RESULTS OF PHASE 2 HUNTINGTON'S DISEASE TRIAL OF ANTI-SEMAPHORIN 4D ANTIBODY PEPINEMAB (SIGNAL) WILL GUIDE CLINICAL TRIAL IN ALZHEIMER'S DISEASE

Elizabeth Evans, PhD

Senior Vice President, Discovery and Translational Medicine

Vaccinex, Inc

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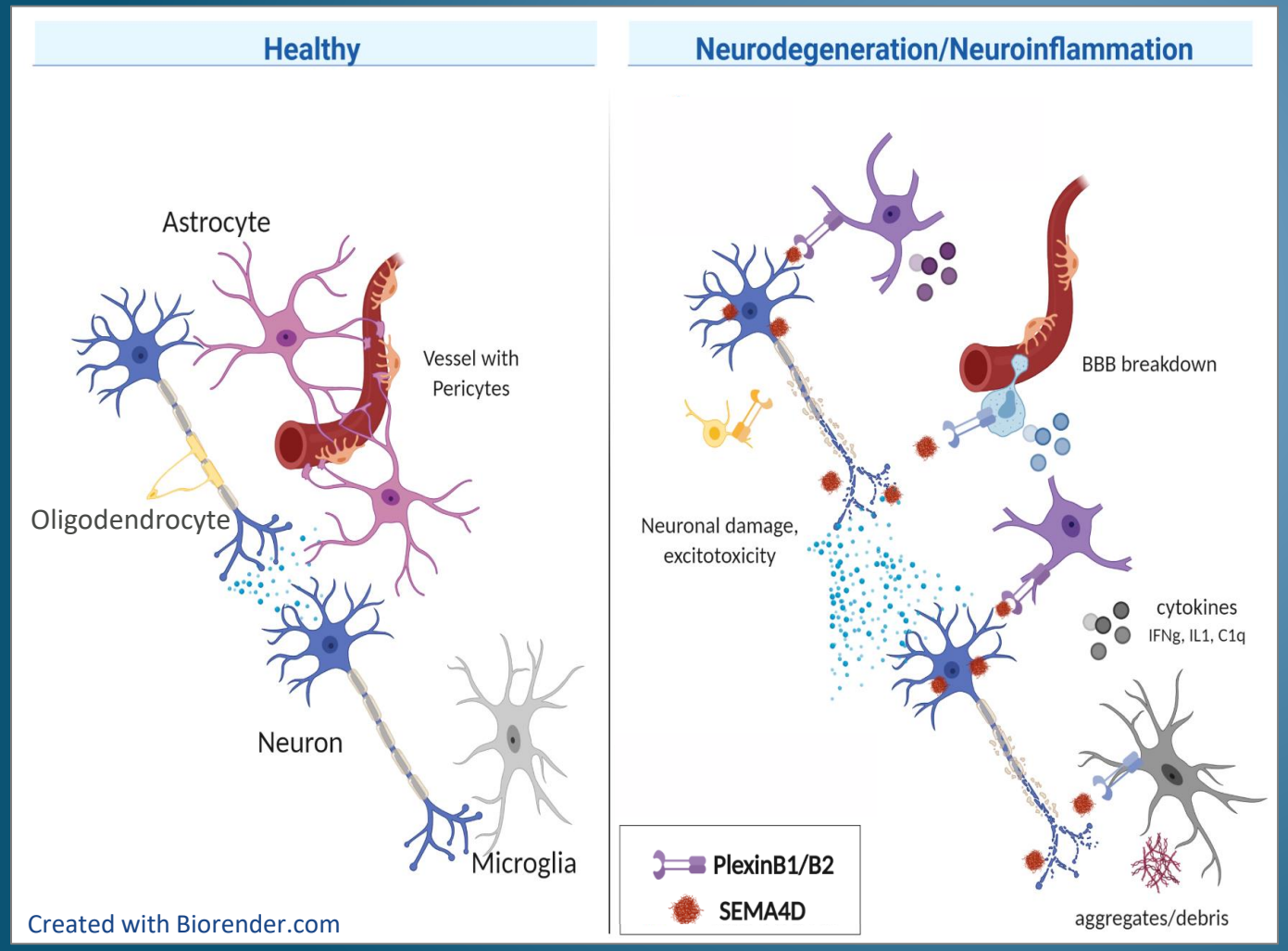
Disclosures

Elizabeth Evans is an employee and stockholder of Vaccinex, Inc

Glial cells respond to damage in the brain

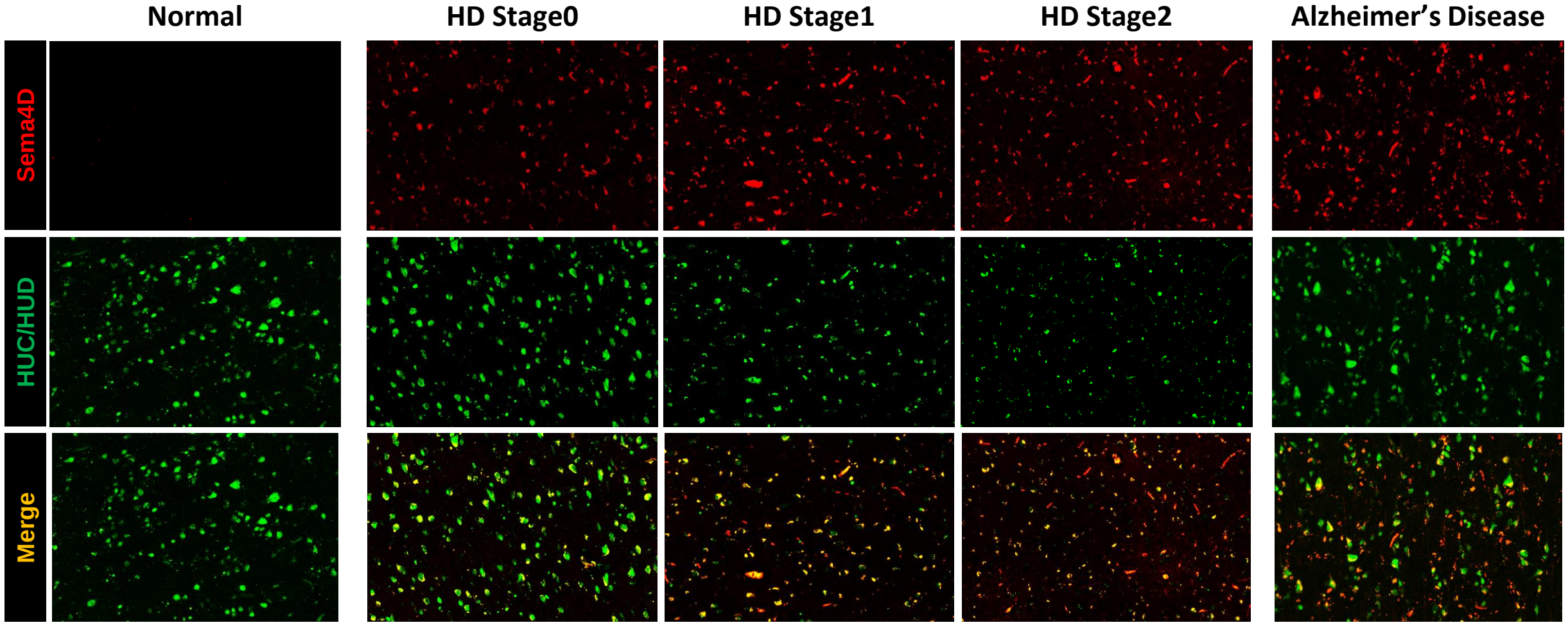


- SEMA4D is upregulated on damaged neurons
- Glial cells express receptors for SEMA4D
- SEMA4D binding to Plexin receptors triggers collapse of cytoskeleton and transformation to inflammatory state

- Pepinemab MAb binds to SEMA4D and blocks its signaling activity. → preserves normal astrocyte morphology and function & averts inflammatory transformation

Smith et al. 2014 Neurobiology of Disease
Southwell et al. 2015. Neurobiology of Disease

SEMA4D is upregulated in neurons during Human AD and HD disease progression



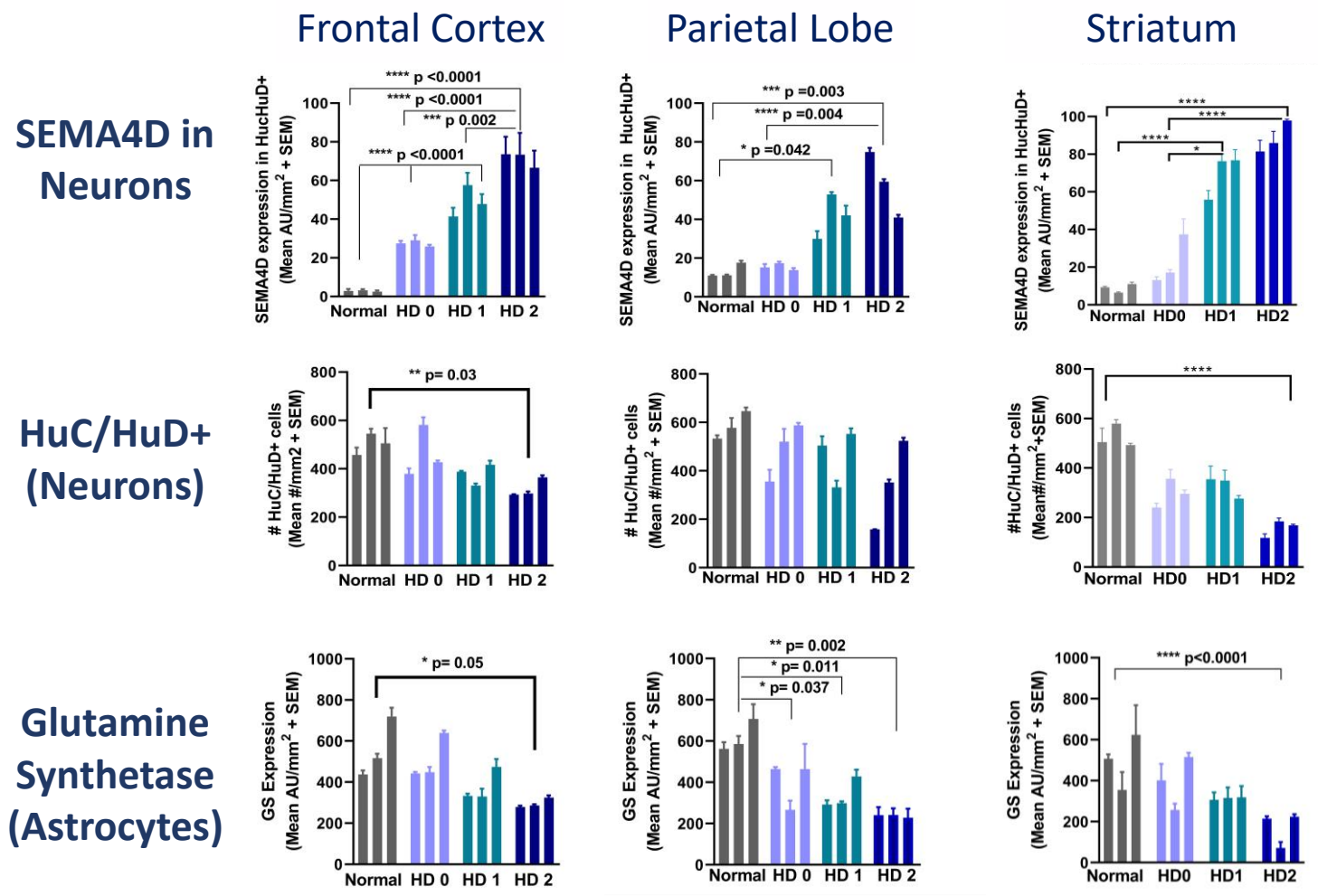
Human autopsy sections of frontal lobe

SEMA4D expression correlates with neuronal loss and astrocyte activation during HD progression

SEMA4D expression is increased

Neuronal survival is reduced

Glutamine Synthetase, an astrocytic enzyme necessary for glutamate recycling, is progressively reduced

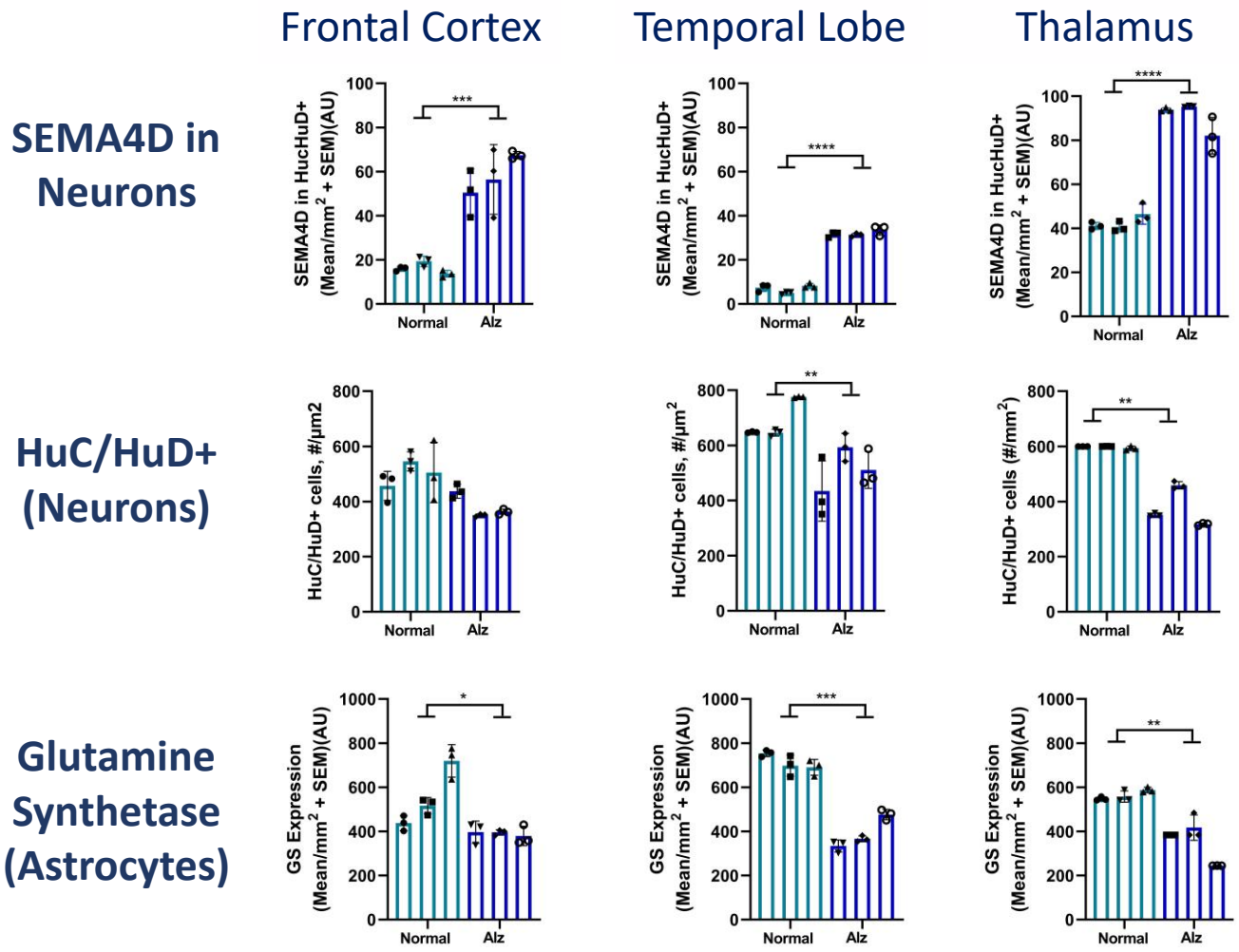


SEMA4D expression correlates with neuronal loss and astrocyte activation in Alzheimer's Disease

SEMA4D expression is increased

Neuronal survival is reduced

Glutamine Synthetase, an astrocytic enzyme necessary for glutamate recycling, is progressively reduced



Treatment Rationale

Antibody blockade of SEMA4D

- preserves normal astrocyte functions (glucose transport and glutamate recycling) and prevents glial transition to inflammatory activity
- ameliorates neuroinflammatory pathology, loss of inhibitory synapses, and cognitive symptoms in preclinical models

HYPOTHESIS: treatment with anti-SEMA4D MAb pepinemab will prevent hypometabolism and inflammatory pathology and restore or delay cognitive loss

- This mechanism of action is believed to be applicable to neurodegenerative diseases including HD and AD

Smith et al. 2014 Neurobiology of Disease
Southwell et al. 2015. Neurobiology of Disease

Pepinemab for treatment of Huntington's disease

SIGNAL

(VX15-2503-N-131)
Early Manifest HD

HUNTINGTON STUDY GROUP
seeking treatments that make a difference

VACCINEX

VX15/2503 (pepinemab) is a humanized IgG4 monoclonal antibody that blocks binding of SEMA4D to its receptors

Huntington's is a Genetically Inherited Disease

HD is caused by mutation in a single gene.
- Every child born to parent with HD has 50% chance of inheriting the mutation and disease.

Neuronal degeneration, neuroinflammation, and severe atrophy is observed in multiple brain regions

Symptoms usually appear between the ages of 30 to 50

There are currently no approved treatments to alter the course of Huntington's Disease

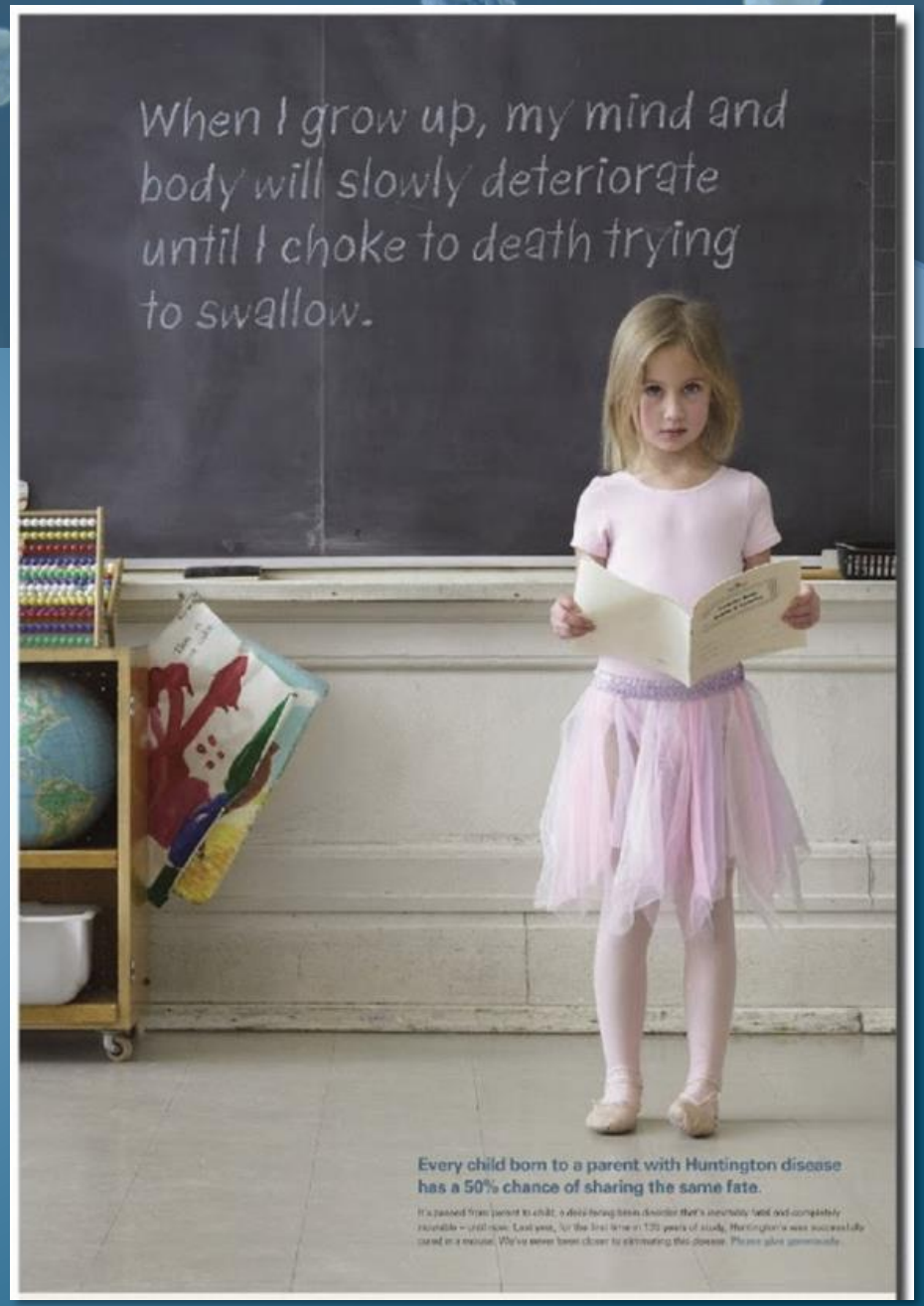
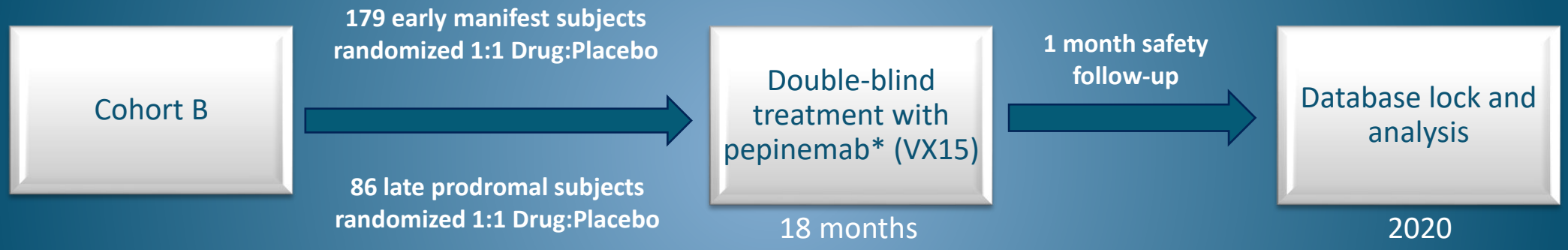


Photo credit: Huntington Society of Canada

SIGNAL: randomized placebo-controlled Phase 2 trial in subjects with early HD



Study Objectives

- Safety and tolerability
- Clinical global impression of change (CGIC) and Cognitive Function measures
- Brain imaging measures

*Pepinemab is a humanized monoclonal antibody (IgG4) that binds and blocks SEMA4D

Abbreviated Safety and Baseline Characteristics – Cohort B1 (EM), ITT population

Pepinemab (PEPI) is well tolerated

	Cohort B1 (EM) (N=179)	
	PBO (N=88) Placebo	**PEPI (N=91) Pepinemab**
Discontinued Treatment Early	**10**	**13**
Had Any SAE (*)	**8**	**4**
Had Any Grade 3+ AE (*)	**14**	**17**
CAG repeat length	44.1 (3.8)	43.5 (3.1)
CAP score (**)	470 (96)	466 (85)
UHDRS-DCL at screening, n(%)		
DCL-4, Unequivocal HD (>99% confident)	88 (100%)	91 (100%)

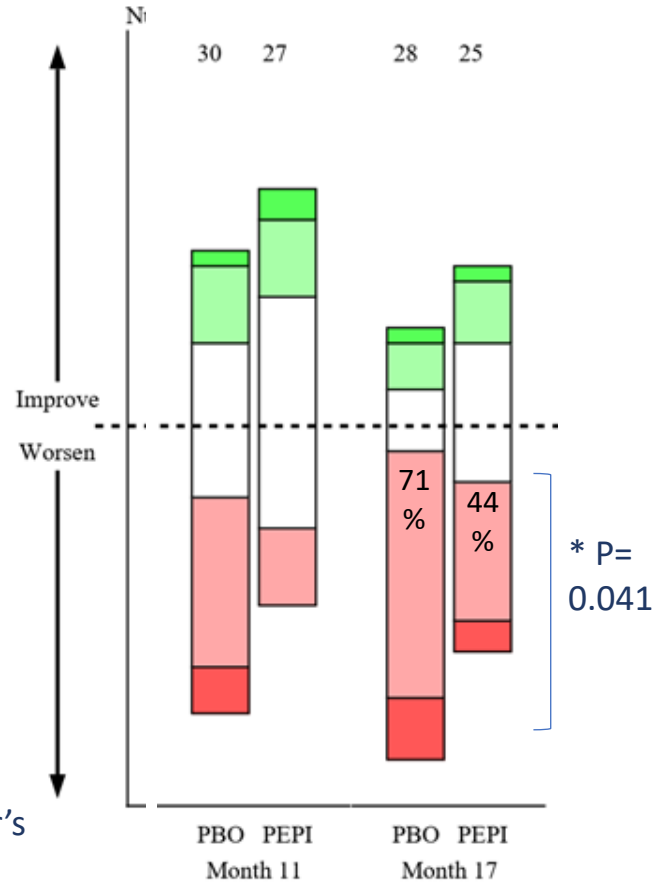
*pre-COVID era; **CAP score = age × (CAG repeat length – 33.66)

Clinical Global Impression of Change - CGIC Subgroup Analysis– Early Manifest HD

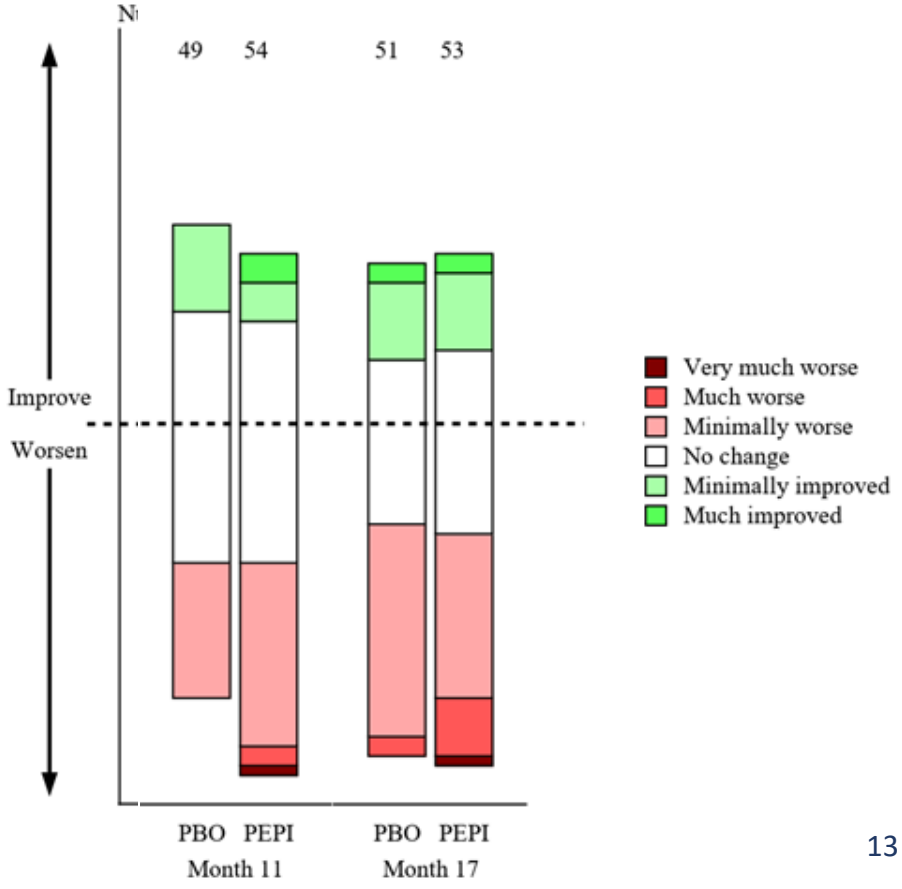
Subjects were less likely to experience decline in CGIC following treatment with pepinemab compared to placebo.

This difference was significant in subjects with more advanced disease (TFC 11).

CGIC – Subjects with Baseline UHDRS TFC 11



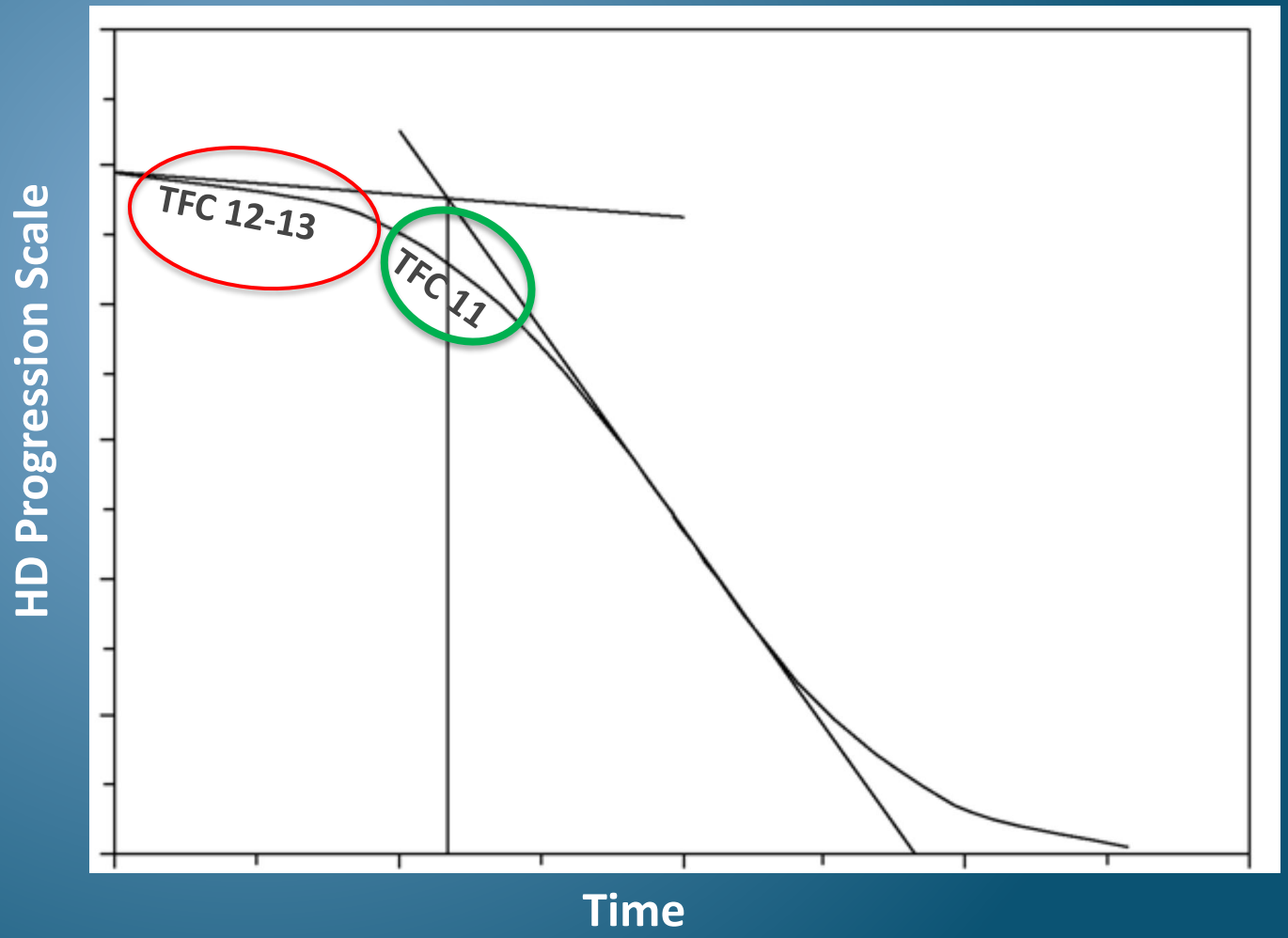
CGIC – Subjects with Baseline UHDRS TFC 12 and 13



*nominal one-sided p-value, Fisher's exact test for worsening score

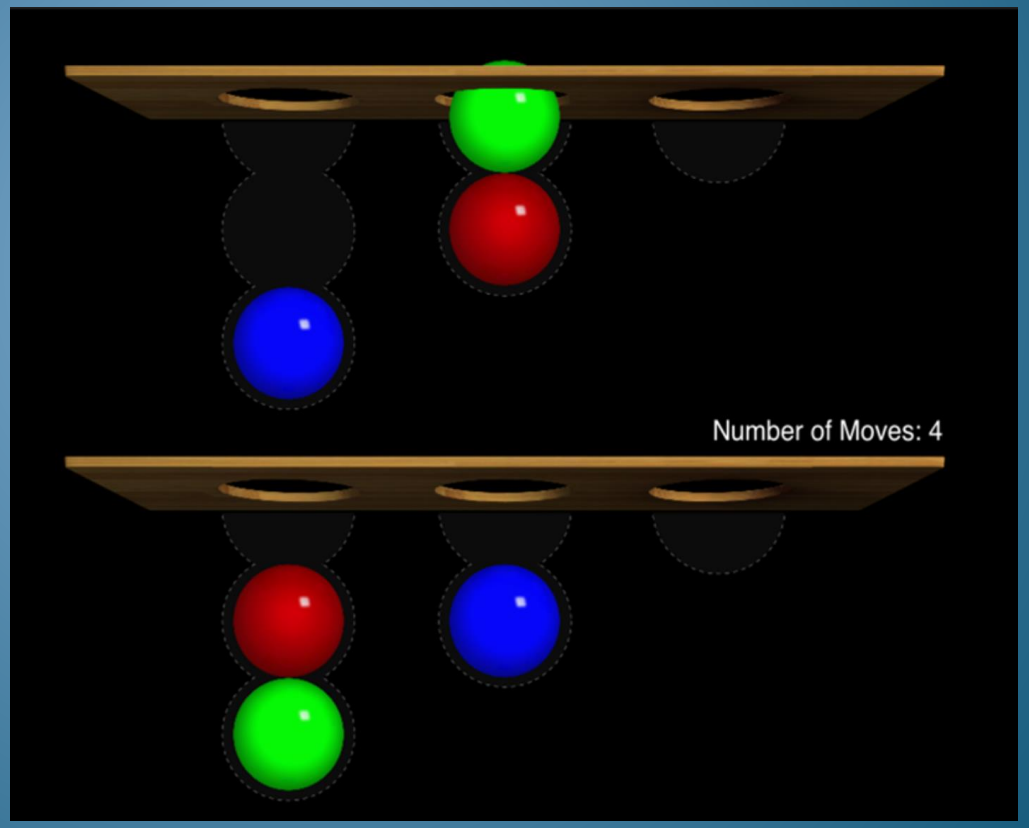
Total Functional Capacity (TFC) in HD disease progression

18-month change may be difficult to detect at top of TFC range



Cognitive function assessments

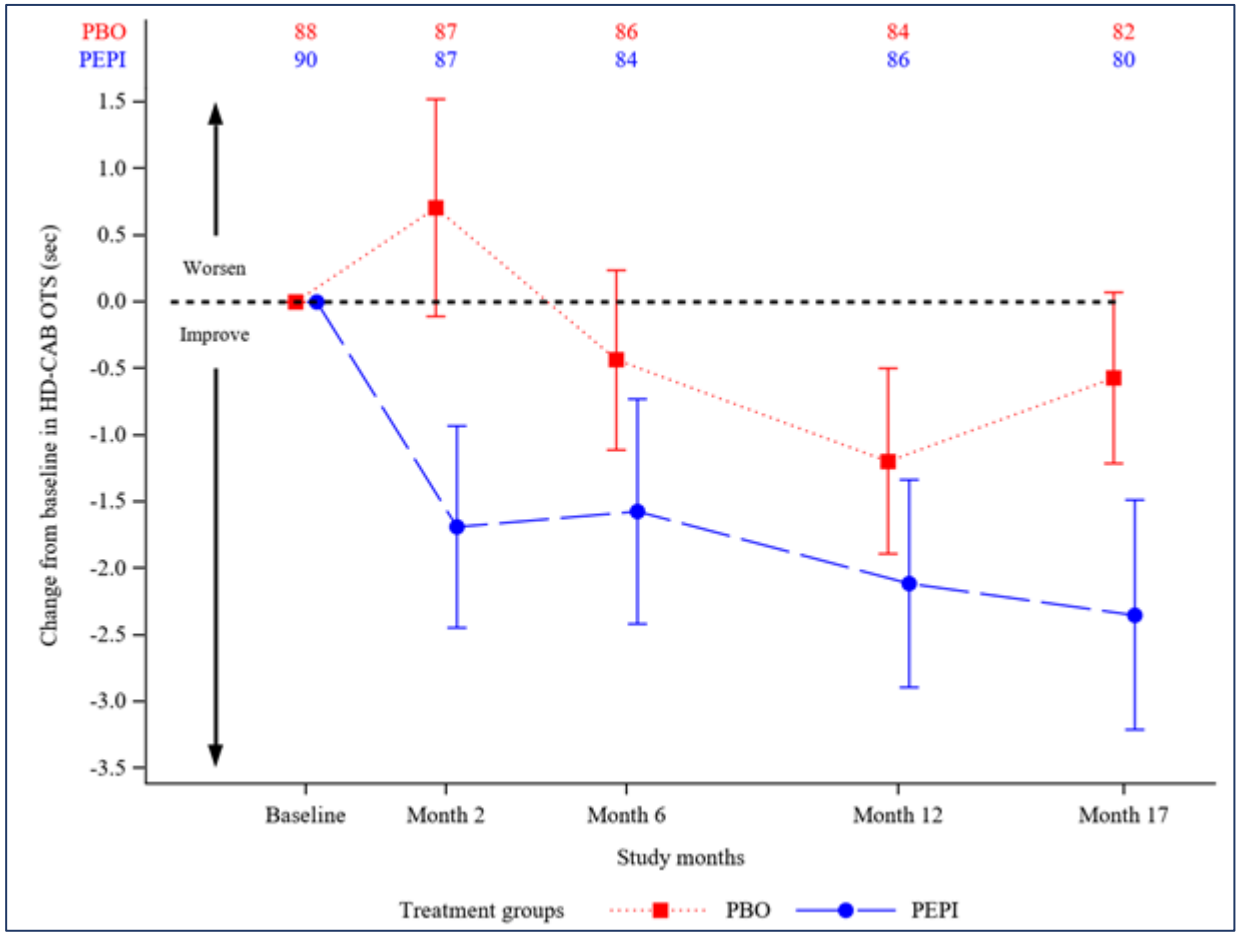
One Touch Stockings is a test of executive function that assesses both spatial planning and the working memory



Cognitive Assessment Co-Primary 2a: Test of Planning and Memory

One Touch Stockings

Early Manifest HD



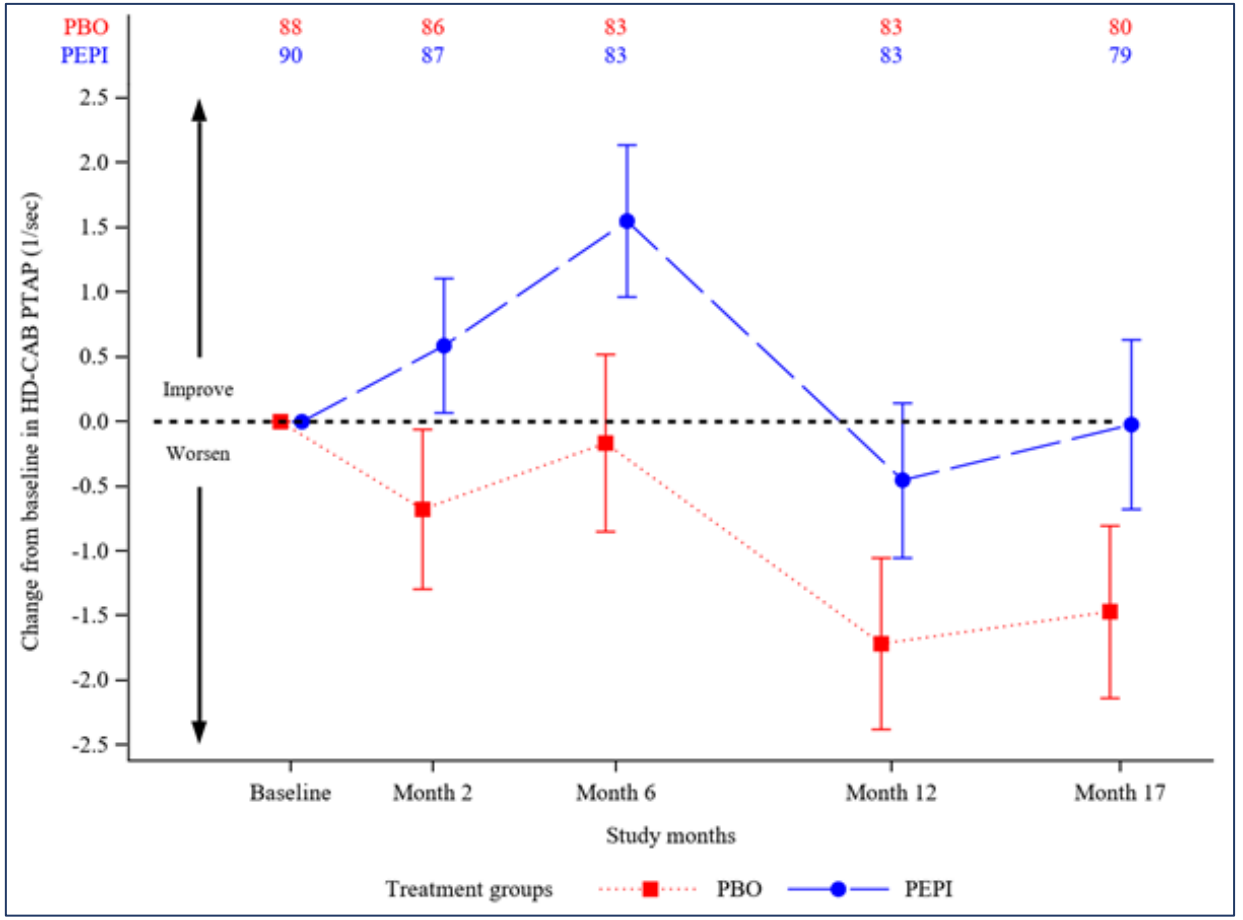
One-sided p-value	Favors PEPI	Success [Critical value]
0.028	Yes	No [0.025] [0.0125]

Difference (PEPI – PBO)
Change from Baseline at Month 17 (95% CI) = -1.98 (-4.00, 0.05)

Cognitive Assessment
Co-Primary 2a: Test of Timing and Processing Speed

Paced Finger Tapping Task

Early Manifest HD



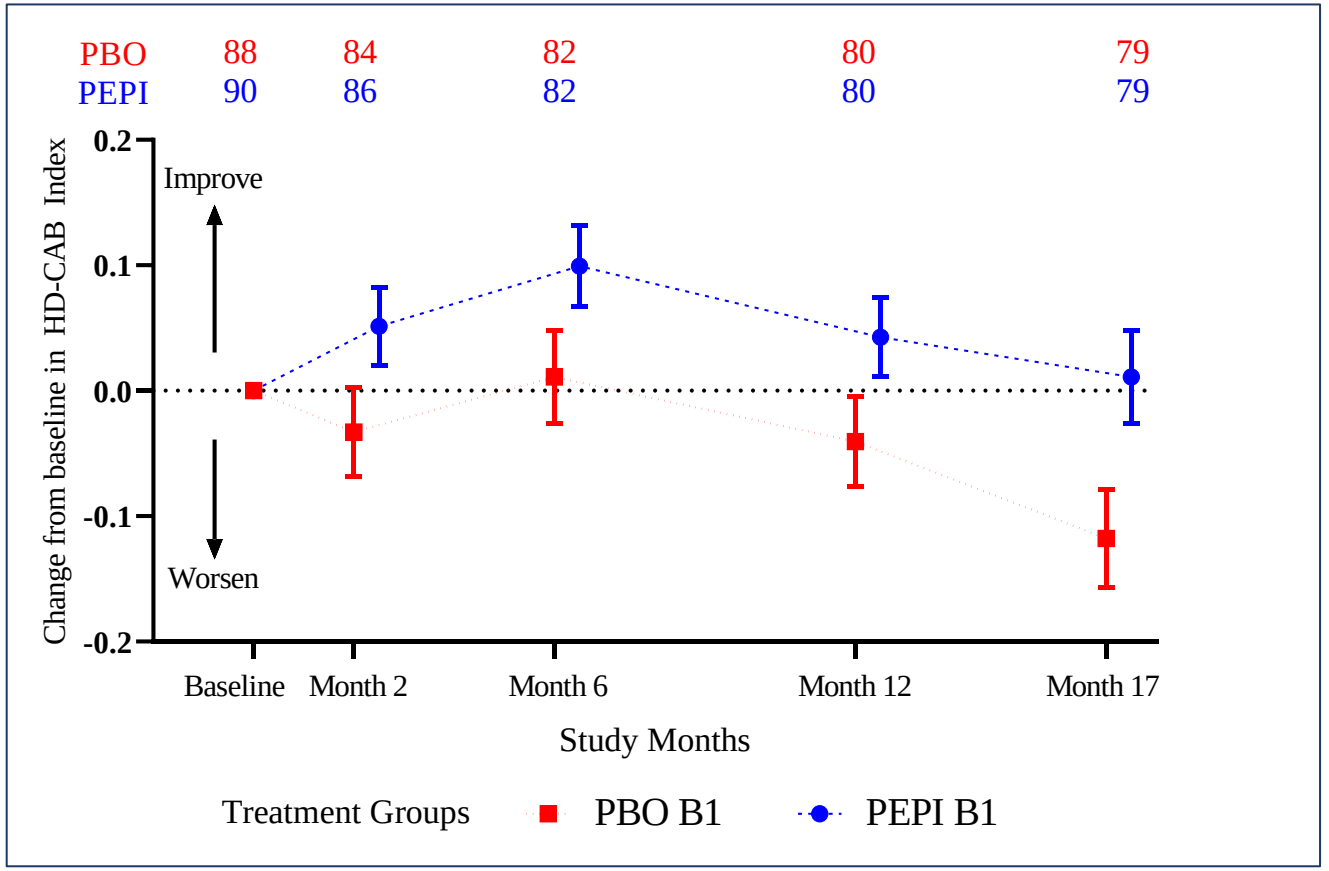
One-sided p-value	Favors PEPI	Success [Critical value]
0.06	Yes	No [0.025] [0.0125]

Difference (PEPI – PBO)
Change from Baseline at Month 17 (95% CI) = 1.43 (-0.37, 3.23)

Cognitive Assessment Battery (HD-CAB)

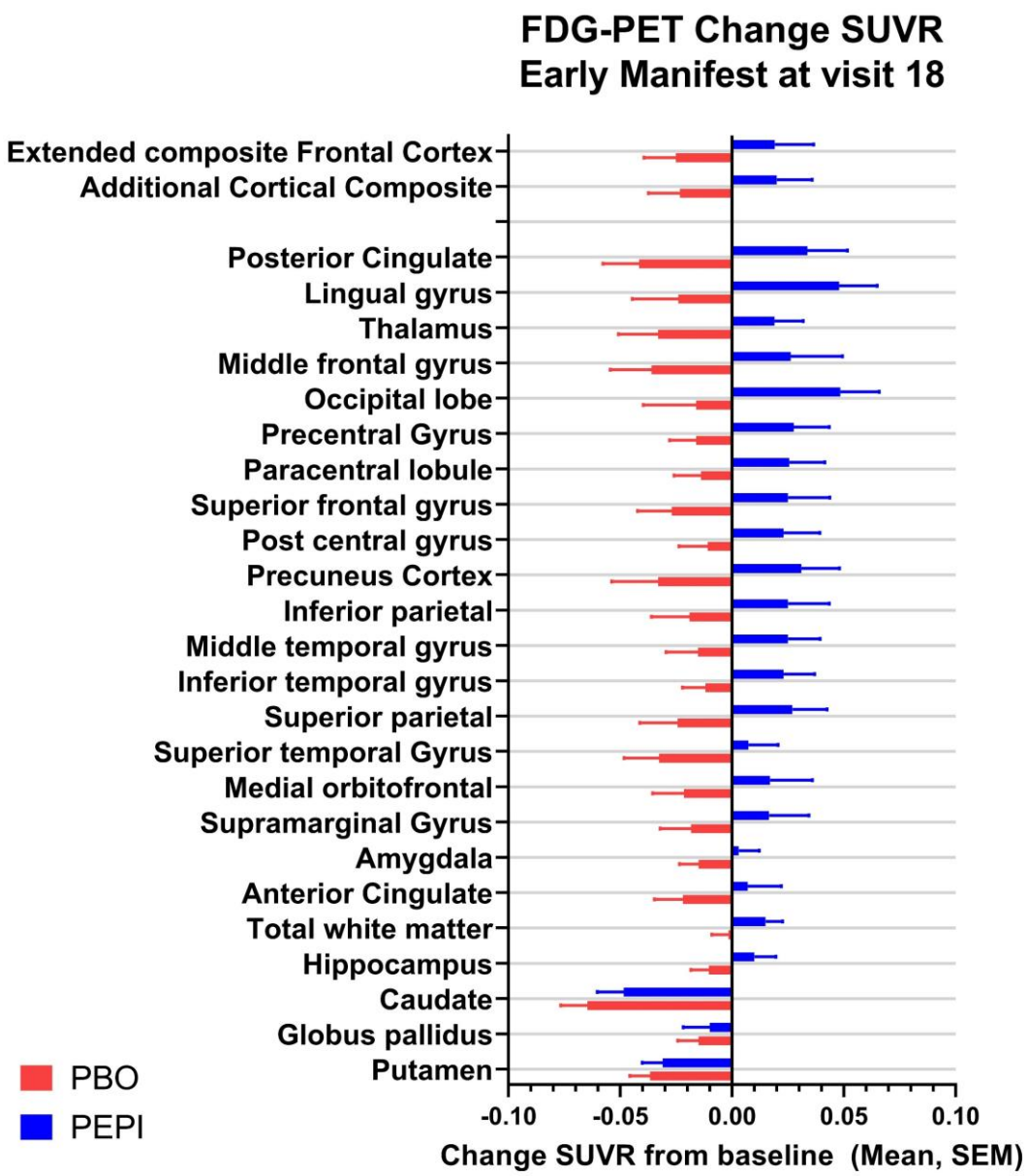
HD-CAB Composite Index of 6 Cognitive Assessments

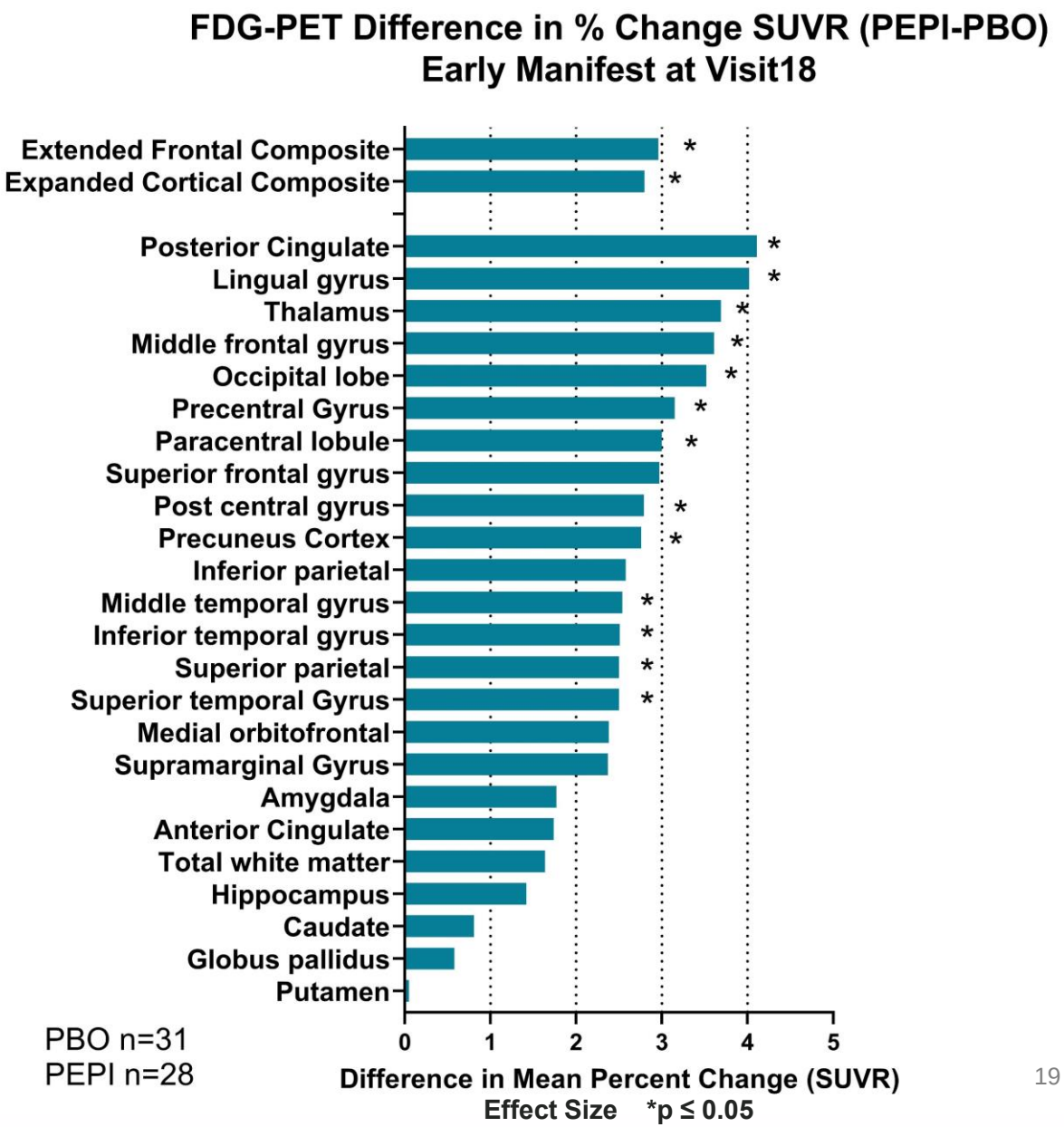
Early manifest HD



One-sided p-value	Favors PEPI	Critical value
0.007	Yes	Yes [0.025]

FDG-PET at 18 Months – Early Manifest: Pepinemab treatment reverses loss of metabolic activity





PBO n=31
PEPI n=28

Summary

HYPOTHESIS: treatment with anti-SEMA4D MAb pepinemab will prevent hypometabolism and inflammatory pathology and restore or delay cognitive loss

MOA: SEMA4D is upregulated during disease progression. Antibody blockade of SEMA4D preserves normal astrocyte functions and prevents glial transition to inflammatory activity

This mechanism of action is believed to be applicable to neurodegenerative diseases including HD and AD

SIGNAL-HD, a Phase2 study in subjects with prodromal and early manifest HD

Pepinemab was well-tolerated and was shown to cross the BBB at the anticipated level of 0.1% or greater of circulating antibody

Reduced deteriorating CGIC in subjects with more advanced TFC11 (p=0.04)

Treatment benefit observed in the HD-CAB cognitive battery (p=0.007)

Reduced brain atrophy (vMRI) and slowed or reversed decline in metabolic activity (FDG-PET)

Treatment benefits were detected in patients with more advanced disease (EM and TFC11)

SIGNAL-AD, a Phase 1b/2a study in AD, is planned to begin enrollment in 2021

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Patients and their families