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

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Pepinemab is an antibody that blocks a key driver of neurodegenerative disease pathology

Mechanism of Action

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, *In Press*)

Antibody blockade of SEMA4D can reduce neuroinflammation, restore normal function of astrocytes and improve synaptic function and behavioral deficits in HD (Feigin et al., **Nature Medicine**, 2022, *In Press*) and in a preclinical model of AD.

Clinical Experience

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.

Alzheimer's Disease

The ongoing SIGNAL-AD study is evaluating the safety, tolerability and the effects on cognition and brain metabolism of pepinemab in early AD.

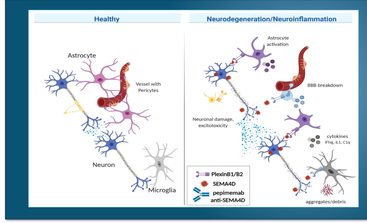
Targeting common pathology in Neurodegeneration

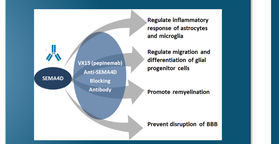
Many current intervention strategies targeting disease-associated biomarkers have had limited efficacy.

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

Targeting dysregulated proteins	Pepinemab: Targets reactive glia
• AD: antibodies to Aβ, Tau; BACE inhibitors • HD: gene therapy to reduce mHTT • **Most have not demonstrated significant disease modifying effects in the clinic**	• Neurons under stress upregulate semaphorin 4D (SEMA4D) • Astrocytes and microglia express plexin B1/B2 receptors for SEMA4D, which triggers activation and inflammation • Pepinemab anti-SEMA4D antibody blocks its activity and the glial cell activation that contributes to and aggravates pathogenesis

SEMA4D regulates Glia activation





Smith, et al. Neurobiology of Disease, 73:254–268. 2015

Evans et al. Journal of Neuroinflammation, 2022, In Press.

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

Alzheimer's Disease: SIGNAL-AD

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

Phase 1/2a Trial Design

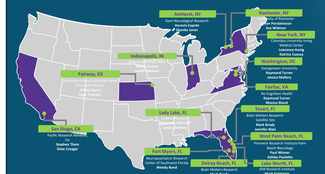
Inclusion Criteria

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

Phase 1 Safety
Randomized 1:1 Double-blind
n=4

Phase 2a: Expansion
placebo — n=20 — Monthly X12 months
pepinemab — n=20 — Monthly 40 mg/kg X12 months
Safety Follow-up

Site Map



Objectives

- **Safety and tolerability**
- **Cognitive Function measures** CDR-SB, ADAS-Cog13, MMSE, CDRS
- **Biomarker Outcomes** Brain Volume (vMRI),Metabolic imaging (FDG-PET)

1Q, 2022: Data Safety Monitoring Board meeting — Complete

2Q, 2022: First randomized participant successfully completed study with no safety concerns

2H 2023: Topline Data

SIGNAL-AD
NCT04381468

Huntington's Disease

SIGNAL NCT02481674

Early Manifest HD *

placebo — n=88 — Monthly X18 months
pepinemab — n=91 — Monthly X18 months
Randomized 1:1 Double-blind
Safety Follow-up 3 month

Data Analysis and Study Objectives

- Safety and Tolerability
- Primary Efficacy Outcomes (mITT) Cognitive Function CGIC
- Key Exploratory and Biomarker Outcomes: Brain Volume (vMRI) Metabolic imaging (FDG-PET) PK/PD – target engagement
- Post-hoc Subgroup Analyses

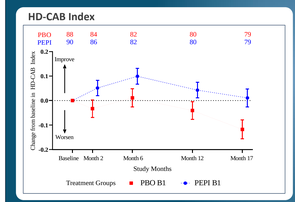
The Phase 2 double-blind, placebo-controlled SIGNAL trial of pepinemab in patients with early manifest Huntington's disease (HD) has been completed and we believe the program is Phase-3 ready.
While the Phase 2 study did not meet the prespecified primary endpoints, pre-specified exploratory and post-hoc analyses supports 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

* Note 86 subjects with Late Prodromal HD were also included in the study

COGNITIVE ASSESSMENT BATTERY (HD-CAB)

SIGNAL
Co-Primary and pre-specified Exploratory analysis



Two-item HD Cognitive Assessment: Pre-specified Co-Primary

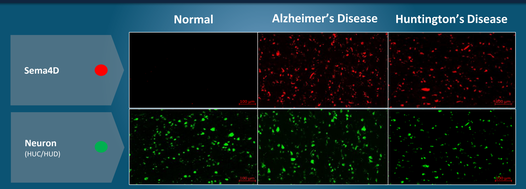
	LS Mean Difference Estimate (95% CI)	One-sided p-value	Favors Pepinemab	Critical value
OTS:	-1.98 (-4.00, 0.05)	0.028	Yes	No [0.025]
PTAP:	1.43 (-0.37, 3.23)	0.060		

HD-CAB Composite Index: Pre-specified Exploratory

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

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

SEMA4D IS UPREGULATED IN NEURONS DURING ALZHEIMER'S AND HUNTINGTON'S DISEASE



Evans et al. Journal of Neuroinflammation, 2022, In Press.

Human autopsy sections of frontal lobe

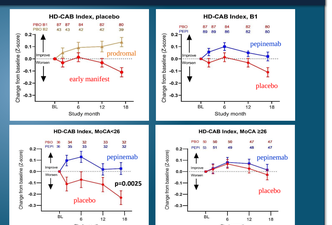
COGNITIVE ASSESSMENT BATTERY (HD-CAB)

Exploratory and Post-hoc analysis to characterize patient populations

1 "Learning effect" is lost when HD symptoms become manifest

2 Pepinemab treatment restores the ability to benefit from experience (ie, to learn)

Potential cognitive benefit of pepinemab is more evident in subjects with greater cognitive deficits at baseline



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

UPDATE from SIGNAL-AD

Phase 1 Safety segment is complete
- ✓ Appears to be well tolerated

Enrollment in Phase 2 expansion segment is ongoing
- ✓ First randomized participant successfully completed study with no safety concerns
- ✓ 12 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.

LESSONS LEARNED from SIGNAL-HD

SIGNAL-HD study established safety and proof of concept for pepinemab
- ✓ Well tolerated
- ✓ Target engagement and CNS penetration

SIGNAL-HD study informed study design for SIGNAL-AD
- ✓ Patient population: data supports the potential cognitive benefit, particularly in patients with mild cognitive deficits -> Exclude MCI
- ✓ KEY Exploratory endpoints: Improved metabolic activity via FDG-PET

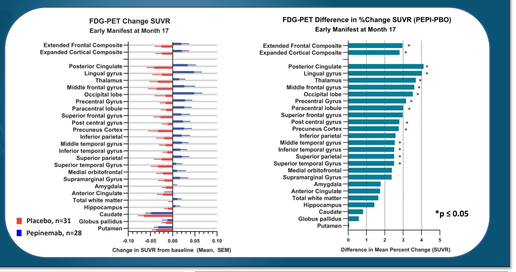
FDG-PET CORRELATES WITH COGNITIVE FUNCTION IN AD

Pre-specified Exploratory Endpoint, Early Manifest cohort, HD SIGNAL

1 FDG-PET measures brain metabolic activity.

2 Decline in FDG-PET is reported to correlate with cognitive impairment in AD

Pepinemab treatment appears to reverse loss of metabolic activity in most brain regions.

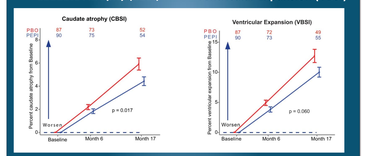


Andrew Feigin et al. **Nature Medicine, 2022,** ***In Press.***

PEPINEMAB APPEARS TO REDUCE BRAIN ATROPHY

Volumetric MRI– Boundary Shift Integral Analysis (BSI)
Pre-specified Exploratory Endpoint, Early Manifest cohort

Caudate Atrophy (CBSI) | **Ventricular Expansion (VBSI)**



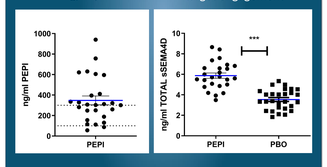
LS Mean Difference Estimate (95% CI):
CBSI: -1.54 (-2.79, -0.29); **p = 0.017**
VBSI:-2.47 (-5.04, 0.10); **p = 0.060**

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

DRUG PENETRATION and TARGET ENGAGEMENT

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



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