SEMA4D blocking antibody, pepinemab, is a novel potential treatment for neurodegenerative disease: clinical proof of concept in HD supports clinical development in AD

Terrence Fisher, PhD
VP, Clinical Sciences

tfisher@vaccinex.com

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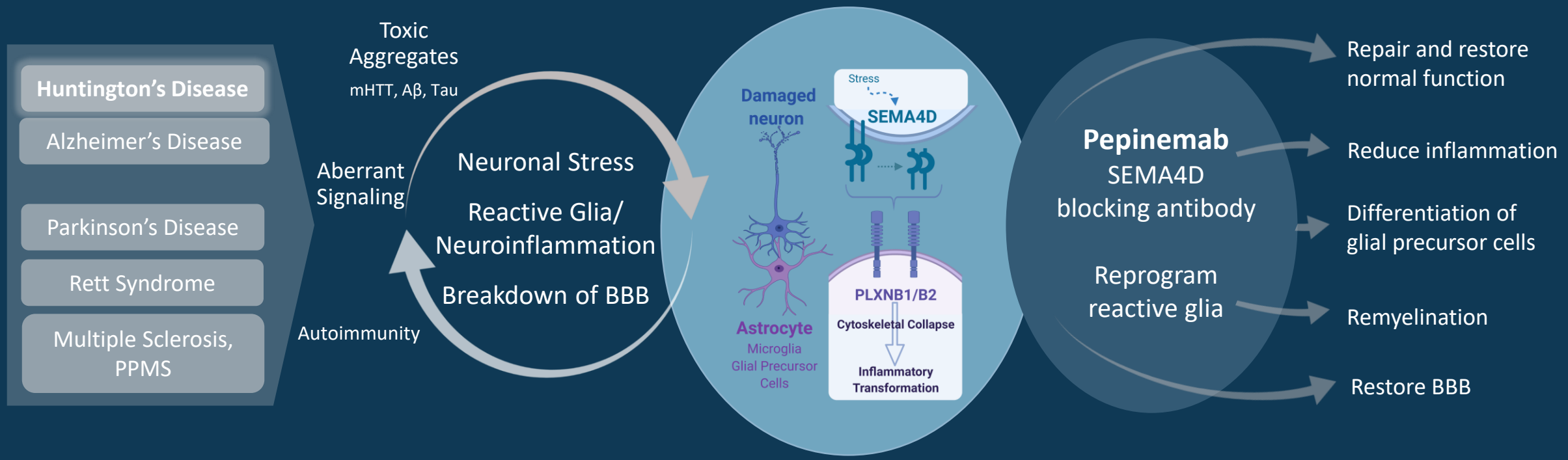
Disclosures

Full time employee: Vaccinex, Inc.

VACCINEX

PEPINEMAB REPROGRAMS UNDERLYING PATHOLOGY IN CNS DISEASE



SEMA4D antibody blockade improves disease phenotype in preclinical models

Anti-semaphorin 4D immunotherapy ameliorates neuropathology and some cognitive impairment in the YAC128 mouse model of Huntington disease

Amber L. Southwell [a], Sonia Franciosi [a], Erika B. Villanueva [a], Yuanyun Xie [a], Laurie A. Winter [b], Janaki Veeraraghavan [b], Alan Jonason [b], Boguslaw Felczak [a], Weining Zhang [a], Vlad Kovalik [a], Sabine Waltl [a], George Hall [a], Mahmoud A. Pouladi [c,d], Ernest S. Smith [b], William J. Bowers [b], Maurice Zauderer [b], Michael R. Hayden [a,*]

2015 Neurobiology of Disease

SEMA4D compromises blood–brain barrier, activates microglia, and inhibits remyelination in neurodegenerative disease

Ernest S. Smith [a], Alan Jonason [a], Christine Reilly [a], Janaki Veeraraghavan [a], Terrence Fisher [a], Michael Doherty [a], Ekaterina Klimatcheva [a], Crystal Mallow [a], Chad Cornelius [a], John E. Leonard [a], Nicola Marchi [b], Damir Janigro [b], Azeb Tadesse Argaw [c], Trinh Pham [c], Jennifer Seils [a], Holm Bussler [a], Sebold Torno [a], Renee Kirk [a], Alan Howell [a], Elizabeth E. Evans [a], Mark Paris [a], William J. Bowers [a], Gareth John [c], Maurice Zauderer [a,*]

[a] *Vaccinex, Inc., Rochester, NY 14620, USA*

2014 Neurobiology of Disease

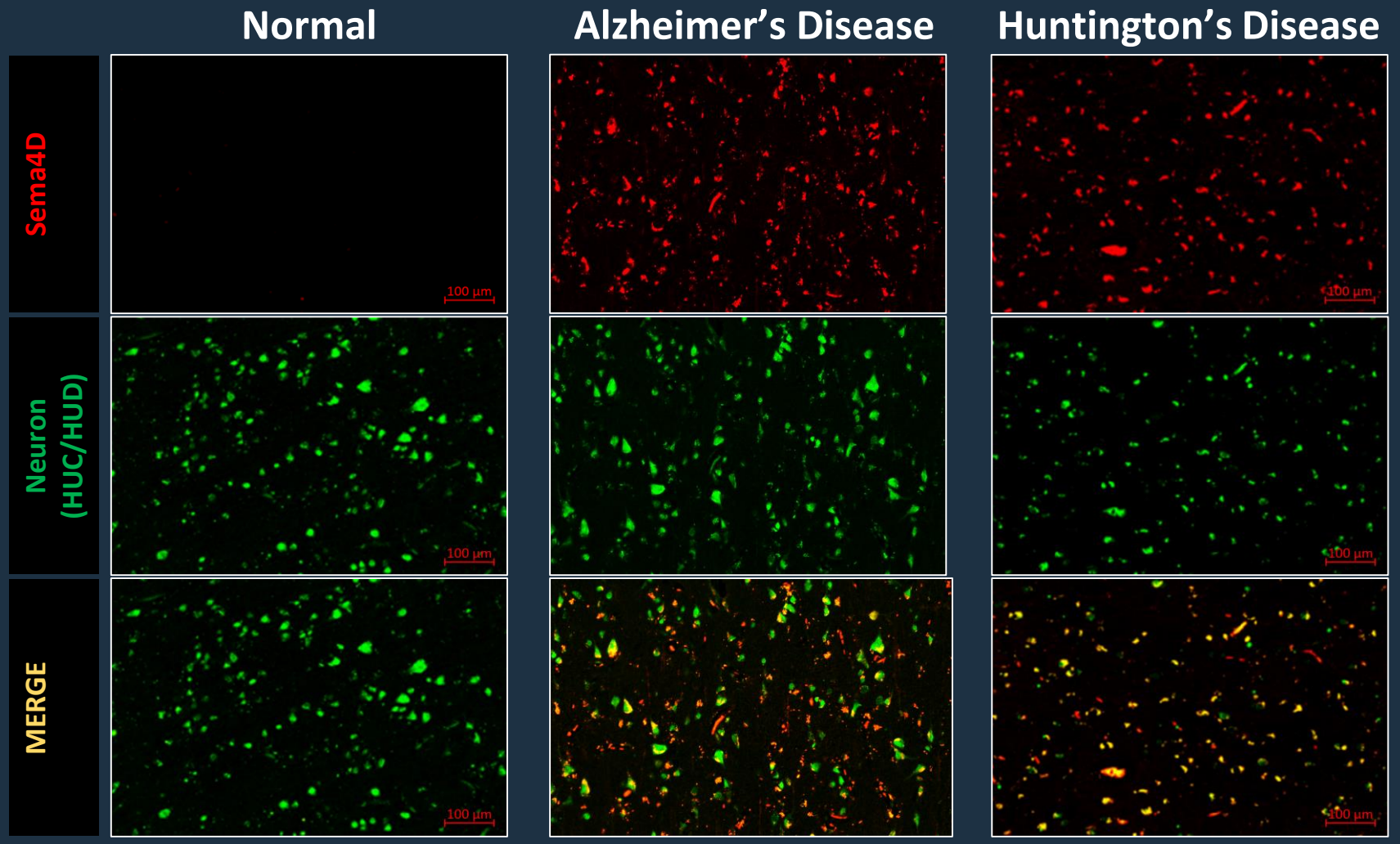
International Journal of *Molecular Sciences* 2021

Article

Anti-Semaphorin 4D Rescues Motor, Cognitive, and Respiratory Phenotypes in a Rett Syndrome Mouse Model

Yilin Mao [1,2], Elizabeth E. Evans [3], Vikas Mishra [3], Leslie Balch [3], Allison Eberhardt [3], Maurice Zauderer [3,†] and Wendy A. Gold [1,2,4,5,*,†]

SEMA4D is upregulated in neurons during underlying disease progression

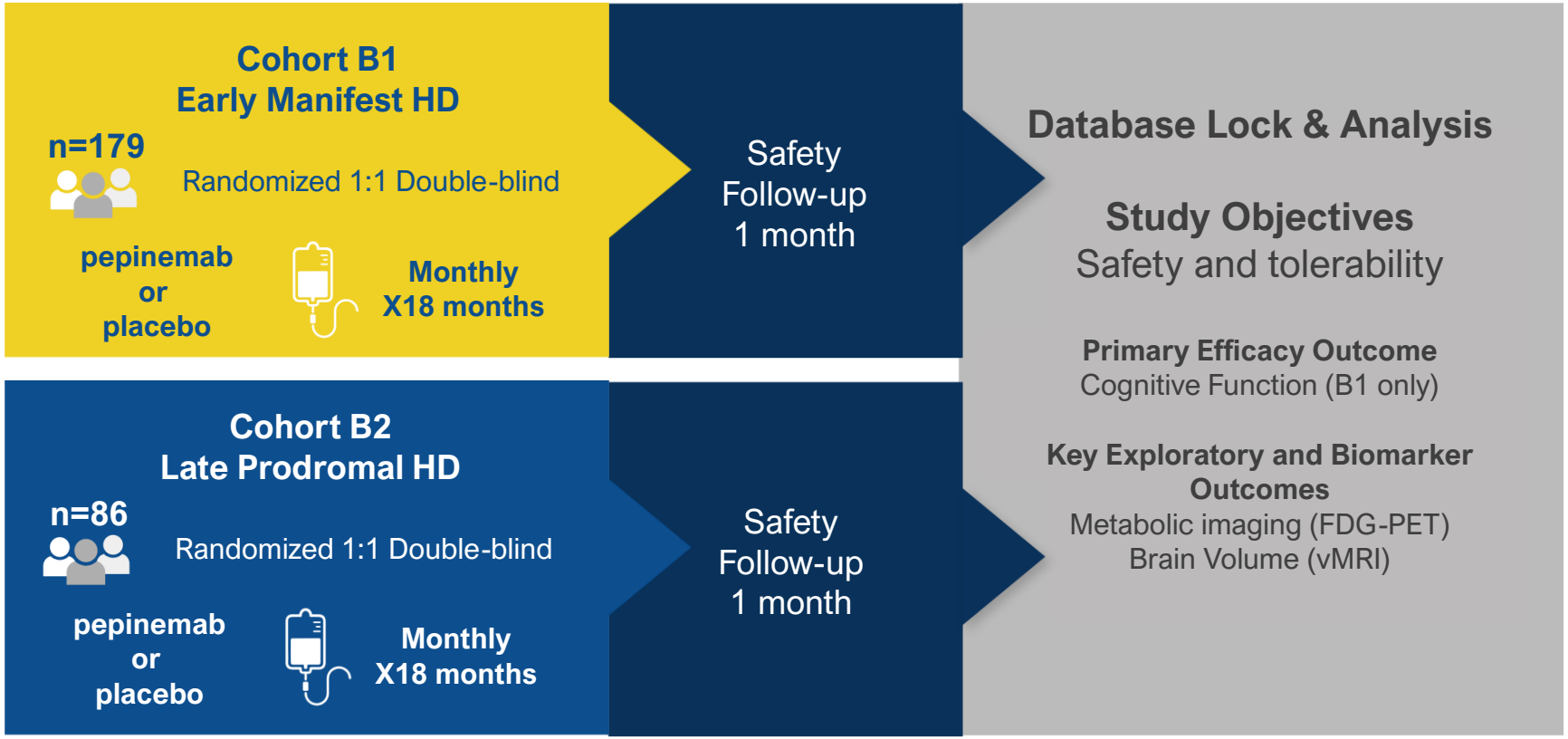


Human autopsy sections of frontal lobe

CLINICAL TRIAL DESIGN: Huntington's Disease

SIGNAL

Orphan Disease and Fast Track Designations



Abbreviated Safety and Baseline Characteristics

mITT population

Pepinemab (PEPI) SEMA4D blocking antibody is well tolerated

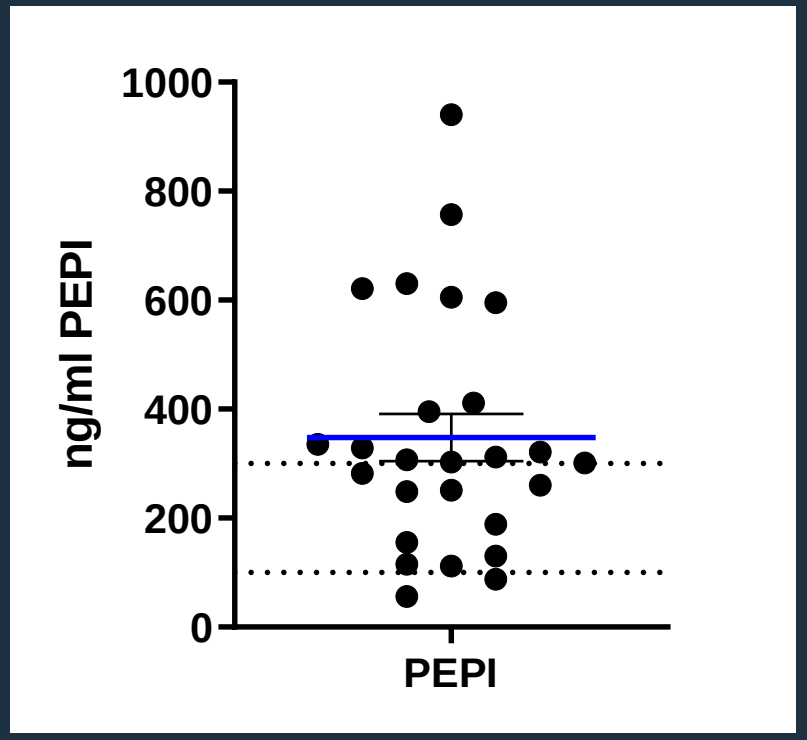
Early Manifest Cohort B1	Placebo (n=88)	Pepinemab (n=91)
Discontinued Treatment Early	10	13
Had any SAE (*)	8	4
Had any Grade 3+ AE (*)	14	17
CAG repeat length	44.1	43.5
CAP score**	470	466
UHDRS-DCL at screening DCL-4, Unequivocal HD (>99% confident)	88 (100%)	91 (100%)
UHDRS-TFC at screening, n (%)		
11 12 13	33 (38%) 18 (20%) 37 (42%)	29 (32%) 37 (41%) 24 (27%)
MoCA score, mean (SE)	26.02 (2.04)	26.14 (2.30)
MoCA <26 subgroup	23.97 (0.94)	23.78 (1.07)
MoCA ≥26 subgroup	27.44 (1.21)	27.72 (1.34)

*pre-COVID era;
**CAP score = age × (CAG repeat length – 33.66)

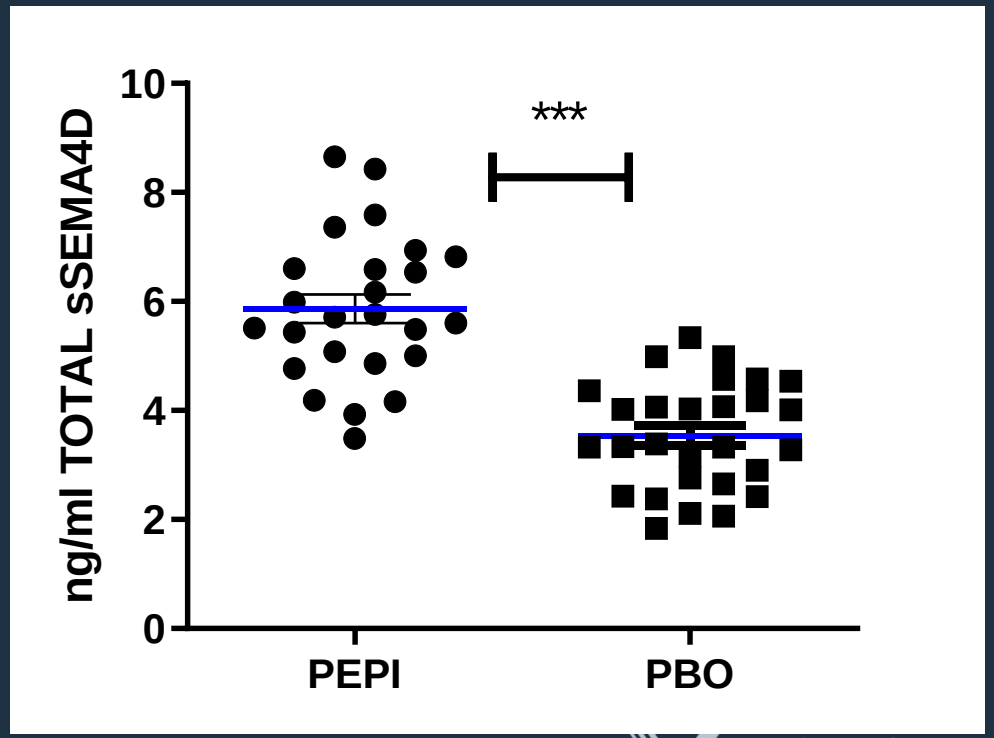
Pepinemab is detected at expected levels in CSF

PK/PD

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



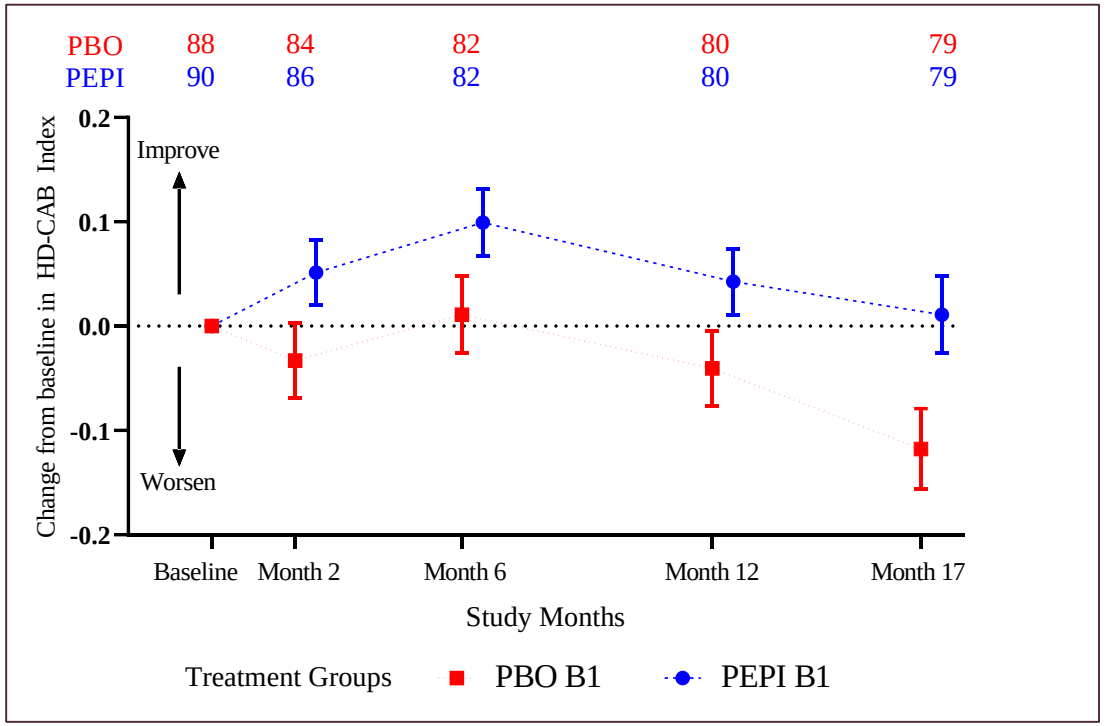
sSEMA4D increases in subjects dosed with pepinemab – suggesting target engagement



COGNITIVE ASSESSMENT BATTERY (HD-CAB)

Early Manifest HD: Intent to treat population (mITT)

HD-CAB Composite Index of 6 Cognitive Assessments



HD-CAB Composite Index:

LS Mean Difference Estimate (95% CI)	One-sided p-value	Favors PEPI	Critical value
0.13 (0.03, 0.23)	**0.007**	**Yes**	**Yes [0.025]**

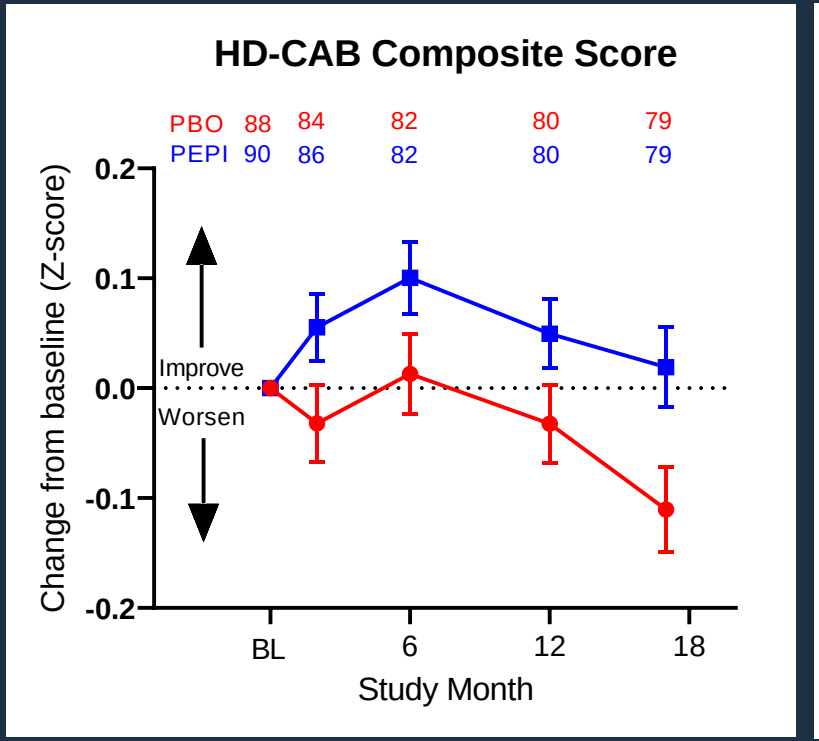
Co-Primary: Two-item HD Cognitive Assessment

LS Mean Difference Estimate (95% CI)	One-sided p-value	Favors PEPI	Critical value
OTS: -1.98 (-4.00, 0.05)	**0.028**	**Yes**	**Yes [0.025]**
PTAP: 1.43 (-0.37, 3.23)	**0.060**		

HD-CAB stratified by baseline MoCA

(Montreal Cognitive Assessment)

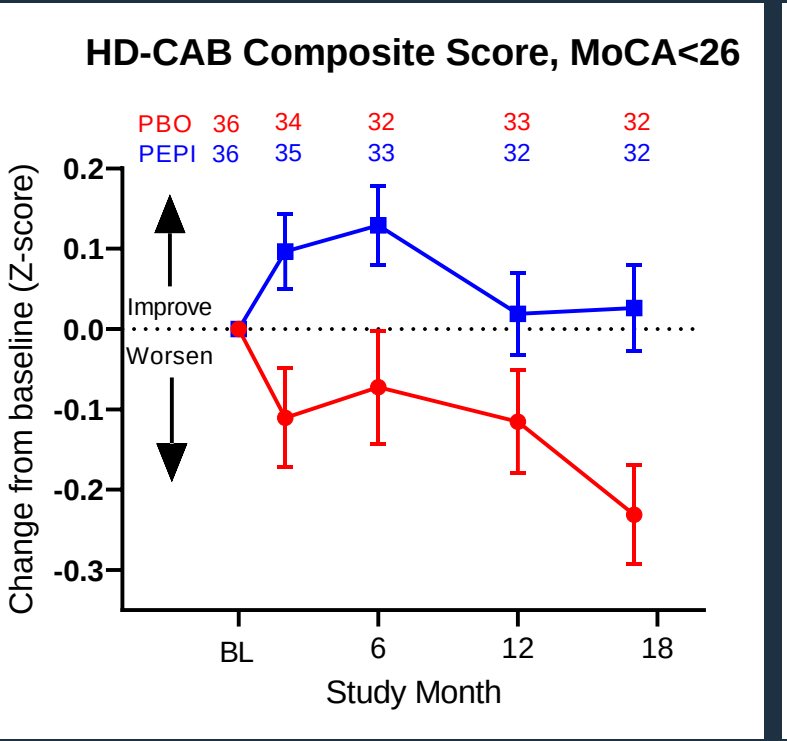
mITT



LS Mean Estimate (SE), month 17

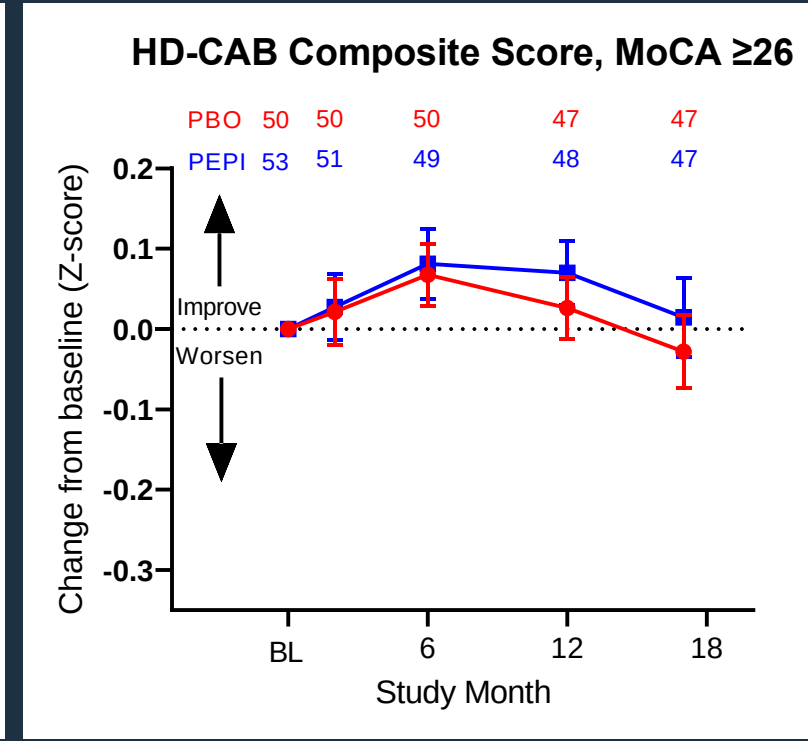
mITT: 0.13 (0.05), **p=0.007**

MoCA < 26



MoCA <26: 0.24 (0.08), **p=0.0025**

MoCA ≥ 26



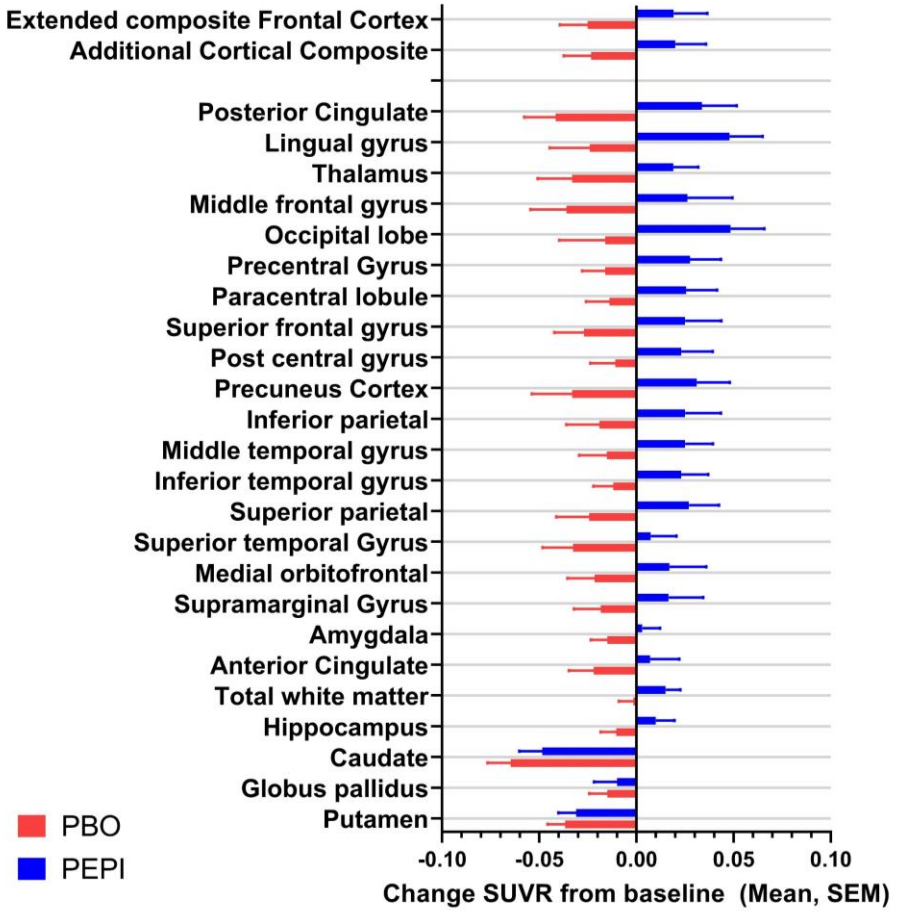
MoCA ≥26: 0.06 (0.06), **p=0.197**

FDG-PET CORRELATES WITH COGNITIVE FUNCTION

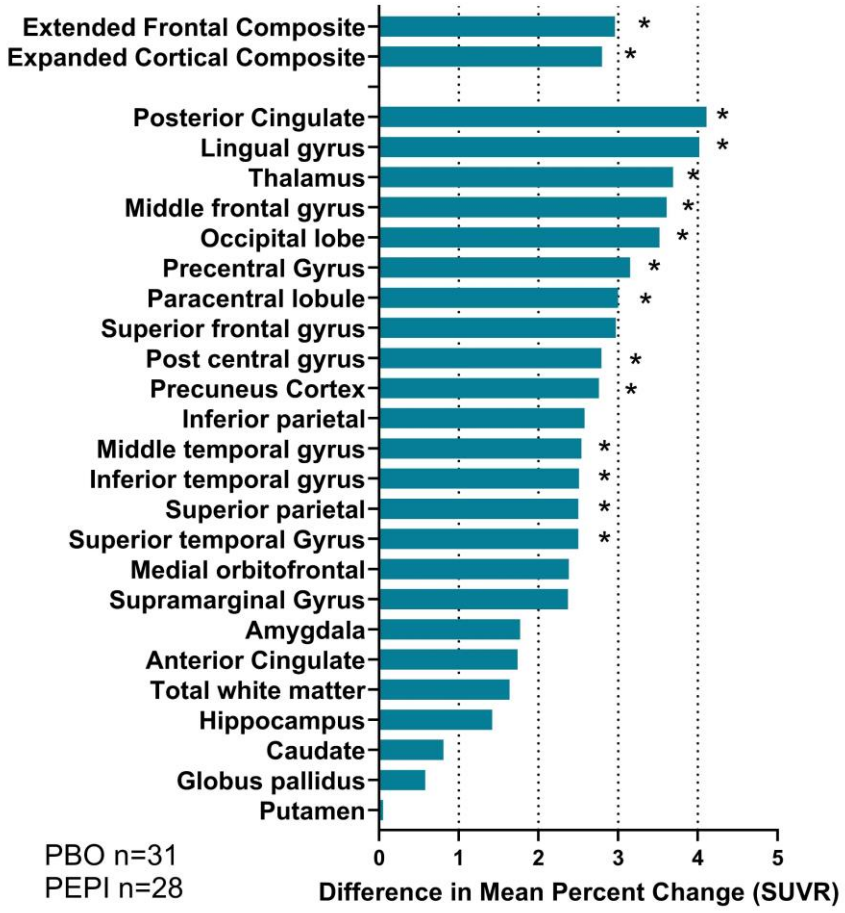
Early Manifest HD

Pepinemab treatment reverses loss of metabolic activity

FDG-PET Change SUVR
Early Manifest at Visit 18



FDG-PET Difference in % Change SUVR (PEPI-PBO)
Early Manifest at Visit 18

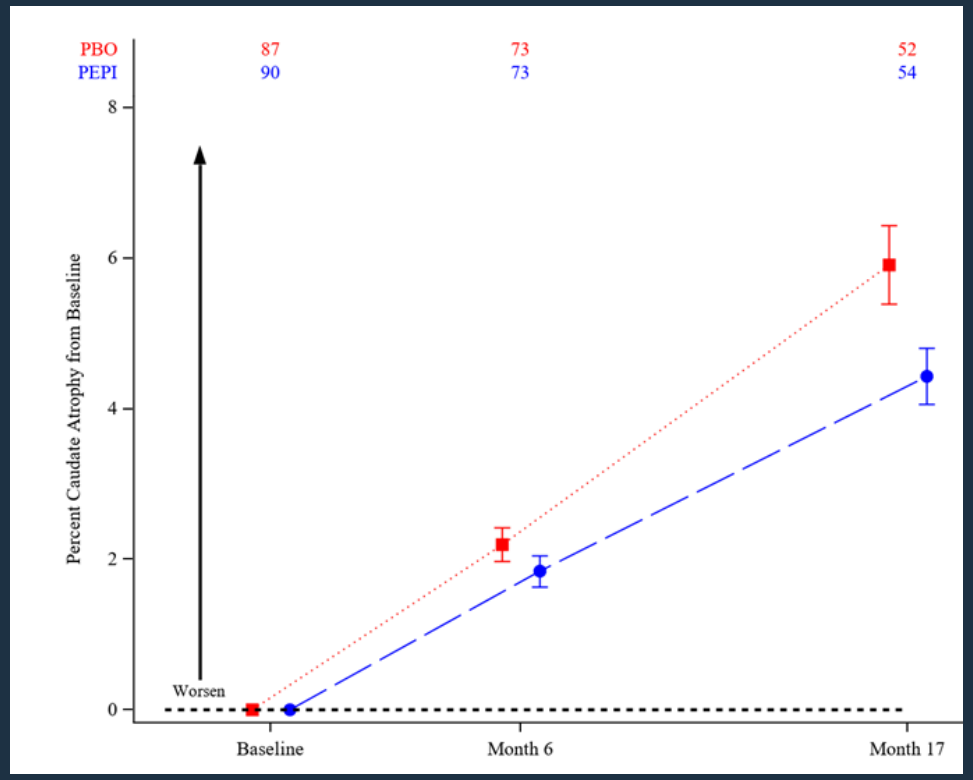


*p ≤ 0.05

Pepinemab reduces brain atrophy

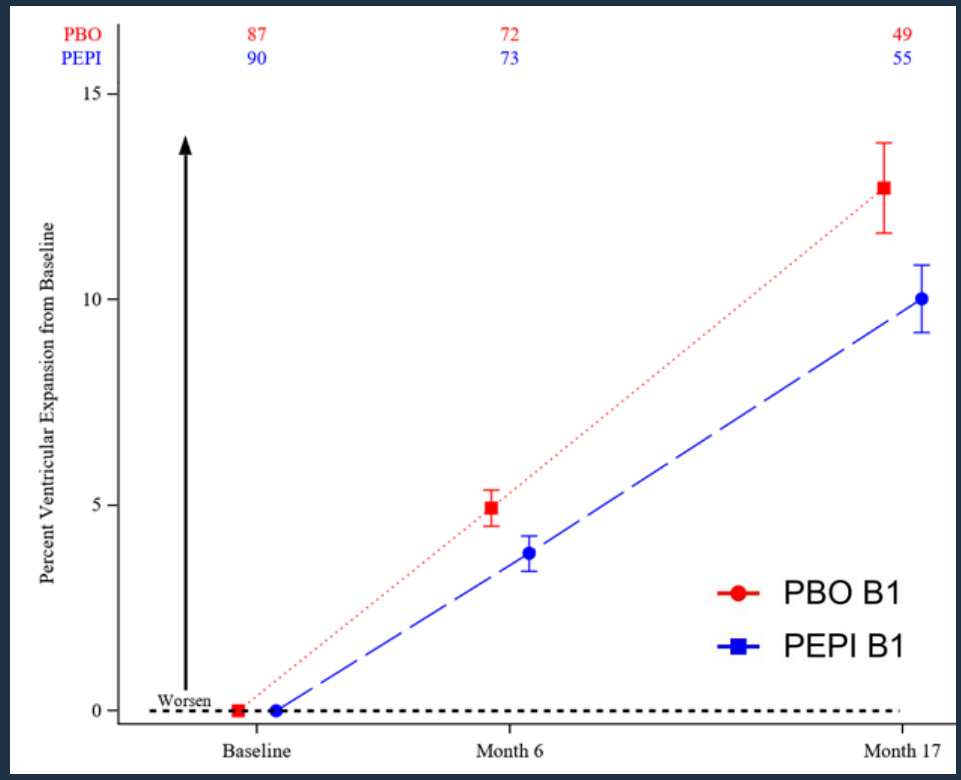
Volumetric MRI– Boundary Shift Integral Analysis
Early Manifest HD

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

SIGNAL Phase 2 Trial
Summary, Lessons Learned, Next Steps

Orphan Disease and Fast Track Designations




Mechanism of Action	Safety and Tolerability	Clinical Activity	Target Engagement
Reduce neuroinflammation and restore normal glia function	**Well tolerated** Intravenous administration	Prespecified primary endpoints were not met Evidence suggests potential cognitive benefit: HD-CAB, Apathy, FDG-PET Greatest benefit from treatment was detected in patients with signs of mildly advanced disease Reduced brain atrophy	Confirmed penetration into CNS at expected level Antigen-antibody complexes detected

Continued clinical development in HD
Initiated phase 1/2 trial in AD

CLINICAL TRIAL DESIGN: Alzheimer's Disease Phase 1b/2a

SIGNAL-AD

Funding by

alzheimer's association

Alzheimer's Drug Discovery Foundation

Patient population: Mild AD (CDR=0.5 or 1.0, MMSE 20-26)

Pepinemab 40mg/kg

n = 20

Every 4 weeks x12

Randomized 1:1 Double blind

Placebo

n = 20

Every 4 weeks x12

Safety Follow-up
4 weeks
After last dose

Study Objectives

Safety and Tolerability

Efficacy

Cognitive Function Measures:
CDR-SB, ADAS-cog13, MMSE, CDRS

Other:
ADCS-ADL, ADCS-CGIC, NPI

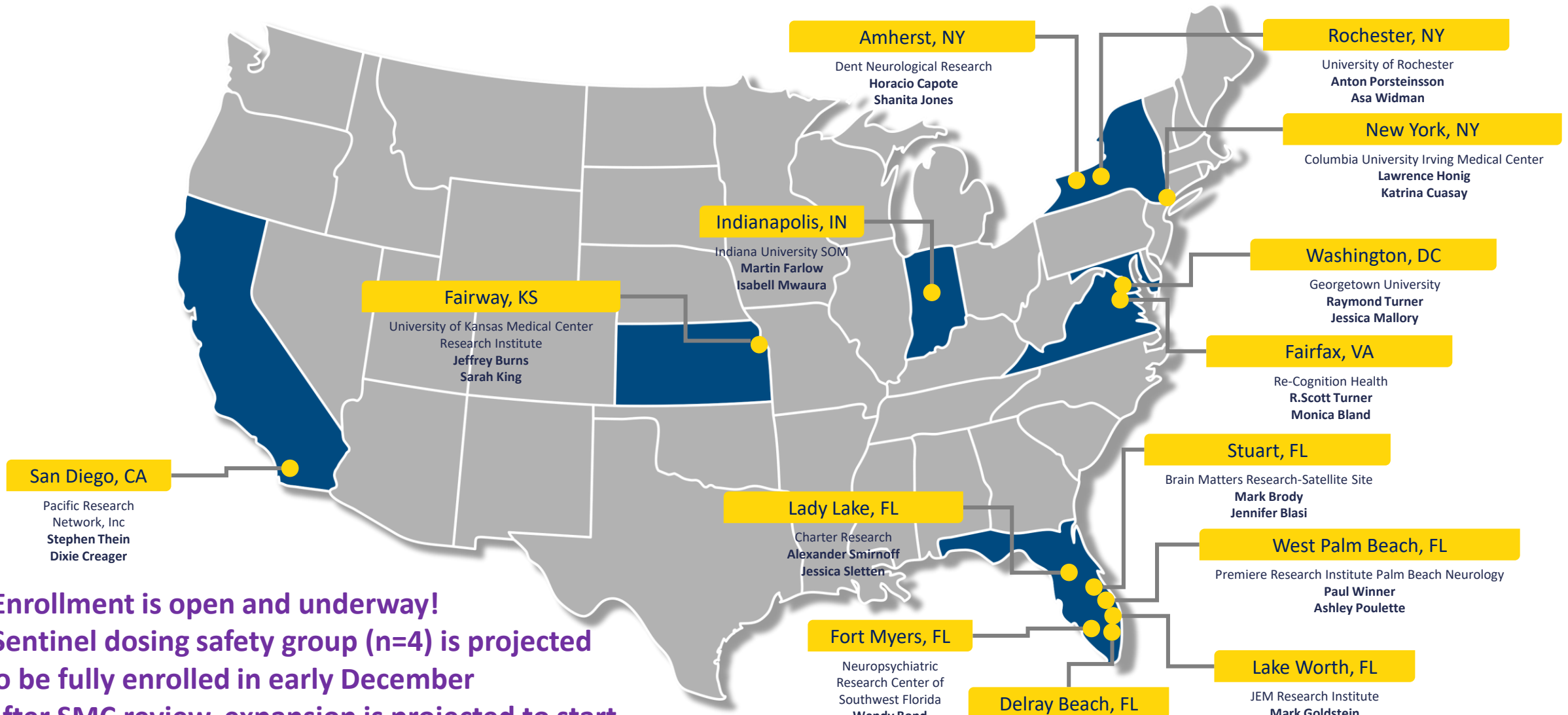
Brain Imaging Measures:
(FDG)-PET and vMRI

Exploratory Biomarkers:
NfL, AB, tau, cytokines, etc.

Funding by:
Alzheimer's Association
Alzheimer's Drug Discovery Foundation

NCT04381468

Signal-AD Site Map



- **Enrollment is open and underway!**
- **Sentinel dosing safety group (n=4) is projected to be fully enrolled in early December**
- **After SMC review, expansion is projected to start at the end of the year**

Acknowledgements

- **CTAD** organizers and attendees
- Patients and their families from **SIGNAL HD** and ongoing **SIGNAL AD** trials !
- PIs and clinical site teams for both studies
- **Andy Feigin, MD** and **HSG**
- **Eric Siemers, MD**
- **IXICO**
- **Statistical Collaborative (SCI)—**Janet Wittes, Kimberly Walters, Lisa Kowarksi
- **Alzheimer's Association** and **Alzheimer's Drug Discovery Foundation**
- **Vaccinex** team

The entire research and development teams, especially:

Liz Evans, Crystal Mallow, Vikas Mishra, Megan Boise, Amber Foster, Alisha Reader, Ernest Smith, John Leonard, and Maurice Zauderer

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Schematics created with BioRender.com