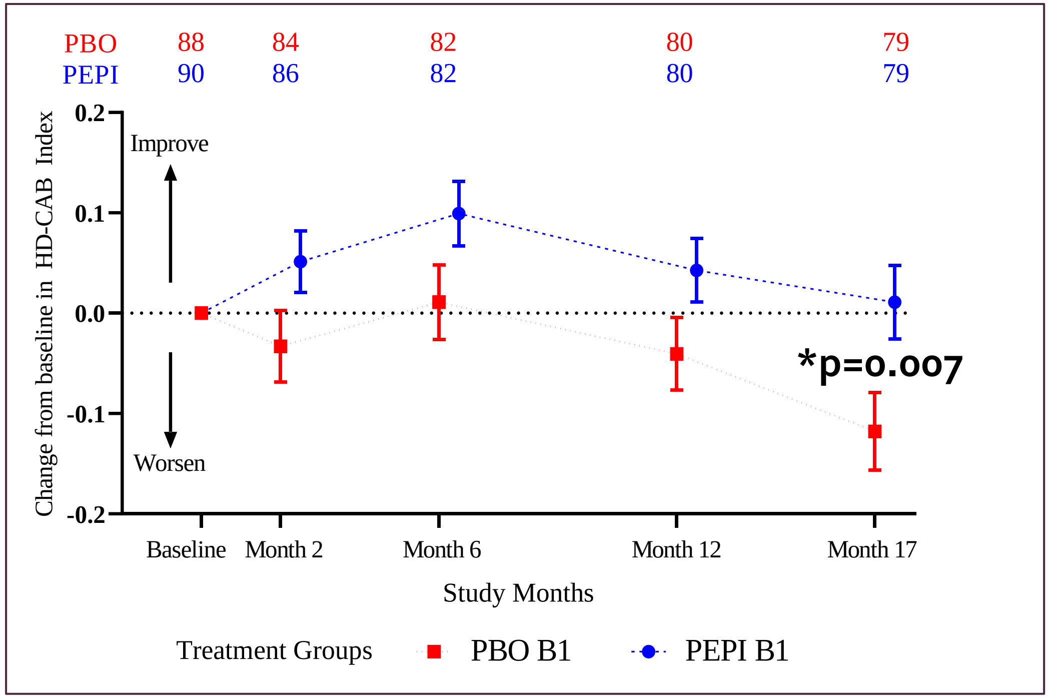
sSEMA4D: PEPI complexes in subjects dosed with pepinemab – suggesting target engagement

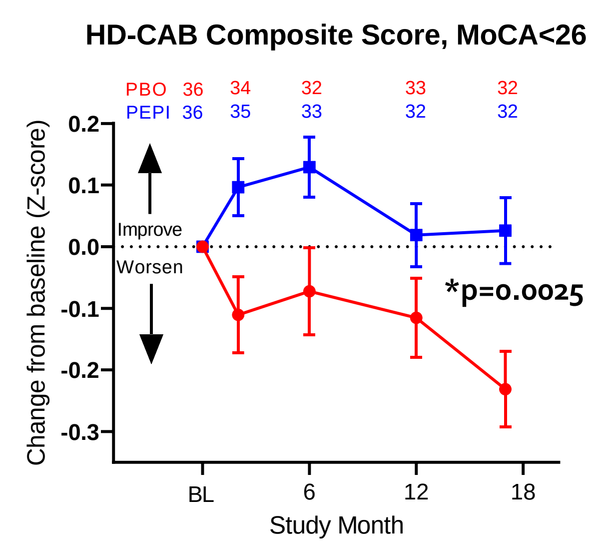


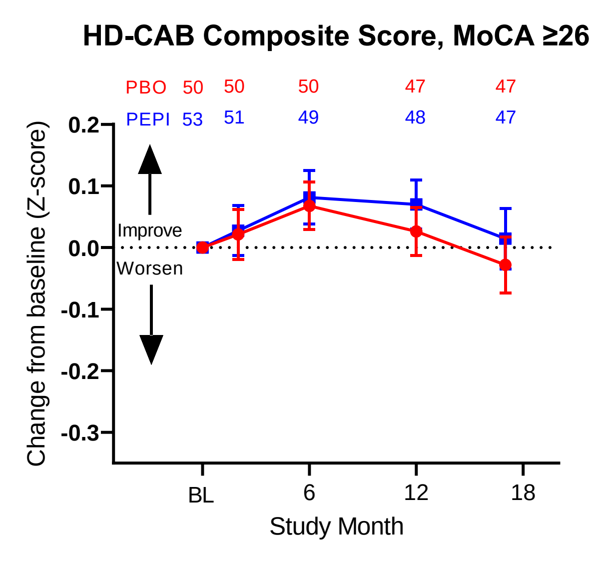
COGNITIVE ASSESSMENT BATTERY (HD-CAB)

Early Manifest HD: Intent to treat population (mITT)

HD-CAB Composite Index of 6 Cognitive Assessments



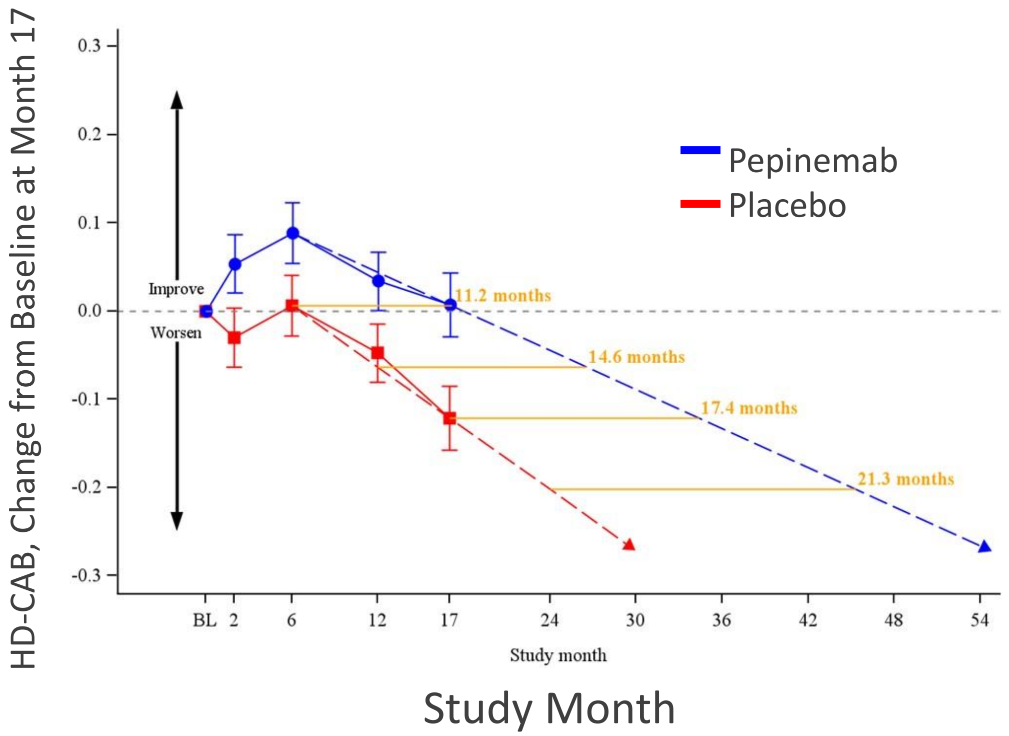




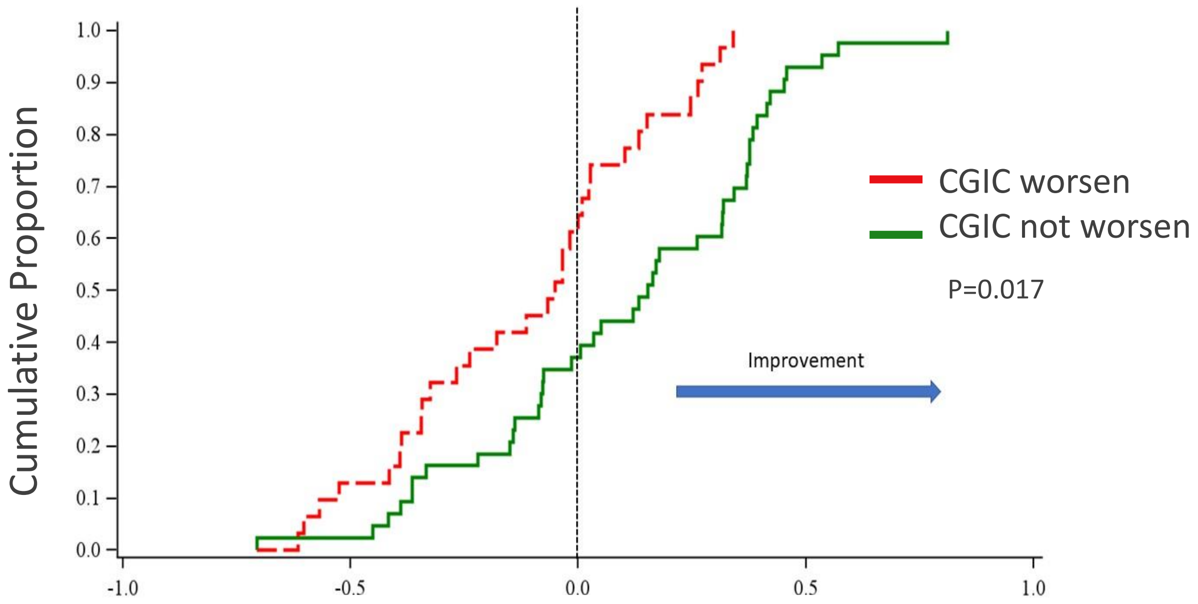
HD-COGNITIVE ASSESSMENT BATTERY (HD-CAB)

Associated with Clinically Meaningful change

Pepinemab delays disease progression



HD-CAB cognitive score correlates with Clinical Global Impression of Change (CGIC) (CDF Analysis)



HD-CAB, Change from Baseline at Month 17

Early Manifest Cohort B1 treated with Pepinemab

FDG-PET CORRELATES WITH COGNITIVE FUNCTION

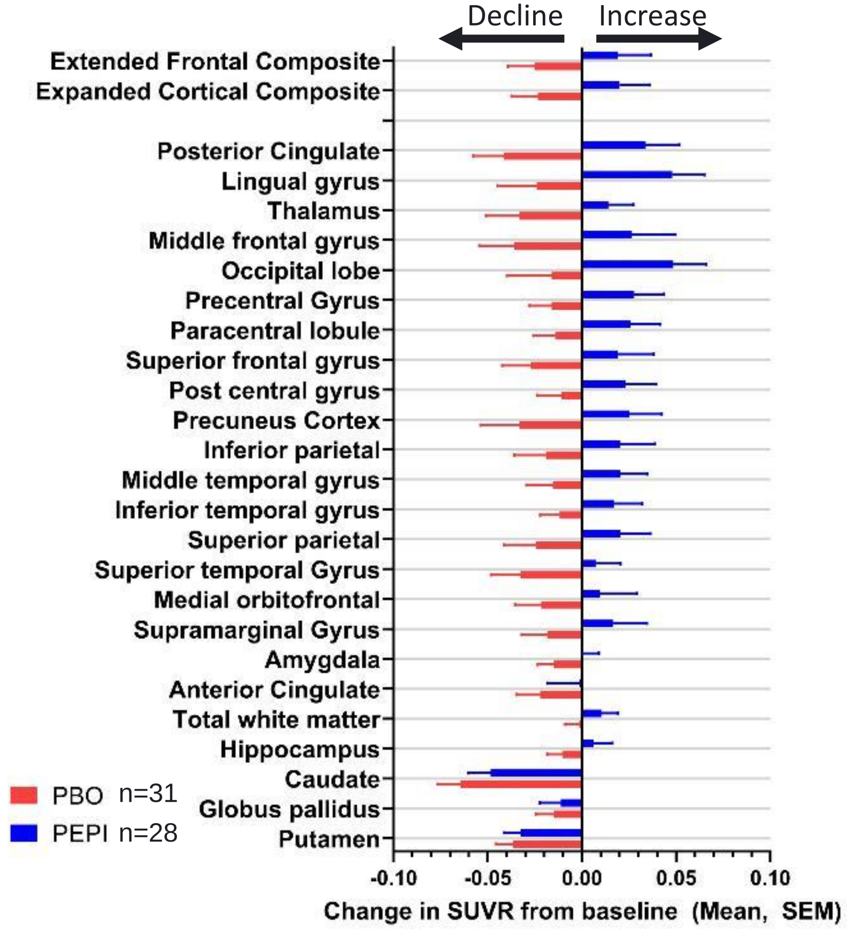
Pre-specified Exploratory Endpoint, Early Manifest cohort

1 FDG-PET measures brain metabolic activity.

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

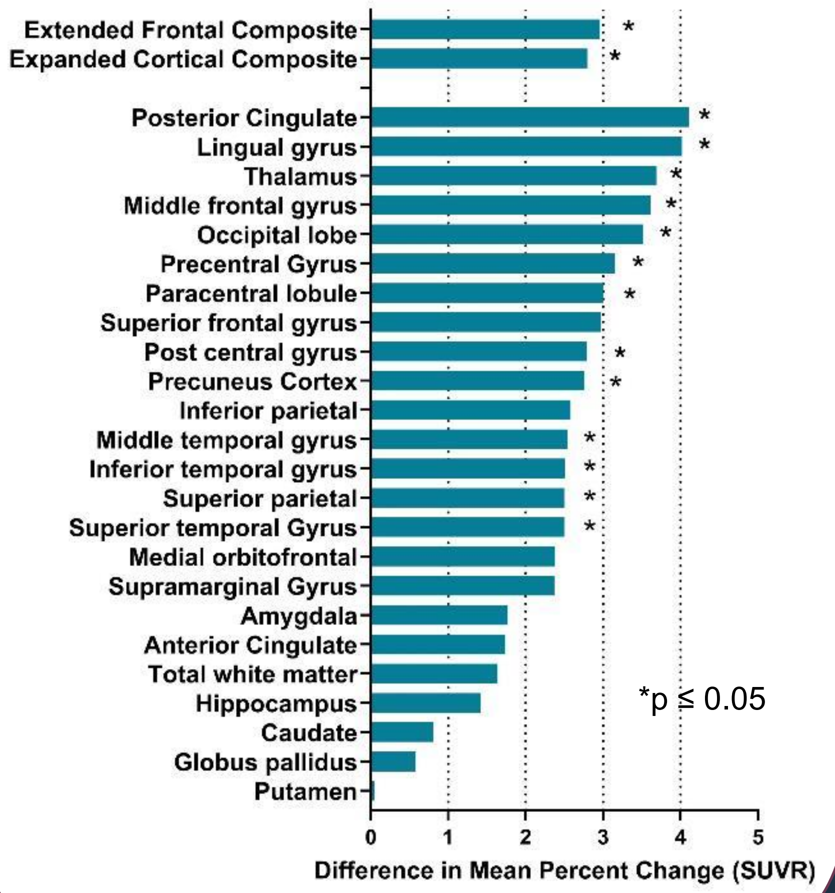
Pepinemab treatment appears to reverse loss of metabolic activity.

Change in FDG-PET at Month 18



SUVR = standardized uptake value ratio

Difference (PEPI-PBO) at Month 18



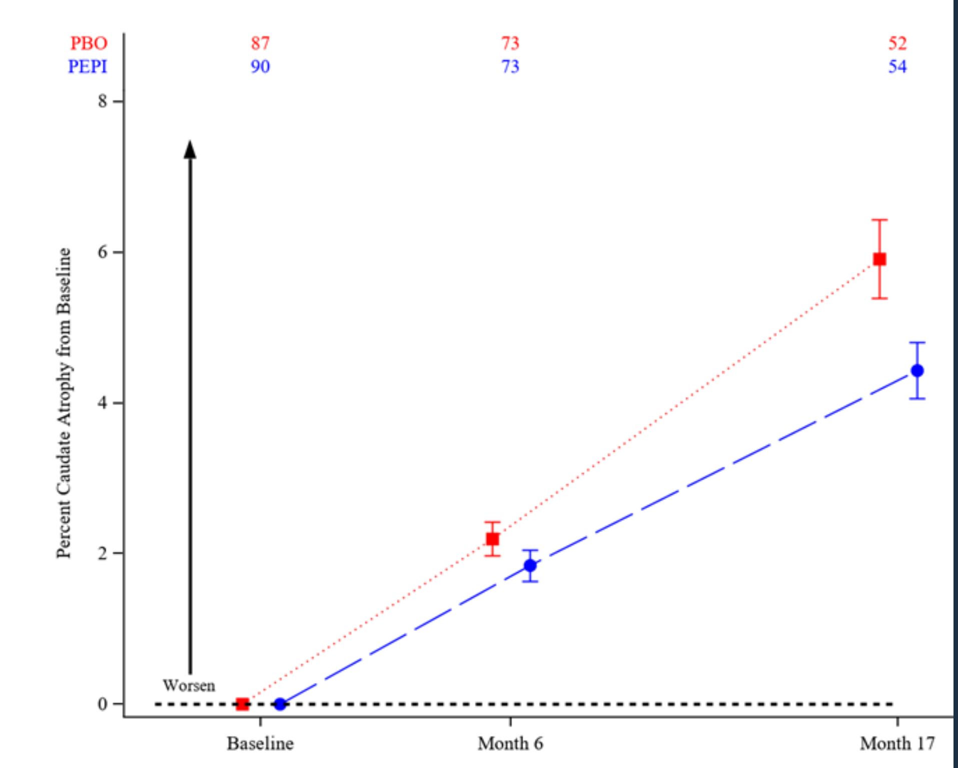
Feigin, A et al. *Nature Medicine* (2022)
https://doi.org/10.1038/s41591-022-01919-8

Pepinemab reduces brain atrophy

Volumetric MRI– Boundary Shift Integral Analysis

Early Manifest HD

CBSI (caudate atrophy)

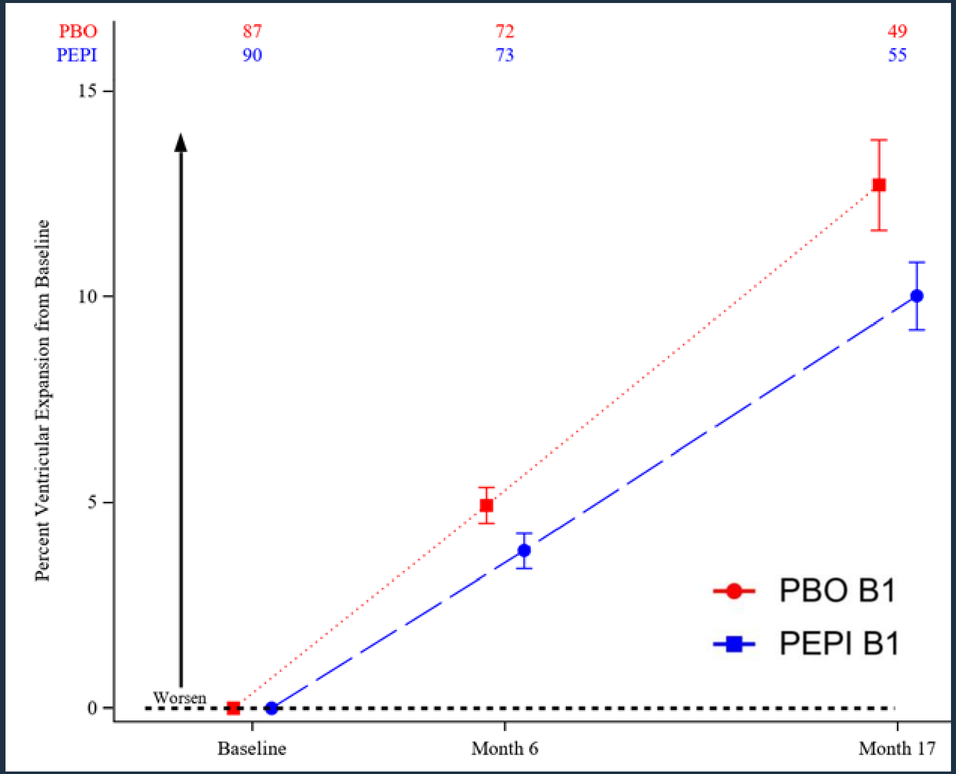


LS Mean Difference Estimate (95% CI):

CBSI: -1.54 (-2.79, -0.29);

p = 0.017

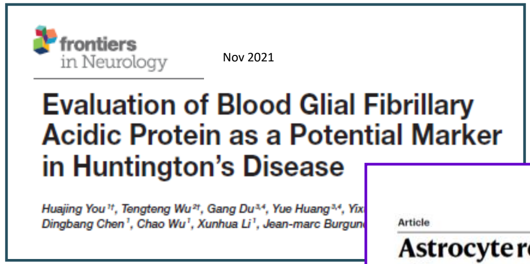
VBSI (ventricular expansion)



VBSI:-2.47 (-5.04, 0.10);

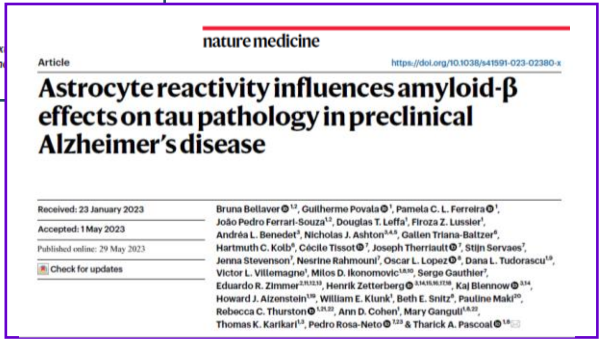
p = 0.060

Glial Fibrillary Acidic Protein (GFAP):
Biomarker for astrocyte activation / dysfunction


frontiers in Neurology

Nov 2021

Evaluation of Blood Glial Fibrillary Acidic Protein as a Potential Marker in Huntington's Disease


nature medicine

Article

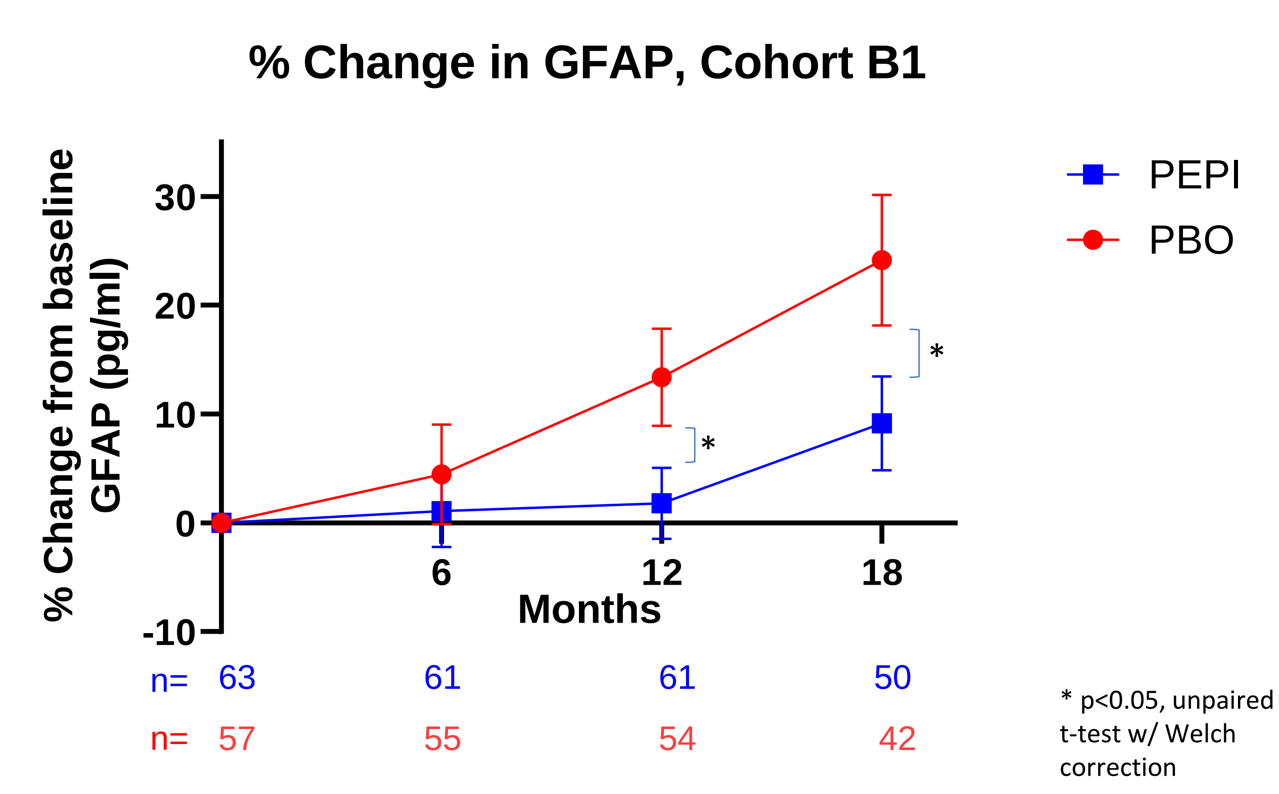
Astrocyte reactivity influences amyloid-β effects on tau pathology in preclinical Alzheimer's disease

- Correlates with cognitive decline and amyloid
- Proposed as the key neuroinflammatory fluid biomarker for the revised ATN criteria

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ42	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	p-tau 217, p-tau 181, p-tau 231	
Core 2		
T_2 (AD tau proteinopathy)	pT205, MTBR-243, non-phosphorylated tau fragments	Tau PET
Biomarkers of non-specific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MR or CT, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD co-pathology		
V vascular brain injury		Anatomic infarction, WMH
S α-synuclein	αSyn-SAA*	

Clifford Jack et al, NIA-AA Revised Clinical Criteria for AD (DRAFT), 9 Oct 2023.

Pepinemab reduced GFAP increase in SIGNAL-HD



Apply lessons learned to AD

- ✓ **PEPI is well-tolerated**
  - > 400 patients treated to date
  - Based on MOA, ARIA is not expected

SIGNAL-AD

- ✓ **MOA of PEPI is relevant in AD**
  - Astrocytes involved in neuroinflammation
  - MOA is alternative and independent to anti-AB, ideal for possible combination

- ✓ **Clinical Proof of Concept in HD is relevant to AD**
  - Slowing in decline of cognitive function
  - Greatest benefit from treatment was detected in patients with signs of mildly advanced disease

- ✓ **Biomarkers relevant to AD that have been shown to correlate with disease progression**
  - **FDG-PET** : reversal of hypometabolism; consistent with MOA to restore astrocyte function
  - **MRI**: reduced brain atrophy
  - **GFAP**: slowing the increase in plasma GFAP; consistent with MOA to reduce astrocyte reactivity

ALZHEIMER'S DISEASE
Ongoing Phase 1b/2 Trial

VACCINEX

SIGNAL-AD NCT04381468

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

Phase 1b: Safety

n=4

Randomized 1:1 Double-blind

Phase 2: Expansion

placebo n=25 — Monthly X12 months — Safety Follow-up

pepinemab n=25 — Monthly 40 mg/kg X12 months — Safety Follow-up

LPLV JUN 2024

Q3 2024

Topline Data

UPDATES

- **Fully enrolled (n=50), 15 patients have completed all visits**
- **DSMB #4; JUL 2023→ No safety issues, unanimous decision to continue with no modifications**
- **No discontinuations**

Mild AD
(CDR=0.5 or 1.0, MMSE 18-26)

Topline Data:

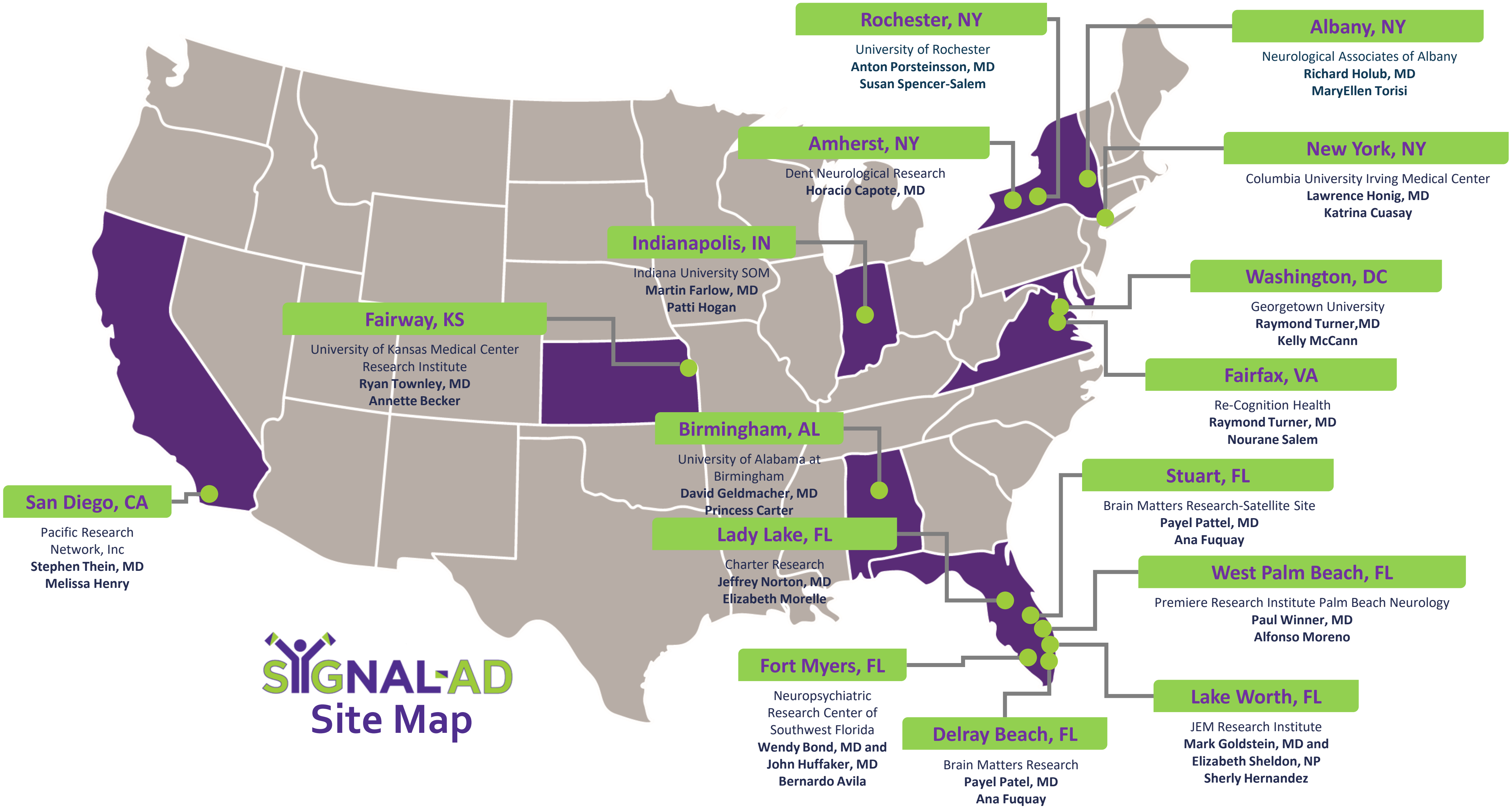
Safety and tolerability

Cognitive Function measures
CDR-SB, ADAS-Cog13, MMSE, CDRS

Biomarker Outcomes
Metabolic imaging (FDG-PET)
Brain Volume (vMRI)
GFAP

16 sites in US

Thanks to all of our patients, caregivers, families, site PIs, SCs and site staff !!



Acknowledgements

"These approvals are encouraging but only the beginning…..alternative / complimentary pathways need to be explored…ultimately it will take a combination approach, similar to those used in cancer treatment, to slow down the progression of the disease and stop AD in its tracks."

CTAD organizers and attendees

Andy Feigin, MD and **HSG**

Eric Siemers, MD

Statistical Collaborative (SCI)

The entire research and development teams, especially:

Liz Evans, Crystal Mallow, Vikas Mishra, Megan Boise, Amber Foster, John Leonard, Yelena Lerman, Joe Townsend, Karin Gringer, Kevin Graczyk, and **Maurice Zauderer**

Schematics created with BioRender.com