

# 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.

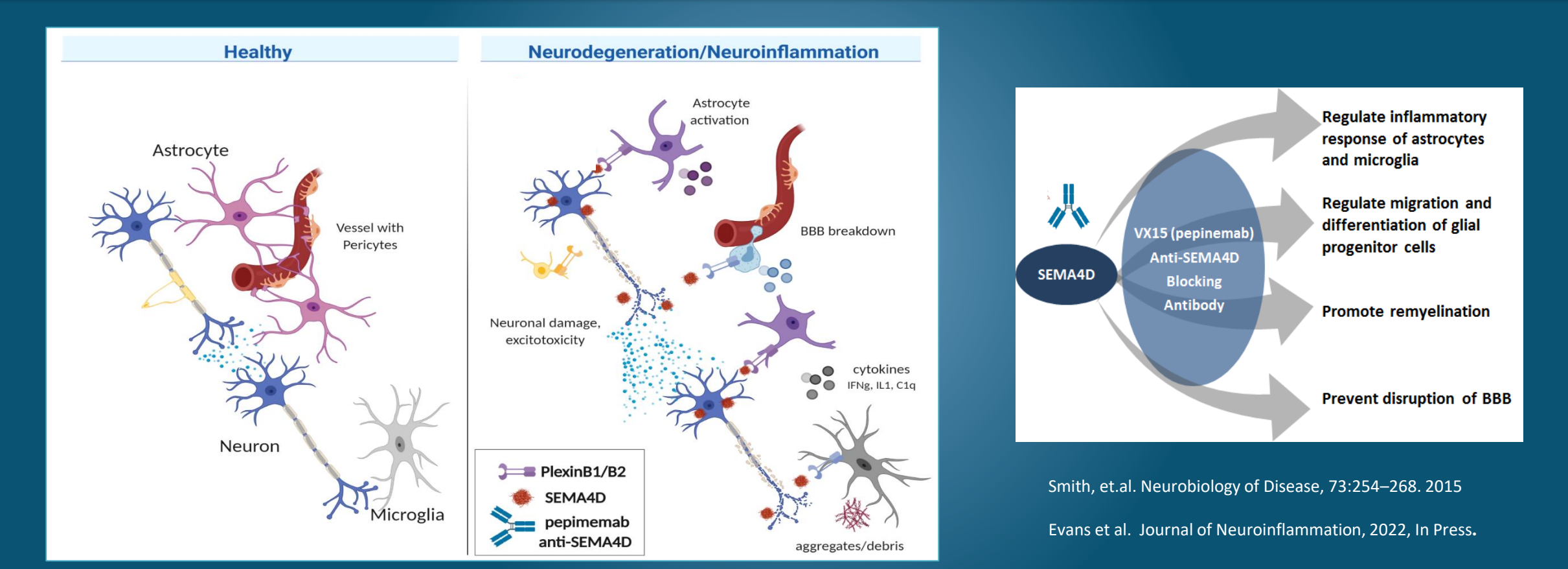
### Alzheimer's Disease

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

<p>Many current intervention strategies targeting disease-associated biomarkers have had limited efficacy.</p> <p><b>An alternative and potentially complementary strategy</b> may target inflammation and underlying disease pathology.</p>	<p><b>Targeting dysregulated proteins</b></p> <ul style="list-style-type: none"> <li>AD: antibodies to Aβ, Tau; BACE inhibitors</li> <li>HD: gene therapy to reduce mHTT</li> </ul> <p><b>Most have not demonstrated significant disease modifying effects in the clinic</b></p>	<p><b>Pepinemab: Targets reactive glia</b></p> <ul style="list-style-type: none"> <li>Neurons under stress upregulate semaphorin 4D (SEMA4D)</li> <li>Astrocytes and microglia express plexin B1/B2 receptors for SEMA4D, which triggers activation and inflammation</li> <li>Pepinemab anti-SEMA4D antibody blocks its activity and the glial cell activation that contributes to and aggravates pathogenesis</li> </ul>
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## SEMA4D regulates Glia activation



## 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) and pepinemab (n=20), both Monthly X12 months

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

**Timeline:** 1Q, 2022 (Data Safety Monitoring Board meeting Complete); 2Q, 2022 (First randomized participant successfully completed study with no safety concerns); 2H 2023 (Topline Data)

**Site Map:** Multi-center study across the United States.

**Study ID:** NCT04381468

## Huntington's Disease

**Early Manifest HD \***

**Phase 2:** placebo (n=88) and pepinemab (n=91), both Monthly X18 months

**Data Analysis and Study Objectives:** Safety and Tolerability; Key Exploratory and Biomarker Outcomes (Brain Volume (vMRI), Metabolic imaging (FDG-PET), PK/PD - target engagement); Primary Efficacy Outcomes (mHTT, Cognitive Function, CAG); Post-hoc Subgroup Analyses

**Results:** 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)

Co-Primary and pre-specified Exploratory analysis

**HD-CAB Index:** Line graph showing improvement in HD-CAB Index score over 18 months for PBO B1 and PEPI B1 groups.

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

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

**HD-CAB Composite Index: Pre-specified Exploratory**

LS Mean Difference (95% CI)	One-sided p-value	Favors	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

Human autopsy sections of frontal lobe

Normal, Alzheimer's Disease, Huntington's Disease

Sema4D staining (red) is significantly increased in neurons in AD and HD compared to normal.

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

## 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

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## 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

**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):** 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

## 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*.

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