Synthesis of key results and conclusions of the SIGNAL phase 2 study of pepinemab as a treatment for early HD

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Science in the Service of Medicine

SCAN ME

Pepinemab antibody blocks a key driver of neurodegenerative disease pathology

Mechanism of Action

Neuroimmune Semaphorin 4D (SEMA4D) is upregulated in neurons in Huntington's Disease (HD) and Alzheimer's Disease (AD) in response to stress associated with disease progression. SEMA4D signals to receptors on astrocytes to trigger reactive inflammation and loss of normal homeostatic functions (Evans et al., ***J. Neuroinflammation***, 2022)

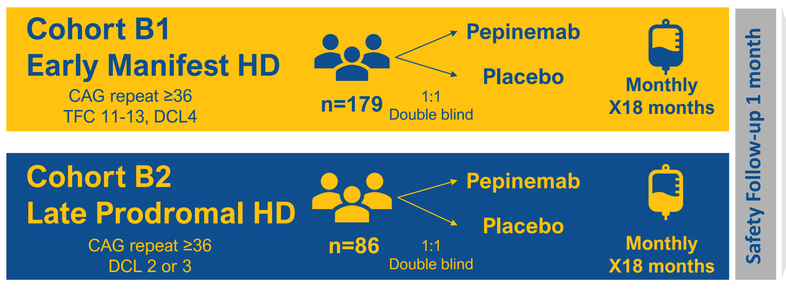
Antibody blockade of SEMA4D reduces neuroinflammation, preserves normal function of astrocytes, and slows or prevents cognitive decline in early manifest HD (Feigin et al., ***Nature Medicine***, 2022).

Aims

We predicted that treatment with SEMA4D blocking antibody would prevent reactive transformation of astrocytes and thereby reduce the decline in brain metabolic activity that is characteristic of HD progression. We investigated the impact of treatment on cognitive, functional and motor activity during clinical progression in the Phase 2 SIGNAL study (NCT02481674). Data from SIGNAL study will inform future trial design.

The ongoing Phase 1/2 SIGNAL-AD study is evaluating the safety, tolerability and effects of pepinemab treatment on brain metabolic activity and cognition in early Alzheimer's Disease (NCT04381468).

SIGNAL Phase 2 Study Design and Key Findings



The Phase 2 randomized, double-blind, placebo-controlled SIGNAL trial of pepinemab in HD has been completed and we believe the program is Phase-3 ready.
While the Phase 2 study **did not meet the pre-specified primary endpoints**, multiple pre-specified exploratory and post-hoc analyses support the potential cognitive benefit of treatment with pepinemab in Early Manifest (EM) HD patients, particularly those with existing mild cognitive deficits. Findings have been published in *Nature Medicine*, Aug 2022

- Pepinemab was generally well tolerated, with a relatively low frequency of serious treatment-emergent adverse events of 5% with pepinemab, compared to 9% with placebo.
- Highly significant improvement (p=0.007) in the Huntington's Disease Cognitive Assessment Battery (HD-CAB) Index
- Significant benefit in reducing apathy severity (p=0.017)
- 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 of interest (ROI), with the important exception of caudate and putamen.

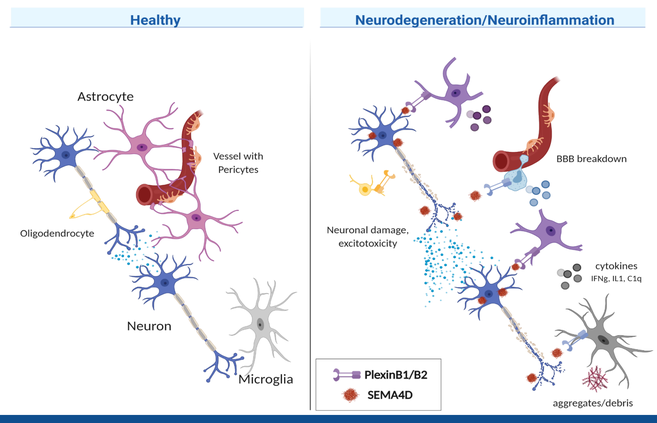
Summary of SIGNAL endpoints	Early Manifest	Late Prodromal
Functional and Global		
CGIC (Co-Primary)	No	No
CGIC subgroup TFC=11 (post hoc)	p#=0.04	No
Cognitive		
OTS (Co-Primary)	p#=0.028	No
PTAP (Co-Primary)	p#=0.060	No
HD-CAB Index (Exploratory)	YES, p=0.007	No
HD-CAB Index subgroup MoCA<26 (post hoc)	YES, p=0.0025	
Apathy Severity (post hoc)	YES, p=0.017	
Learning effects (post hoc)	YES	
Motor Activity		
TMS (Exploratory)	No	No
Q-motor (Secondary)	No	No
Imaging (Exploratory)		
vMRI: caudate atrophy	YES, p=0.017	No
FDG-PET SUVR	YES, cortical (not striatum)	

sided p-value

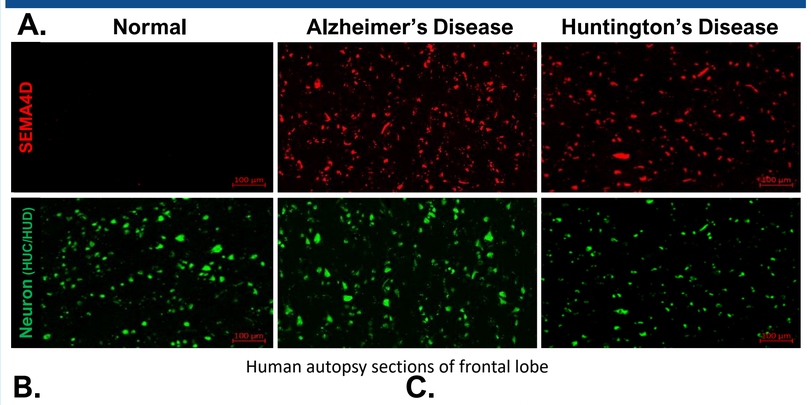
BACKGROUND

Many intervention strategies targeting primary neurodegenerative disease-associated changes, such as mutant HTT (HD) and β-amyloid (AD), have had limited efficacy.

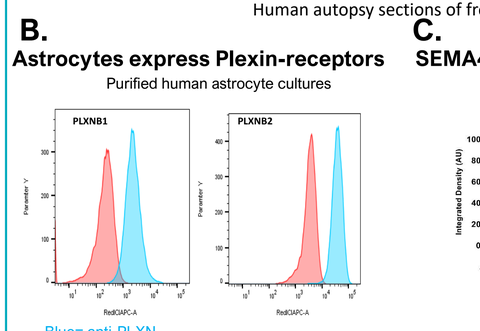
An *alternative and potentially complementary* strategy is to target inflammation and its role in underlying disease pathology. Glial cells play a central role in support of brain homeostasis and synaptic function, as well as orchestrating potentially deleterious neuroinflammatory processes.

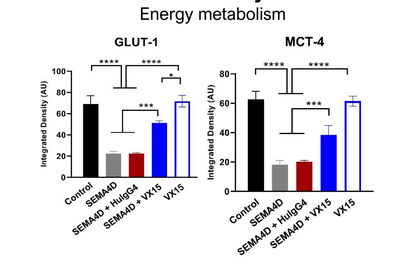


A. Neurons under stress in disease upregulate SEMA4D
B. Astrocytes are intimately associated with neurons and express plexin B1/B2 receptors for SEMA4D
C. SEMA4D binding triggers reactive transformation, including loss of normal homeostatic functions (e.g. downregulation of GLUT-1 glucose transporter and EAAT-2 glutamate receptor) and increased secretion of inflammatory cytokines and neurotoxins.

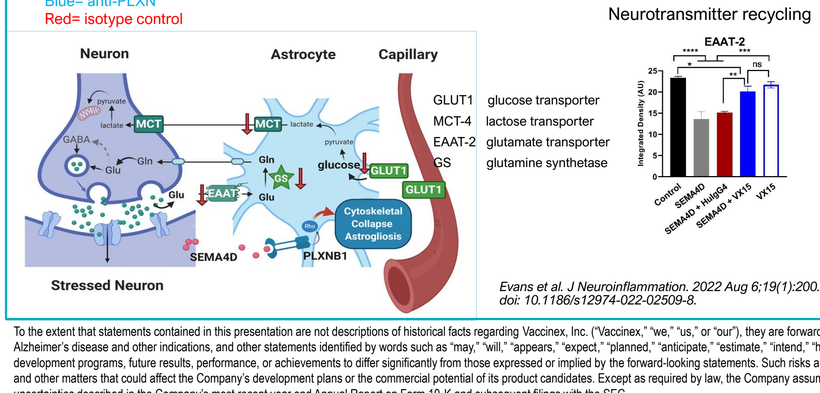


Human autopsy sections of frontal lobe





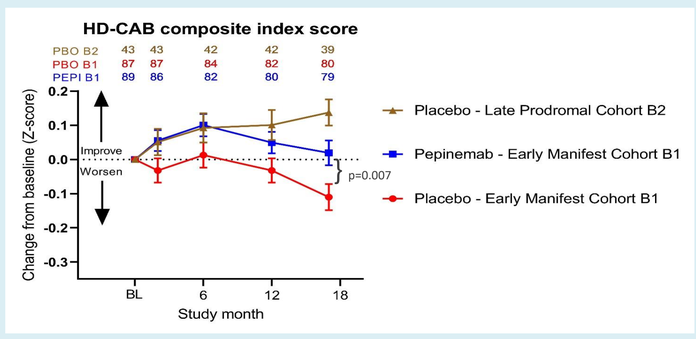
Neurotransmitter recycling

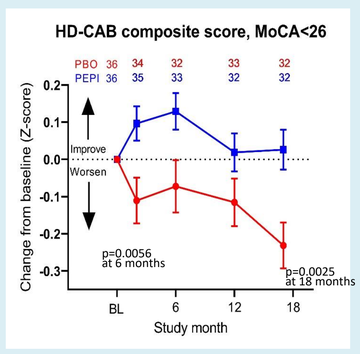


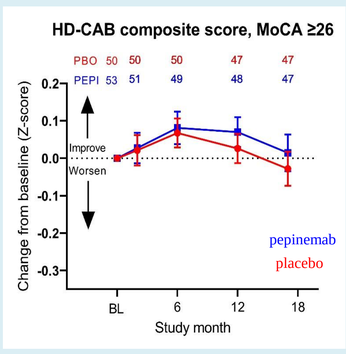
Evans et al. J Neuroinflammation. 2022 Aug 6;19(1):200. doi: 10.1186/s12974-022-02509-8.

COGNITION and LEARNING

- "Learning effect" is lost when HD symptoms become manifest
- Pepinemab treatment restores the ability to benefit from experience (i.e. to learn)

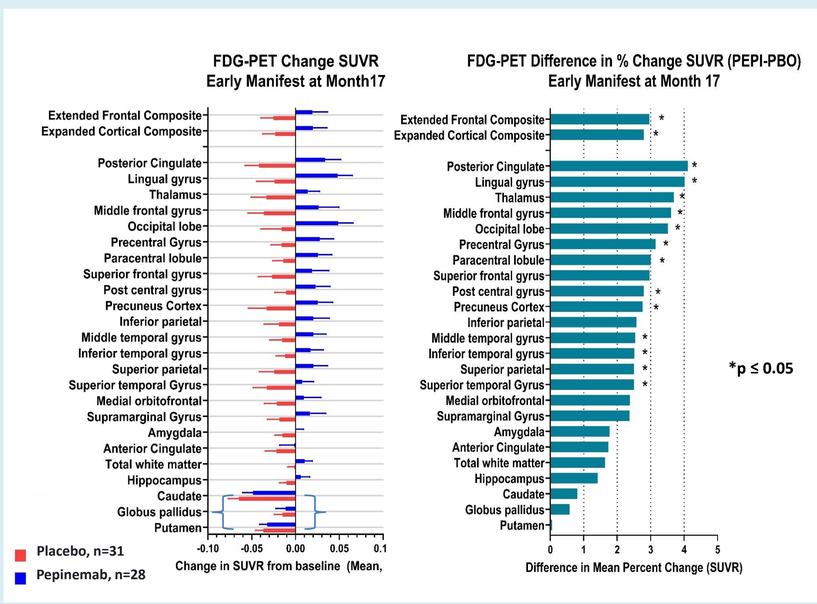




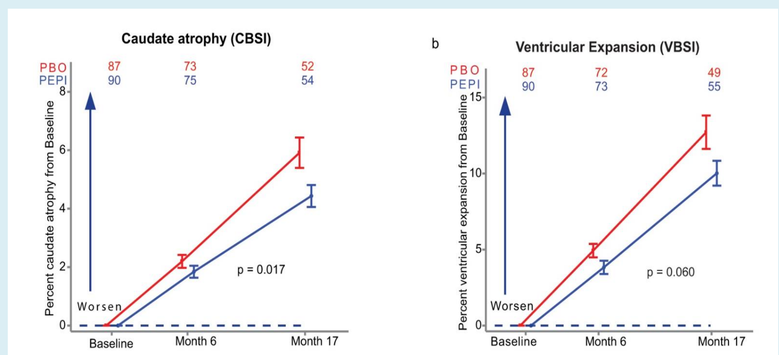


IMAGING in EARLY MANIFEST COHORT B1

PEPINEMAB APPEARS TO REVERSE LOSS OF METABOLIC ACTIVITY



PEPINEMAB APPEARS TO REDUCE BRAIN ATROPHY



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

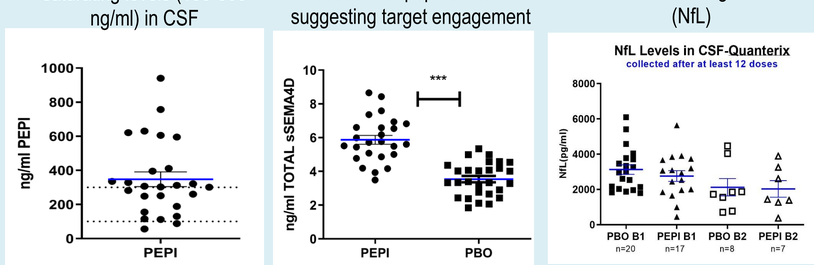
VBSI:-2.47 (-5.04, 0.10); **p = 0.060**

TARGET ENGAGEMENT and BIOMARKERS

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

sSEMA4D / drug complexes increase in CSF of individuals dosed with pepinemab – suggesting target engagement

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

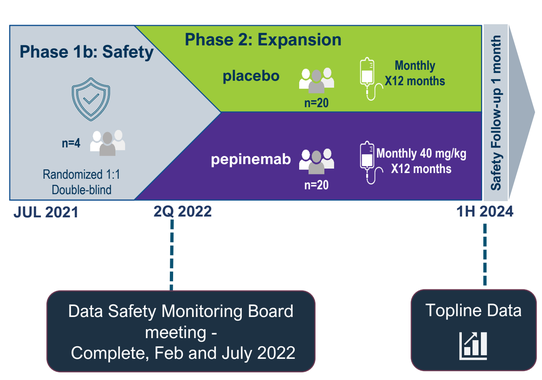


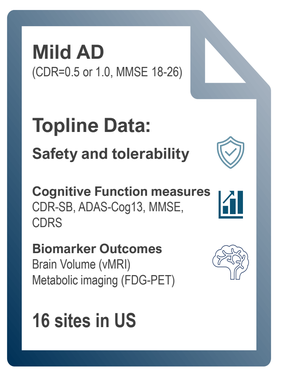
Feigin et al. Pepinemab antibody blockade of SEMA4D in early Huntington's disease: a randomized, placebo-controlled, phase 2 trial. Nat Med. 2022 Aug 8:1–11. doi: 10.1038/s41591-022-01919-8.

ONGOING CLINICAL PROGRAM in AD

SIGNAL-AD

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





NCT04381468

SUMMARY and NEXT STEPS for HD

Data supports a two-stage model of HD pathology

1. initial insult, directly or indirectly related to mHTT, causes stress and damage to neurons that results in early motor symptoms and increased expression of SEMA4D
2. SEMA4D binds to receptors on astrocytes, triggering reactive transformation and secretion of inflammatory cytokines that recruit other inflammatory cells to initiate a damaging cycle of neuroinflammation and neurotoxicity

Next Steps and Challenges:

- Obtain regulatory feedback regarding appropriate endpoints
- Plan Phase 3 trial design, inclusion criteria and clinically meaningful endpoints, including cognition
- Consider funding support with Investors and Partners
- Explore future combination strategies, including Htt-lowering