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 an ongoing Phase 1/2 AD study

VACCINEX
Contact: tfisher@vaccinex.com

CTAD Clinical Trials on Alzheimer's Disease
Poster LP-19

T. Fisher[1], E. Evans[1], M. Boise[1], V. Mishra[1], C. Mallow[1], E. Smith[1], J. Leonard[1], A. Feigin[2], E. Siemers[3], K. Walters[4], E. Sheldon[5], R. Turner[6], M. Farlow[7], A. Porsteinsson[8], R. Townley[9], W. Bond[10], L. Honing[11], M. Zauderer[1].
[1] Vaccinex, Inc.; [2] for the Huntington Study Group, and SIGNAL-HD investigators and coordinators; [3] Siemers Integration LLC, [4] for Statistics Collaborative, [5] for JEM Research, [6] for Re-Cognition Health, [7] for Indiana University, [8] for University of Rochester, [9]University of Kansas Medical Center Research Institute, [10] for Neuropsychiatric Research Center of Southwest Florida,[11] for Columbia University

SCAN ME

Alzheimer's Disease

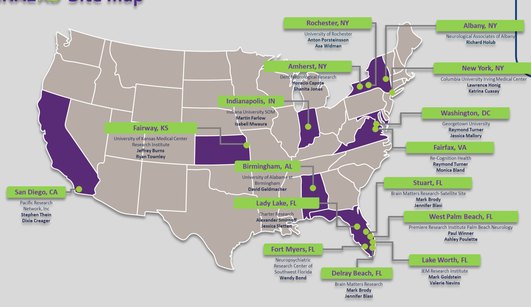
SEMA4D Blockade Safety and Brain Metabolic Activity in Alzheimer's Disease (AD) - Phase 1/2a Trial Design
A Multi-center, Randomized, Double-Blind, Placebo-Controlled Safety and Biomarker Study of Pepinemab Anti-SEMA4D Antibody in early-AD

SIGNAL-AD
NCT04381468

Inclusion Criteria

Mild AD
(CDR=0.5 or 1.0, MMSE 17-26)

SIGNAL-AD Site Map



Randomized 1:1
Double-blind
n=40

placebo	n=20	Monthly X12 months	
pepinemab	n=20	Monthly 40 mg/kg X12 months	

Safety Follow-up

Phase 1 Safety

Phase 2a: Expansion

1Q 2022
Data Safety Monitoring Board meeting
Complete

Enrolling

1H 2024
Topline Data

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

Objectives

Safety and tolerability

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

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

UPDATE from SIGNAL-AD

Phase 1 Safety segment: Complete
- ✓ Appears to be well tolerated
- ✓ No SAE's reported

Phase 2 expansion segment: Enrolling
- ✓ Two randomized participants successfully completed study with no safety concerns
- ✓ 17 participants randomized to date

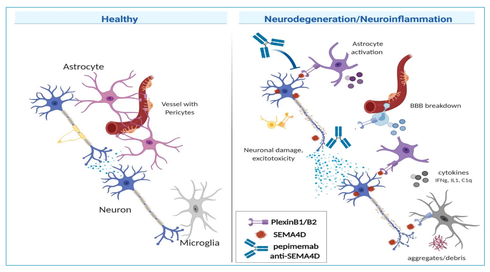
Funded in part by the Alzheimer's Drug Discovery Foundation and by a grant from the Alzheimer's Association under its 2020 Part the Cloud Program.

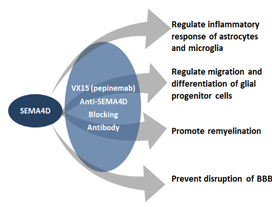
Mechanism of Action

Semaphorin 4D (SEMA4D) is upregulated in Alzheimer's Disease (AD) and Huntington's Disease (HD) in response to stress in CNS. SEMA4D signals to receptors on glial cells to trigger reactive inflammation and loss of normal homeostatic functions (Evans et al. J Neuroinflammation. 2022 Aug 6;19(1):200. doi: 10.1186/s12974-022-02509-8.)

Antibody blockade of SEMA4D reduces neuroinflammation, restores some normal functions of astrocytes and improves synaptic function and behavioral deficits in HD (Feigin et al. Nat Med. 2022, 28:2183-2193. doi: 10.1038/s41591-022-01919-8).

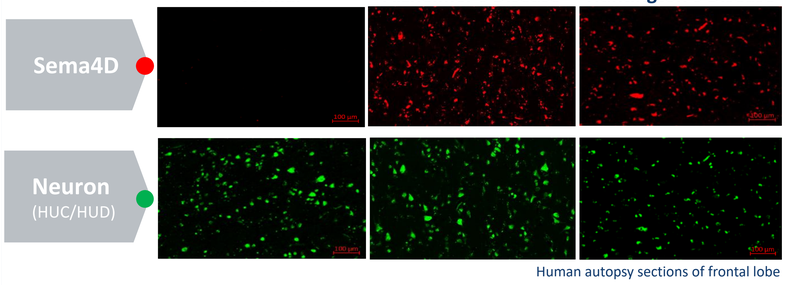
SEMA4D Regulates Glia Activation and Inflammation





Smith, et.al. Neurobiology of Disease, 73:254–268 (2015)
Evans et al. Journal of Neuroinflammation, Aug 6;19(1):200 (2022)

SEMA4D is Upregulated in Neurons during Alzheimer's and Huntington's Disease

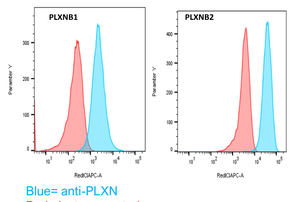


Human autopsy sections of frontal lobe

Pepinemab Targets Reactive Glia

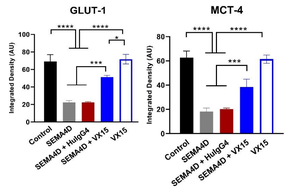
- Neurons under stress upregulate SEMA4D
- Astrocytes and microglia express plexin B1/B2 receptors for SEMA4D, which triggers reactive gliosis
- Pepinemab antibody blocks SEMA4D activity and glial cell reactivity that contributes to and aggravates pathogenesis

Astrocytes express Plexin-receptors



Blue= anti-PLXN
Red= isotype control

SEMA4D effect on astrocyte functions
Energy metabolism



Purified human astrocyte cultures

Clinical Experience in HD

Pepinemab was well tolerated, showed promise of slowing or preventing cognitive decline and a striking increase in brain metabolic activity in most brain regions as measured by FDG-PET in a Phase 2 clinical trial of participants with early HD.

Huntington's Disease Clinical Trial

SIGNAL NCT02481674

Cohort B1 Early Manifest CAG repeat ≥36 TFC 11-13, DCL 4	n=179	Randomized drug:placebo (1:1) Q4W X18 months	Safety Follow-up 1 month
Cohort B2 Late Prodromal CAG repeat ≥36 DCL 2 or 3	n=86	Randomized drug:placebo (1:1) Q4W X18 months	

Data Analysis and Study Objectives

Safety and Tolerability

Primary Efficacy Outcomes (mITT)
Cognitive Function
CGIC

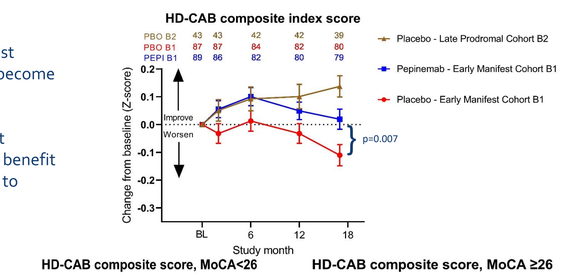
Key Exploratory and Biomarker Outcomes
Huntington's Disease-Cognitive Assessment Battery (HD-CAB)
Brain Volume (vMRI)
Metabolic imaging (FDG-PET)
PK/PD – target engagement

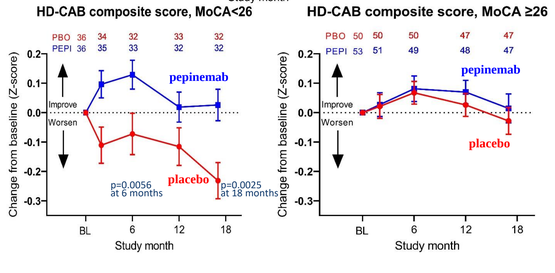
Post-hoc Subgroup Analyses

The Phase 2 double-blind, placebo-controlled SIGNAL trial of pepinemab in patients with early manifest Huntington's disease (HD) has been completed and we believe the program is Phase-3 ready. While the Phase 2 study did not meet the prespecified co-primary endpoints, multiple pre-specified exploratory and post-hoc analyses support the potential cognitive benefit of treatment with pepinemab in HD patients, particularly those with mild cognitive deficits:
- Highly significant improvement (p=0.007) in the (Huntington's Disease-Cognitive Assessment Battery (HD-CAB) Index score
- Significant benefit in reducing apathy severity (p=0.017, 1-sided)
- Reduced atrophy (p=0.017) in caudate region of striatum
- A striking increase in brain metabolic activity as measured by FDG-PET in most brain regions

Cognitive Assessment Battery (HD-CAB)
Exploratory and Post-hoc analysis to characterize patient sub-populations

1. "Learning effect" is lost when HD symptoms become manifest
2. Pepinemab treatment restores the ability to benefit from experience (i.e., to learn)
3. Potential cognitive benefit of pepinemab is more evident in subjects with greater cognitive deficits at baseline

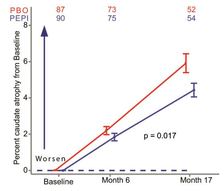




Andrew Feigin et al. **Nature Medicine, 2022.**

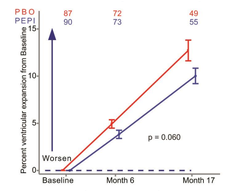
Pepinemab appears to reduce brain atrophy
Volumetric MRI– Boundary Shift Integral Analysis (BSI)
Pre-specified Exploratory Endpoint, Early Manifest cohort

Caudate Atrophy (CBSI)



LS Mean Difference Estimate (95% CI):
CBSI: -1.54 (-2.79, -0.29); **p = 0.017**

Ventricular Expansion (VBSI)



VBSI:-2.47 (-5.04, 0.10); **p = 0.060**

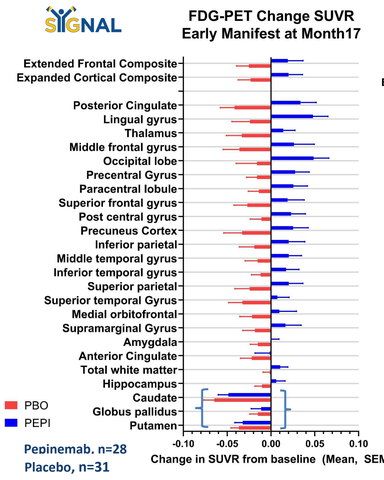
Andrew Feigin et al. **Nature Medicine, 2022**

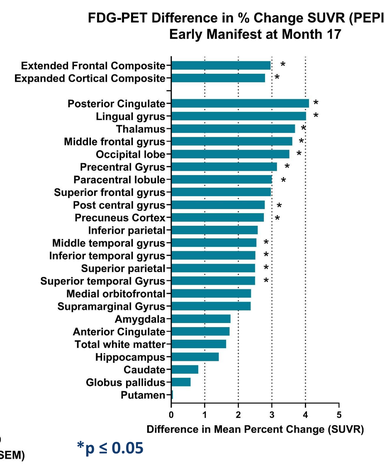
Multiple prior studies have reported that decline in FDG-PET SUVR correlates with cognitive decline and disease progression in AD. Reactive gliosis and neurodegeneration can each contribute significantly to reduced metabolic activity and decline in FDG-PET signal.

Pepinemab appears to reduce decline in FDG-PET
Pre-specified Exploratory Endpoint, Early Manifest HD

- FDG-PET declines in the Early Manifest HD placebo group in 26 brain regions over 18 months disease progression, as previously observed for AD.
- Pepinemab treatment appears to reverse this loss of metabolic activity in most brain regions but not in caudate and putamen, the brain regions that are initially affected and degenerate most rapidly in early HD. Our interpretation is that pepinemab prevents or reverses reactive gliosis that contributes importantly to SEMA4D-dependent FDG-PET decline in cortical regions, but that an earlier phase of pathology in caudate and putamen is due to immediate toxicity of mutant huntingtin not to SEMA4D-dependent gliosis, and is, therefore, not reversed by pepinemab.

SIGNAL





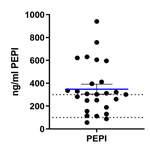
*p ≤ 0.05

The ongoing SIGNAL-AD study will evaluate the effect of pepinemab treatment on cognition and brain metabolism in early AD, where degeneration is first manifest in the entorhinal cortex.

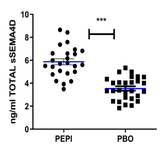
Biomarkers and Target Engagement

SIGNAL

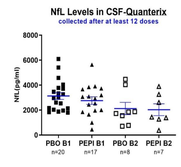
Most subjects dosed with pepinemab have ≥ saturating levels (100-300 ng/ml) in CSF



sSEMA4D complexes increase in subjects dosed with pepinemab – suggesting target engagement



No significant change in CSF levels of Neurofilament Light Chain (NfL)



Feigin et al. Pepinemab antibody blockade of SEMA4D in early Huntington's disease: a randomized, placebo-controlled, phase 2 trial. Nat Med. 2022 Aug 8:1–11. doi: 10.1038/s41591-022-01919-8.

Summary: Targeting Common Pathology in Neurodegeneration

Many current intervention strategies targeting disease-associated biomarkers (e.g., Aβ or mutant HTT) have had limited efficacy.

An alternative and potentially complementary strategy is to target inflammation and underlying disease pathology.

Results from completed trial in people with HD helped inform trial design for ongoing SIGNAL-AD trial.