ALZHEIMER'S ASSOCIATION
AAIC 24

Vaccinex, Inc.
Unique Targets
Novel Mechanisms
New Medicines

RESULTS OF SIGNAL-AD, A RANDOMIZED, PHASE 1B/2 TRIAL TO EVALUATE SAFETY AND EFFICACY OF TARGETING REACTIVE ASTROCYTES WITH PEPINEMAB, SEMA4D BLOCKING ANTIBODY, IN PEOPLE WITH MCI OR MILD ALZHEIMER'S DEMENTIA

Eric Siemers, MD
Principal Investigator, SIGNAL AD

ALZHEIMER'S ASSOCIATION
AAIC 24

DISCLOSURES

Chief Medical Officer and Current Employee
Acumen Pharmaceuticals Inc.

Current Consulting Agreement
Vaccinex, Inc.

Other Consulting Agreements (2021 or later)
Cogstate Ltd.
Cortexyme, Inc.
Gates Ventures LLC
Hoffman La-Roche Ltd.
Partner Therapeutics, Inc.
US Green Valley Pharmaceuticals, Inc.

Stock Positions
Minor shareholder: Eli Lilly and Company
Stock options and minor shareholder: Acumen Pharmaceuticals Inc.

ALZHEIMER'S ASSOCIATION
AAIC 24

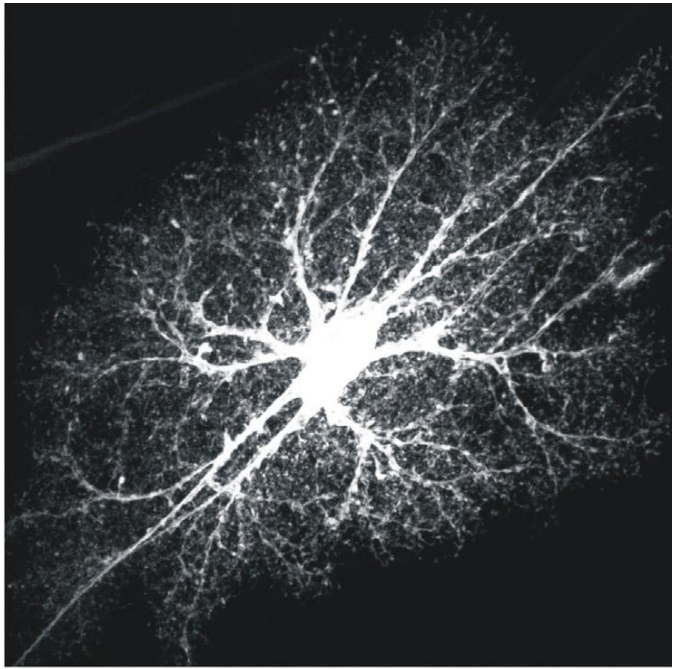
DISCLOSURES

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.

Astrocytes reach out to touch and interact with other brain cells

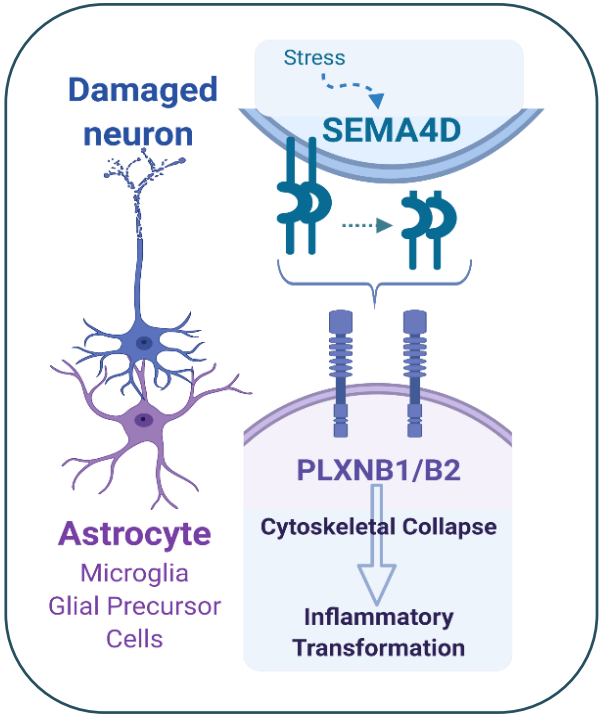


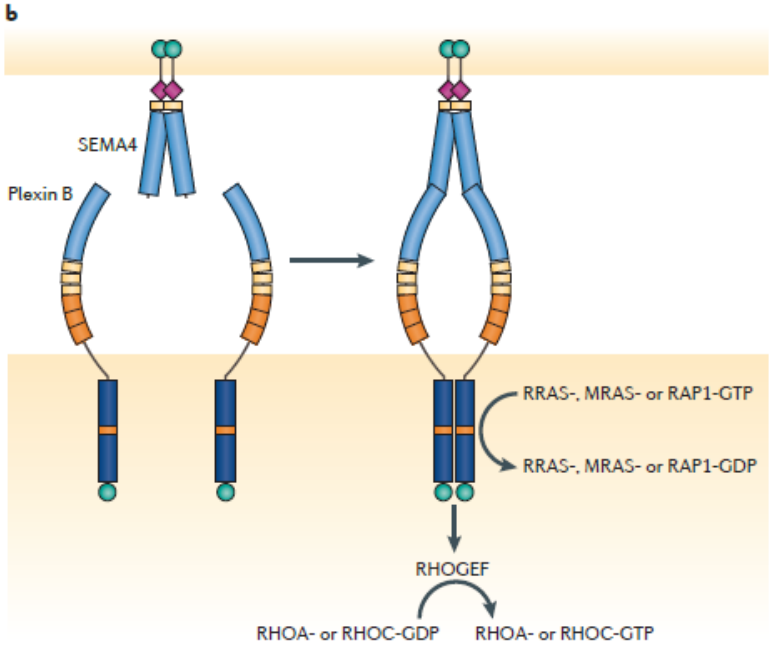
Astrocyte “arms” provide essential functional support to neurons.

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

How do astrocytes sense damage and what triggers the conversion to reactive state in neurodegenerative diseases?

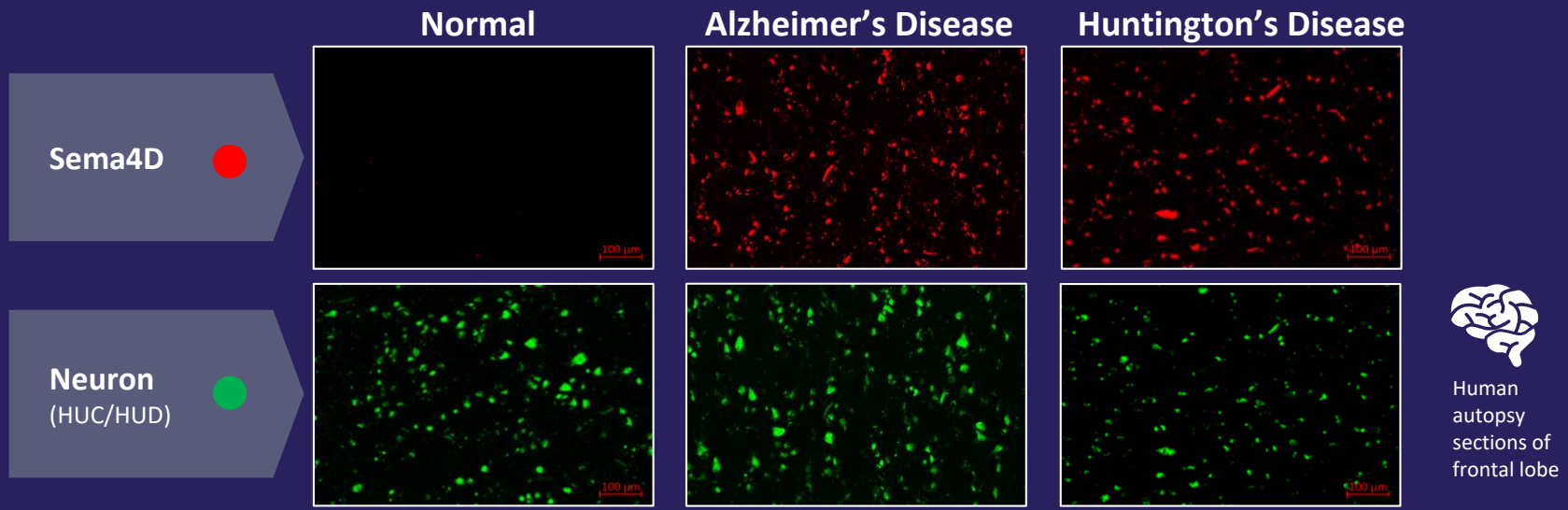
Semaphorin/Plexin neuro-immune signaling pathway is upregulated in Huntington's Disease and Alzheimer's Disease





Worzfeld, T., Offermanns, S. Semaphorins and plexins as therapeutic targets. Nat Rev Drug Discov ***13****, 603–621 (2014). https://doi.org/10.1038/nrd4337*

SEMA4D IS OBSERVED TO BE UPREGULATED IN NEURONS DURING DISEASE PROGRESSION



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

Huntington's disease Phase 2 trial

NCT02481674

nature medicine

ARTICLES

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

Check for updates

OPEN

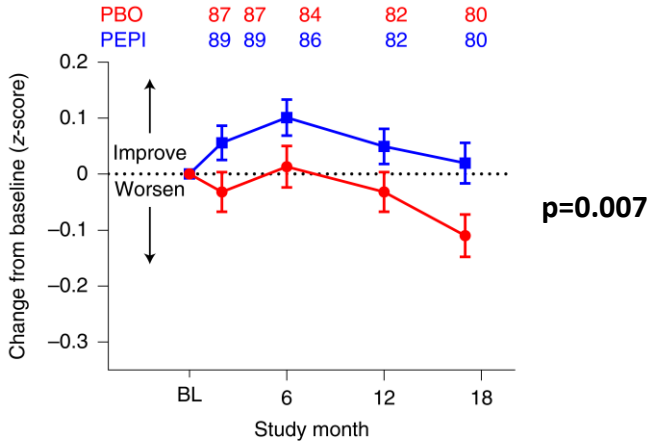
Pepinemab antibody blockade of SEMA4D in early Huntington's disease: a randomized, placebo-controlled, phase 2 trial

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*

HD-COGNITIVE ASSESSMENT BATTERY (HD-CAB)
Exploratory and Post-hoc analysis

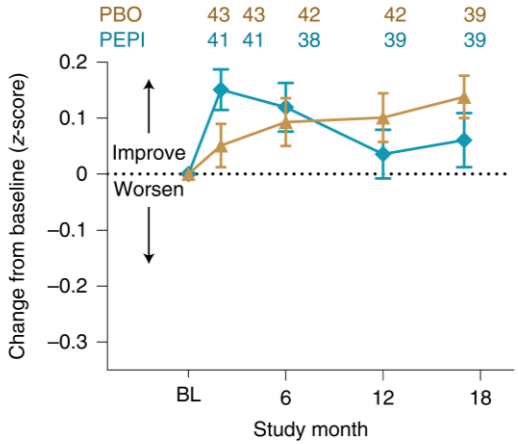
NCT02481674 SIGNAL

- The HD-CAB is a battery of cognitive tests designed specifically for use in late prodromal/ early HD clinical trials. It includes 6 tests [Symbol Digit Modalities Test, Paced Tapping, One Touch Stockings of Cambridge (abbreviated), Emotion Recognition, Trail Making B, and the Hopkins Verbal Learning Test] selected based on representation of the cognitive domains affected in HD



p=0.007

Early Manifest HD: Intent to treat population (mITT)



p=NS

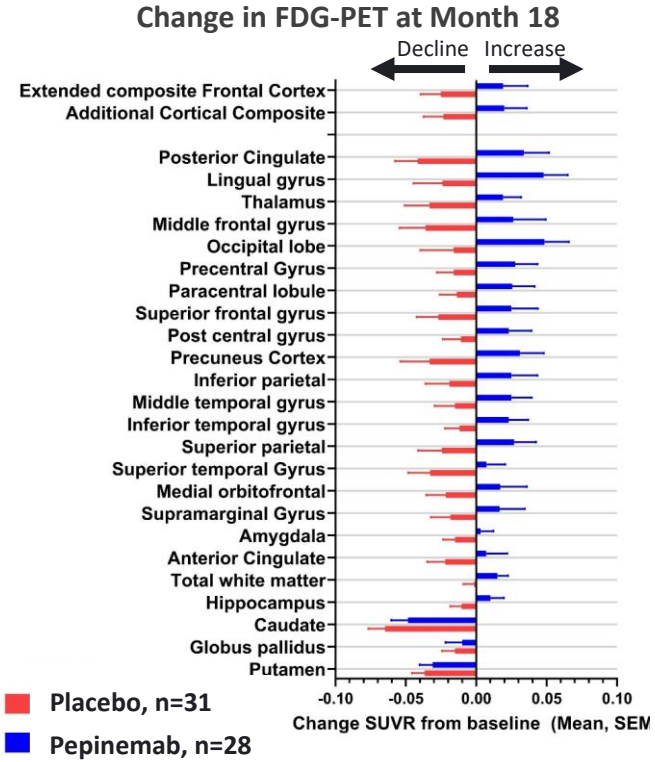
Late prodromal HD: Intent to treat population (mITT)

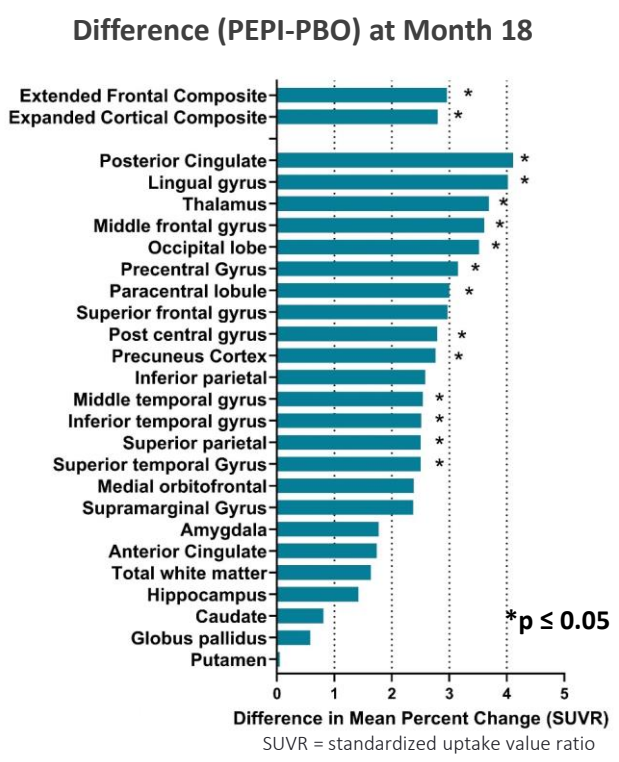
Nature Medicine (2022)
28:2183-2193

Apparent change in FDG PET in “Early Manifest” HD cohort

Pre-specified Exploratory Endpoint

NCT02481674 SIGNAL





SUVR = standardized uptake value ratio

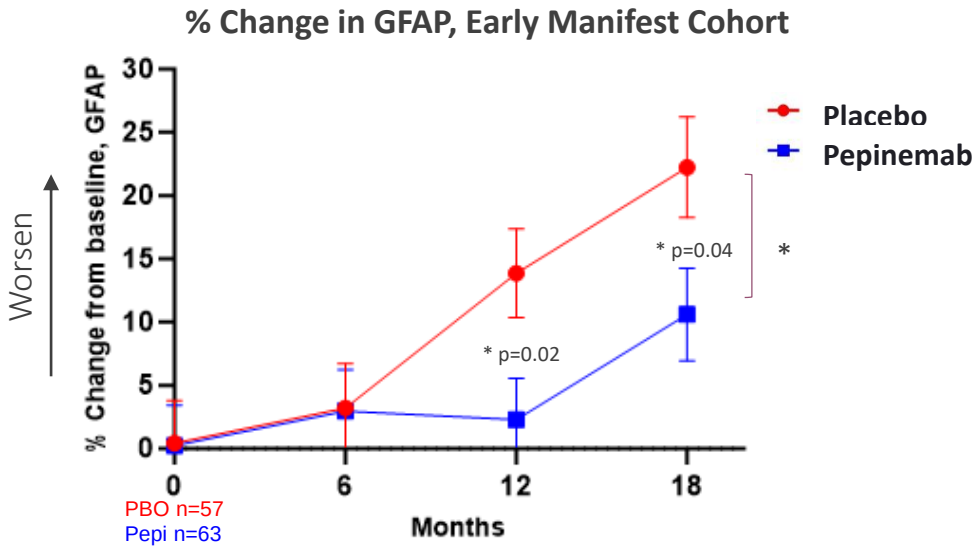
Nature Medicine (2022) 28:2183-2193

Glial Fibrillary Acidic Protein (GFAP)

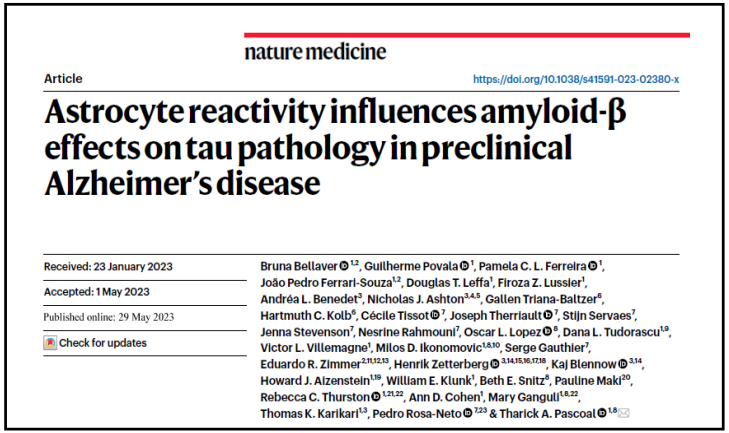
Biomarker for astrocyte activation / dysfunction

NCT02481674 SIGNAL

Pepinemab reduced plasma GFAP in SIGNAL-HD



* % 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.



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

Received: 23 January 2023

Accepted: 1 May 2023

Published online: 29 May 2023

Check for updates

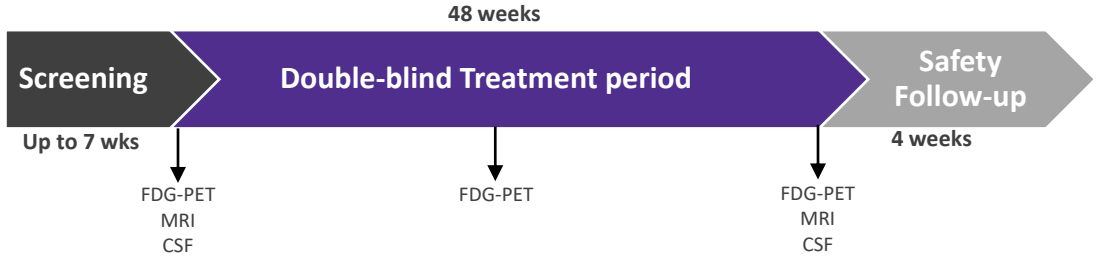
Bruna Bellaver[1,2], Guilherme Povala[1], Pamela C. L. Ferreira[1], João Pedro Ferrari-Souza[1,2], Douglas T. Leffa[1], Firoza Z. Lussier[1], Andréa L. Benedet[3], Nicholas J. Ashton[3,4,5], Gallen Triana-Baltzer[6], Hartmuth C. Kolb[6], Cécile Tissot[7], Joseph Therriault[7], Stijn Servaes[7], Jenna 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[2,11,12,13], Henrik Zetterberg[3,14,15,16,17,18], Kaj Blennow[3,14], Howard J. Aizenstein[1,19], William E. Klunk[1], Beth E. Snitz[8], Pauline Maki[20], Rebecca C. Thurston[1,21,22], Ann D. Cohen[1], Mary Ganguli[1,8,22], Thomas K. Karikari[1,3], Pedro Rosa-Neto[7,23] & Tharick A. Pascoal[1,8]

ALZHEIMER'S DISEASE

Phase 1b/2 Trial Design

NCT04381468
SIGNAL-AD

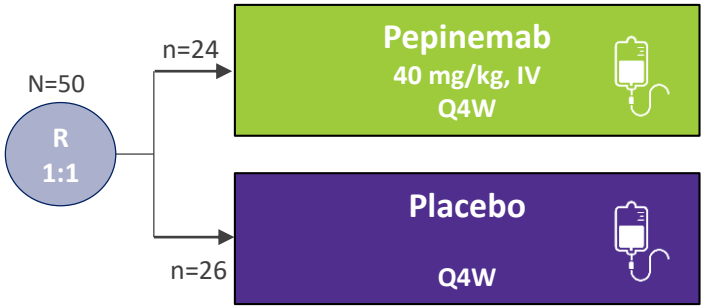
Funding by alzheimer's association® Alzheimer's Drug Discovery Foundation



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 ADCS-ADL, MMSE, and ADCS-CGIC	
Exploratory	• **Subgroup analysis: including CDR-GS 0.5 or 1 (MCI or mild dementia)** • **PK/PD**	

ALZHEIMER'S DISEASE

Abbreviated Demographics and Baseline Characteristics

Topline Demographics, Number (%) of Patients	Pepinemab 40 mg/kg (N=24)	Placebo (N=26)	All Patients (N=50)
Age (years)			
Mean (SD)	72.4 (7.23)	72.1 (7.69)	72.3 (7.40)
Min, Max	55, 82	55, 83	55, 83
Sex [n (%)]			
Male	6 (25.0)	15 (57.7)	21 (42.0)
Female	18 (75.0)	11 (42.3)	29 (58.0)
Race [n (%)]			
White	20 (83.3)	23 (88.5)	43 (86.0)
Non-White	4 (16.7)	3 (11.5)	7 (14.0)
Baseline Mini Mental State Examination (MMSE)			
Mean (SD)	21.8 (4.31)	21.2 (3.20)	21.5 (3.75)
Min, Max	13.0, 29.0	14.0, 26.0	13.0, 29.0
Baseline Clinical Dementia Rating – Sum of Boxes (CDR-SB)			
Mean (SD)	3.9 (1.66)	4.8 (2.13)	4.4 (1.94)
Range(min, max)	1.0, 8.0	2.0, 11.0	1.0, 11.0
Baseline Clinical Dementia Rating – Global Score (CDR-GS)			
0.5	14 (58.3)	11 (42.3)	25 (50.0)
1.0	10 (41.7)	13 (50.0)	23 (46.0)
Baseline APOE-4 Carrier Status [n (%)]			
Non-carrier	9 (37.5)	6 (23.1)	15 (30.0)
Heterozygous	9 (37.5)	15 (57.7)	24 (48.0)
Homozygous	6 (25.0)	5 (19.2)	11 (22.0)
Duration of Disease (years)			
Mean (SD)	1.9 (1.83)	1.3 (1.28)	1.5 (1.57)
Min, Max	0.2, 8.7	0.0, 4.5	0.0, 8.7

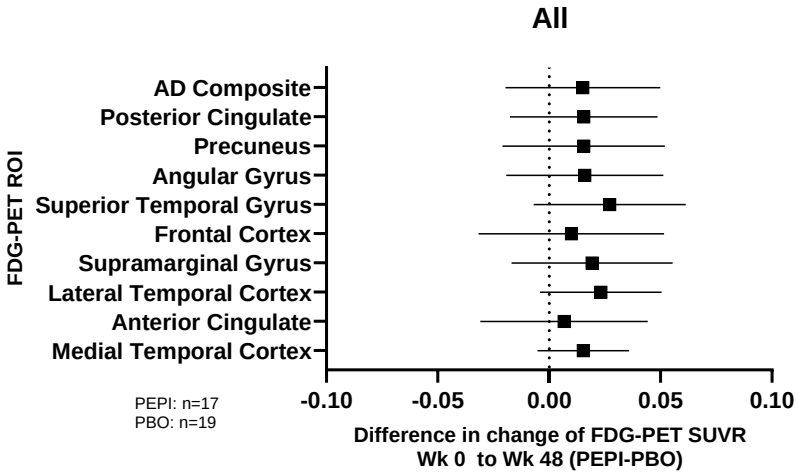
ALZHEIMER'S DISEASE

Safety and Tolerability

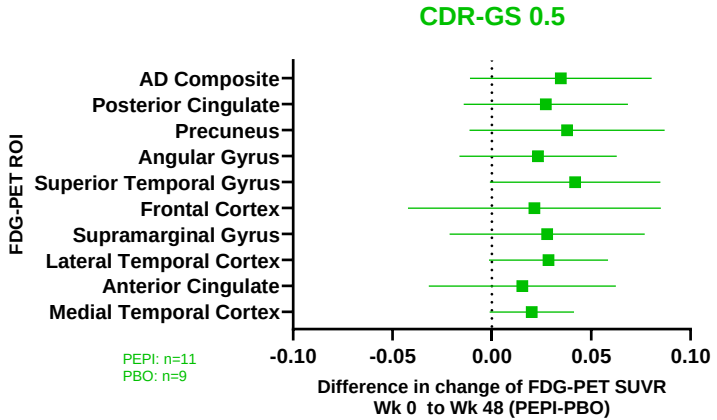
Topline Safety Results, Number (%) of Patients	Pepinemab 40 mg/kg (N=24)	Placebo (N=26)	All Patients (N=50)
	n (%)	n (%)	n (%)
TEAE	21 (87.5)	23 (88.5)	44 (88.0)
Serious TEAE	1 (4.2)	7 (26.9)	8 (16.0)
TEAE with CTCAE Grade ≥ 3	2 (8.3)	4 (15.4)	6 (12.0)
TEAE Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)
Serious 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)

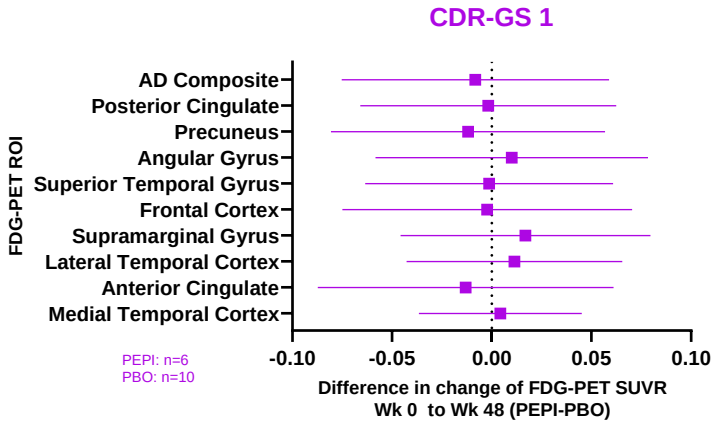
ALZHEIMER'S DISEASE
FDG-PET Imaging Biomarker

Forest Plots for FDG-PET Standard Uptake Value Ratio (SUVR)
Difference in Change from Baseline at Week 48



Worsen





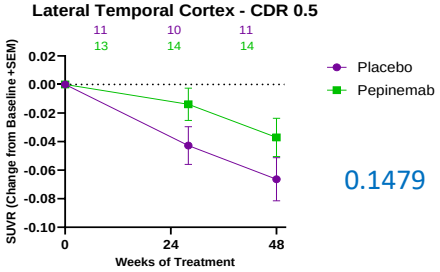
Figures display point estimates and 95% confidence intervals estimated from a fitted MMRM model

FDG-PET Imaging Biomarker

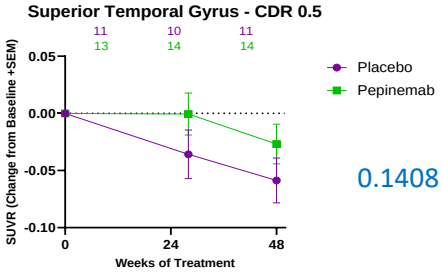
CDR-GS = 0.5 Subgroup, Pons Reference

NCT04381468

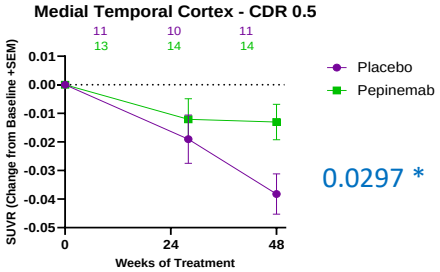
SIGNAL-AD



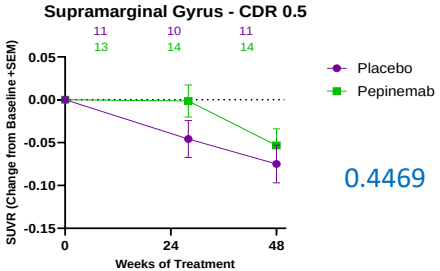
0.1479



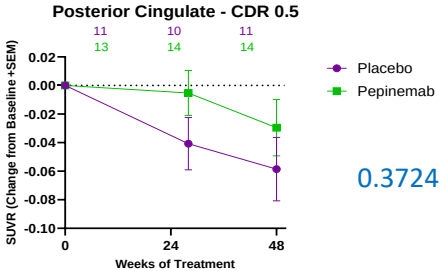
0.1408



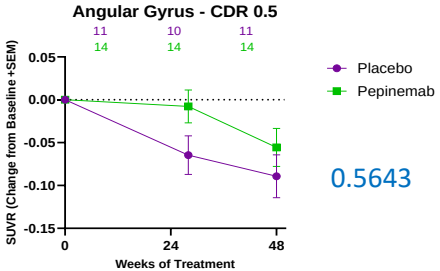
0.0297 *



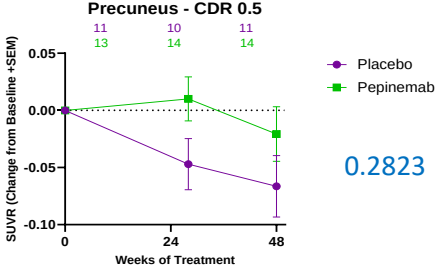
0.4469



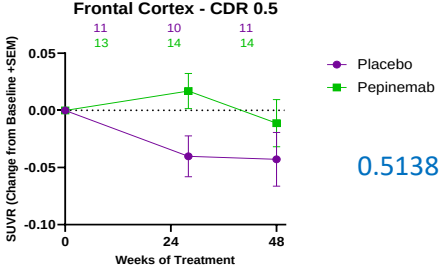
0.3724



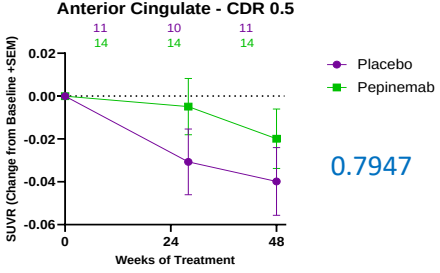
0.5643



0.2823



0.5138



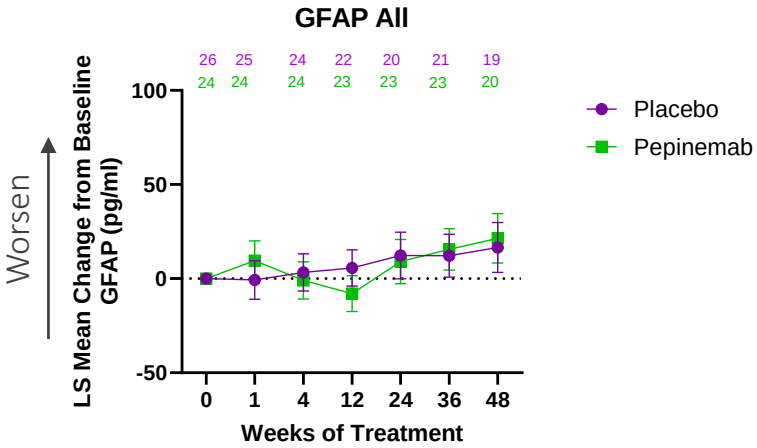
0.7947

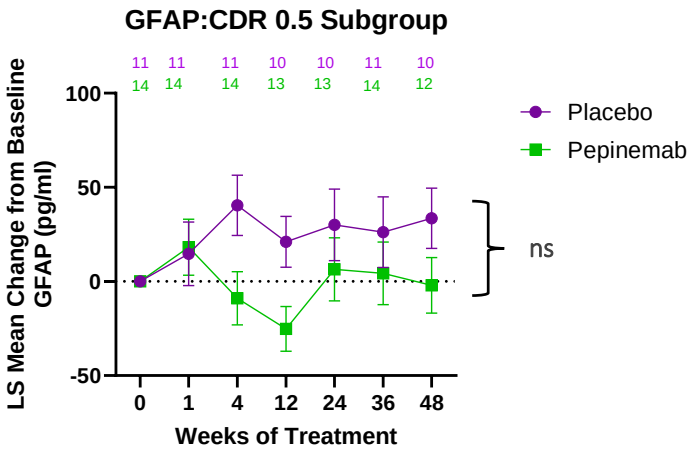
Worsen

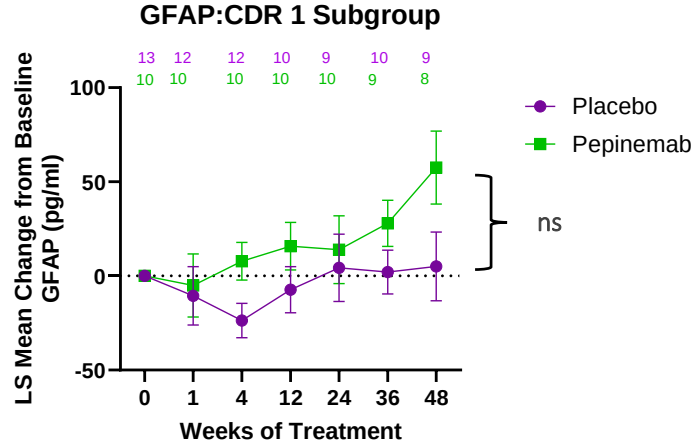
Figures display LS mean (SE) estimated from a fitted MMRM model. p values are indicated in blue

Fluid Biomarkers

plasma GFAP

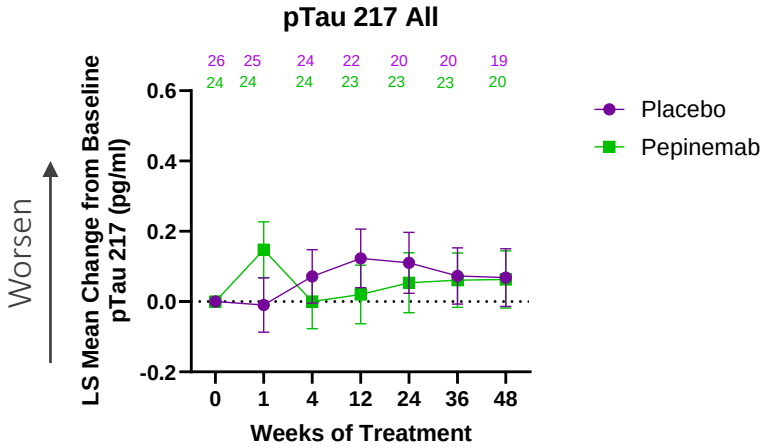


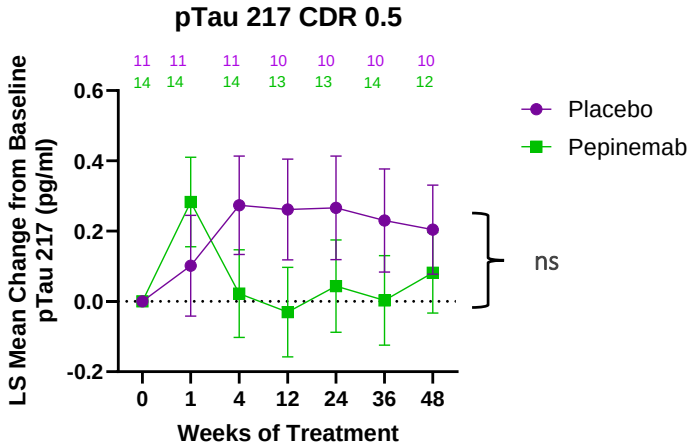


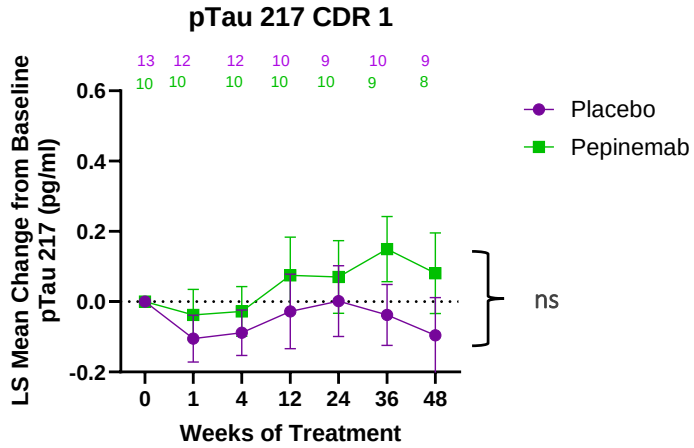


Fluid Biomarkers

plasma pTau-217







PEPINEMAB: SUMMARY AND CONCLUSIONS

SIGNAL-AD

- **Pepinemab was well-tolerated in this Phase 1b/2 SIGNAL-AD study. Safety and PK were consistent with previous clinical experience.**
- **Cognitive and GFAP findings in a Phase 2 HD study suggested greater efficacy in more impaired patients based on clinical evaluations**
- **AD findings in a Phase 1b/2 study suggested a greater response in FDG PET in less impaired patients**
- **Clinical characteristics of HD and AD may not be identical with regard to the relationship between the clinical stage and expectation of investigational drug effect**
  - People with “prodromal HD”, with a CAG mutation without symptoms, may be more similar to people with pre-clinical AD
  - For patients with “early manifest HD” pathology may be more similar to people with MCI due to AD
  - Patients with more advanced HD, who may have been more similar to mild dementia due to AD were not studied in SIGNAL-HD
- **Greater collaboration between scientists studying a variety of neurodegenerative diseases may lead to a greater understanding of neurodegenerative diseases collectively**

ALZHEIMER'S ASSOCIATION AAIC 24

Thanks, and Gratitude

Participants, caregivers and their families!

SIGNAL-AD

Funding support:

alzheimer's association

Alzheimer's Drug Discovery Foundation

SIGNAL-AD study investigators and staff

Vaccinex Clinical Development and Research Teams:

Maurice Zauderer PhD, President and CEO
Elizabeth Evans PhD, COO, Sr VP Discovery & Translational Medicine
Terry Fisher PhD, Sr VP Clinical Development

John Leonard PhD, Megan Boise, Amber Foster, Yelena Lerman PhD, Karin Gringer, Joe Townsend, Vikas Mishra PhD and Crystal Mallow

WCG Clinical Services/Statistics Collaborative Initiative, IXICO, Signant Health, Amsterdam UMC

SIGNAL

Andrew Feigin MD, Huntington Study Group investigators and staff