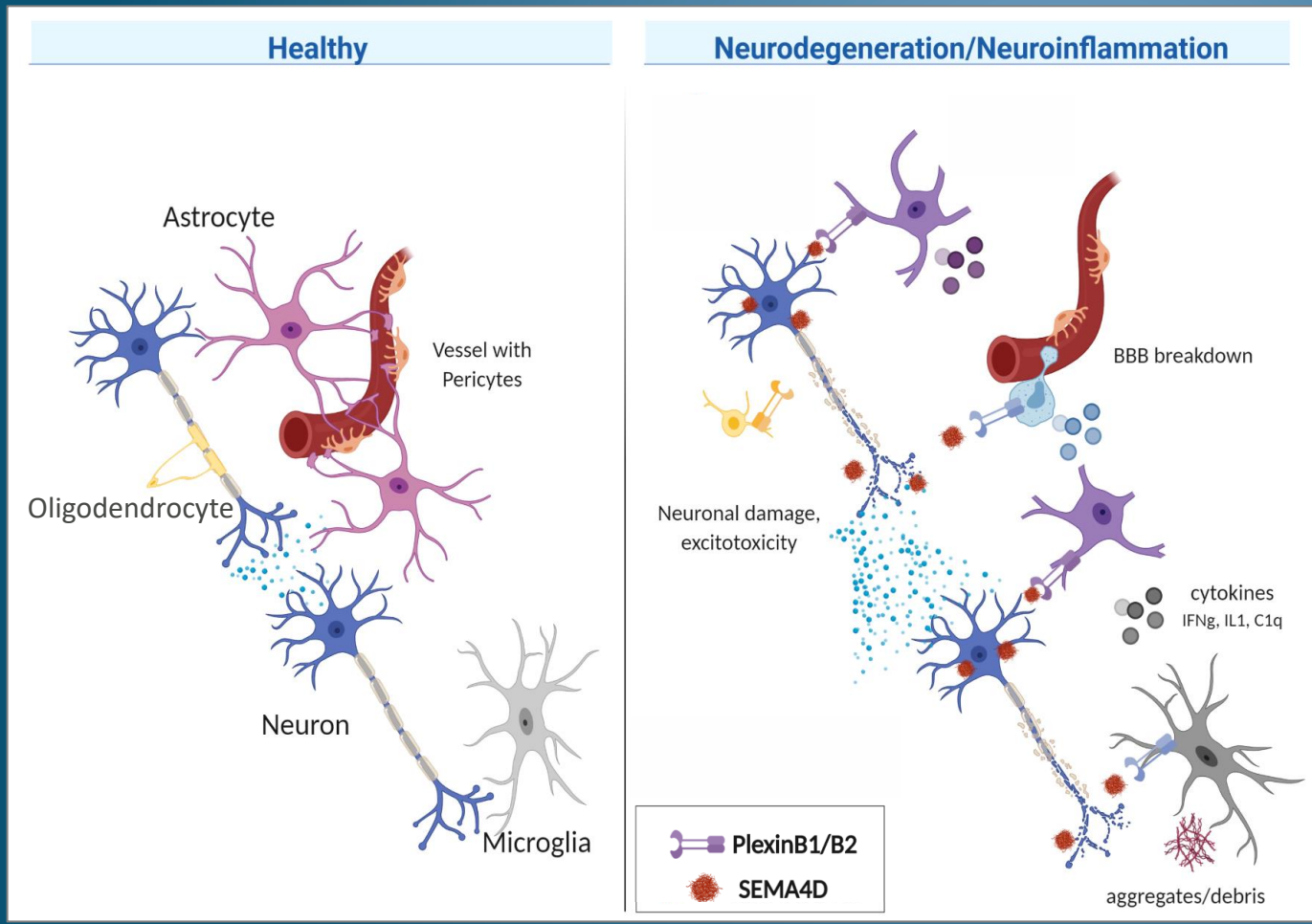


Results of phase 2 SIGNAL trial of the SEMA4D blocking antibody suggest pepinemab is a novel potential treatment for neurodegenerative disease

T. Fisher¹, E. Evans¹, A. Reader¹, V. Mishra¹, C. Mallow¹, L. Balch¹, A. Howell¹, E. Smith¹, J. Leonard¹, A. Feigin², E. Siemers³, J. Wittes⁴ M. Zauderer¹. ¹ Vaccinex, Inc.; ²for the Huntington Study Group, and SIGNAL investigators and coordinators; ³ Siemers Integration LLC; ⁴ for Statistics Collaborative



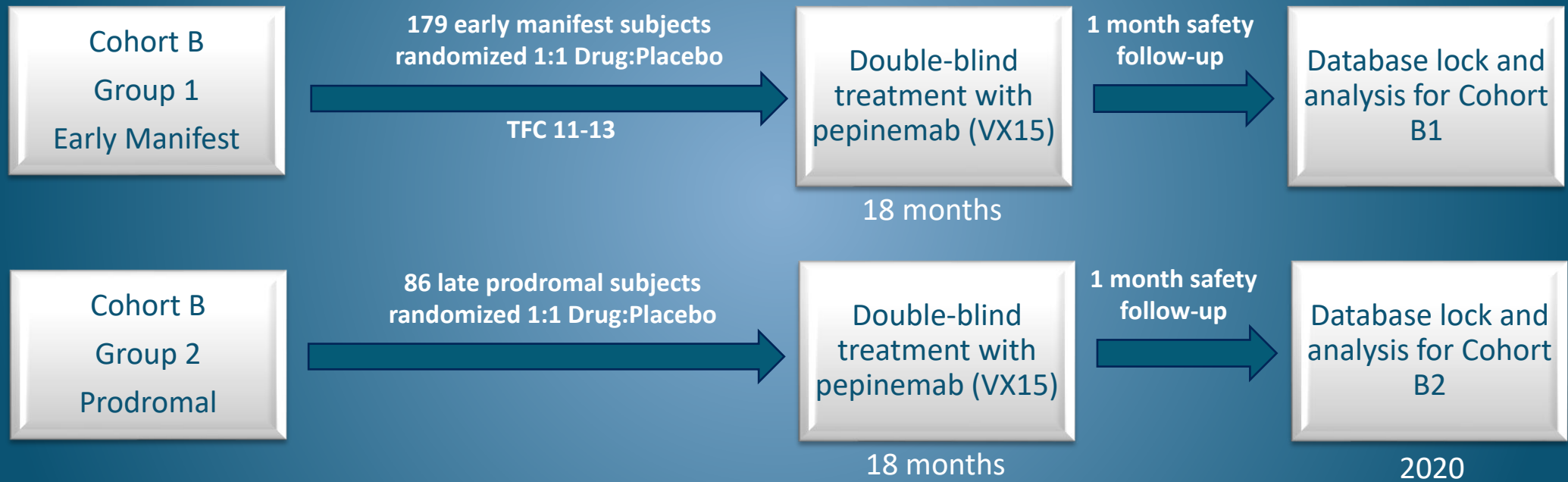
Glial cells respond to damage induced by mutant Huntingtin protein and other neurotoxins

SEMA4D is upregulated during disease progression

Chronic reactive gliosis and inflammation exacerbates neurodegeneration

Blocking SEMA4D can reduce neurodegenerative processes in preclinical models

SIGNAL: randomized placebo controlled trial in subjects with early HD



Study Objectives

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

Abbreviated Safety and Baseline Characteristics Cohort B1 and B2, ITT population

Pepinemab (PEPI)
SEMA4D blocking
antibody is
well tolerated

	Cohort B1 (N=179)		Cohort B2 (N=86)	
	PBO (N=88)	PEPI (N=91)	PBO (N=45)	PEPI (N=41)
Discontinued Treatment Early	10	13	2	0
Had Any SAE (*)	8	4	4	2
Had Any Grade 3+ AE (*)	14	17	6	8
CAG repeat length	44.1 (3.8)	43.5 (3.1)	42.8 (2.3)	42.4 (2.7)
CAP score (**)	470 (96)	466 (85)	374 (72)	404 (98)
UHDRS-DCL at screening, n(%)				
0,1 – Normal or non-specific signs	0	0	0	0
2 – May be HD (50%-89% confident)	0	0	31 (69%)	29 (71%)
3 – Likely HD (90%-98% confident)	0	0	14 (31%)	12 (29%)
4 – Unequivocal HD (>99% confident)	88 (100%)	91 (100%)	0	0

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

Cognitive Assessment

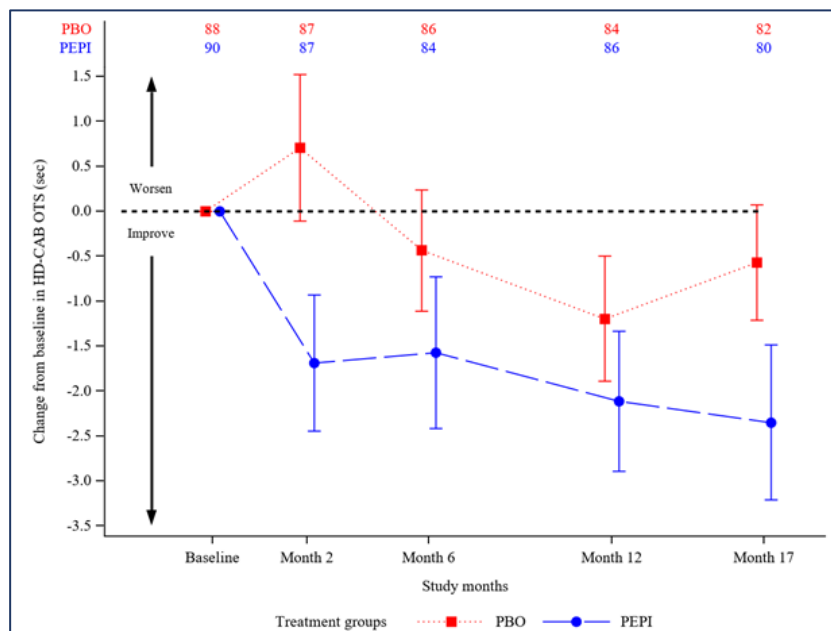
Co-Primary 1a: Test of Planning and Memory

Co-Primary 1b: Test of Timing and Processing Speed

1a: One Touch Stockings

Early Manifest HD

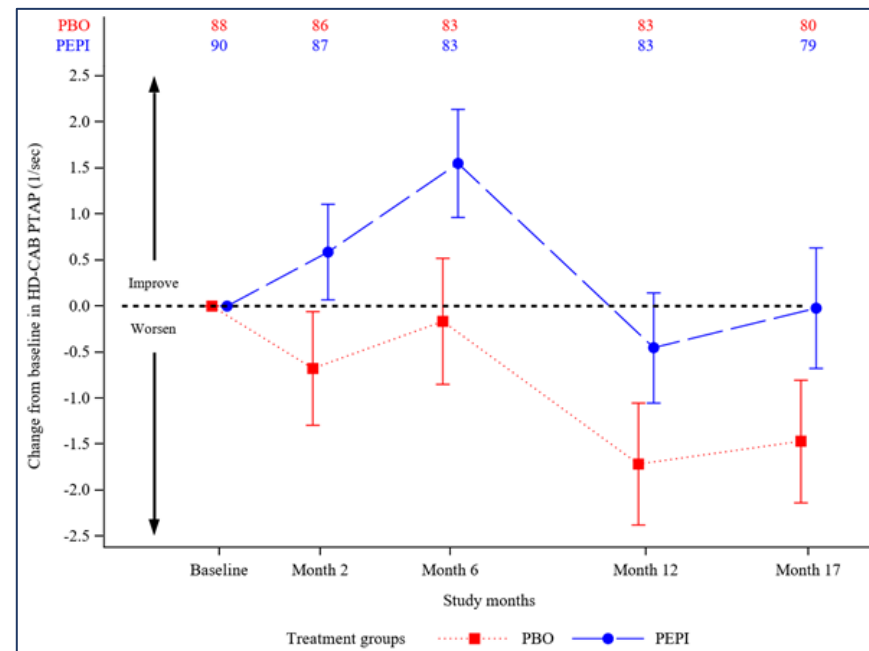
One-sided p-value	Favors PEPI	Success [Critical value]
0.028	Yes	No [0.025] [0.0125]



1b: Paced Finger Tapping Task

Early Manifest HD

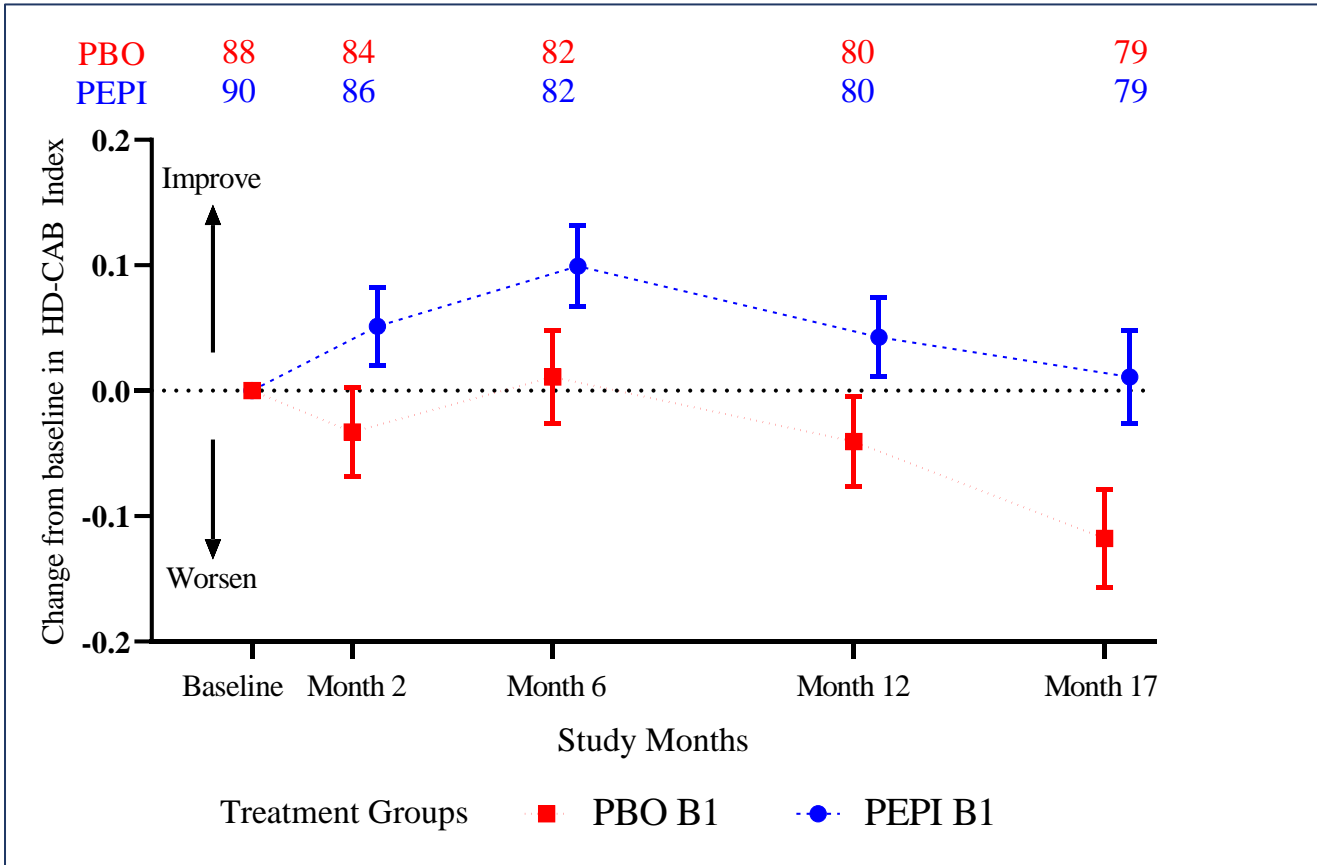
One-sided p-value	Favors PEPI	Success [Critical value]
0.06	Yes	No [0.025] [0.0125]



Cognitive Assessment Battery: Prespecified Exploratory analysis, HD-CAB Composite Score

HD-CAB Composite
Index of 6 Cognitive
Assessments

Early manifest HD



PBO	88	84	82	80	79
PEPI	90	86	82	80	79

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

Cognitive Assessment Battery: Prespecified Exploratory analysis, HD-CAB Composite Score

B1. Early Manifest

Population / Parameter	PBO		PEPI		Difference, PEPI - PBO	
	N ^a	Mean (SE)	N ^a	Mean (SE)	Estimate (95% CI)	One-Sided p-value (+ Favors PEPI) ^b
Cohort B1 mITT (N=178)	88		90			
OTS (sec) ^c	88	-0.33 (0.72)	89	-2.30 (0.73)	-1.98 (-4.00, 0.05)	0.028 (+)
PTAP (1/sec) ^d	87	-1.67 (0.65)	89	-0.24 (0.64)	1.43 (-0.37, 3.23)	0.060 (+)
SDMT ^e	88	-3.59 (0.70)	89	-2.97 (0.71)	0.62 (-1.35, 2.59)	0.27 (+)
EMO ^f	88	-0.09 (0.33)	89	0.28 (0.33)	0.37 (-0.55, 1.30)	0.22 (+)
HVLT-R ^g	88	0.21 (0.73)	89	0.65 (0.73)	0.44 (-1.59, 2.47)	0.34 (+)
TMT-B (sec) ^h	88	8.27 (4.24)	89	1.06 (4.26)	-7.21 (-19.09, 4.66)	0.12 (+)
HD-CAB Index (Cohort B1 reference)ⁱ	87	-0.12 (0.04)	89	0.01 (0.04)	0.13 (0.03, 0.23)	0.007 (+)

B2. Prodromal

Population / Parameter	PBO		PEPI		Difference, PEPI - PBO	
	N ^a	Mean (SE)	N ^a	Mean (SE)	Estimate (95% CI)	One-Sided p-value (+ Favors PEPI) ^b
Cohort B2 mITT (N=86)	45		41			
OTS (sec) ^c	44	-0.89 (0.74)	41	-0.94 (0.74)	-0.05 (-2.14, 2.05)	0.49 (+)
PTAP (1/sec) ^d	44	0.08 (1.02)	41	-1.00 (1.04)	-1.08 (-3.98, 1.82)	0.77 (-)
SDMT ^e	45	1.07 (1.05)	41	-0.29 (1.09)	-1.36 (-4.38, 1.65)	0.82 (-)
EMO ^f	44	0.35 (0.47)	41	-0.42 (0.47)	-0.77 (-2.09, 0.55)	0.88 (-)
HVLT-R ^g	45	2.86 (0.83)	41	3.25 (0.86)	0.39 (-1.99, 2.77)	0.38 (+)
TMT-B (sec) ^h	45	-9.58 (3.63)	41	0.72 (3.76)	10.30 (-0.21, 20.80)	0.98 (-)
HD-CAB Index (Cohort B2 reference)ⁱ	44	0.18 (0.06)	41	0.08 (0.06)	-0.11 (-0.27, 0.06)	0.90 (-)

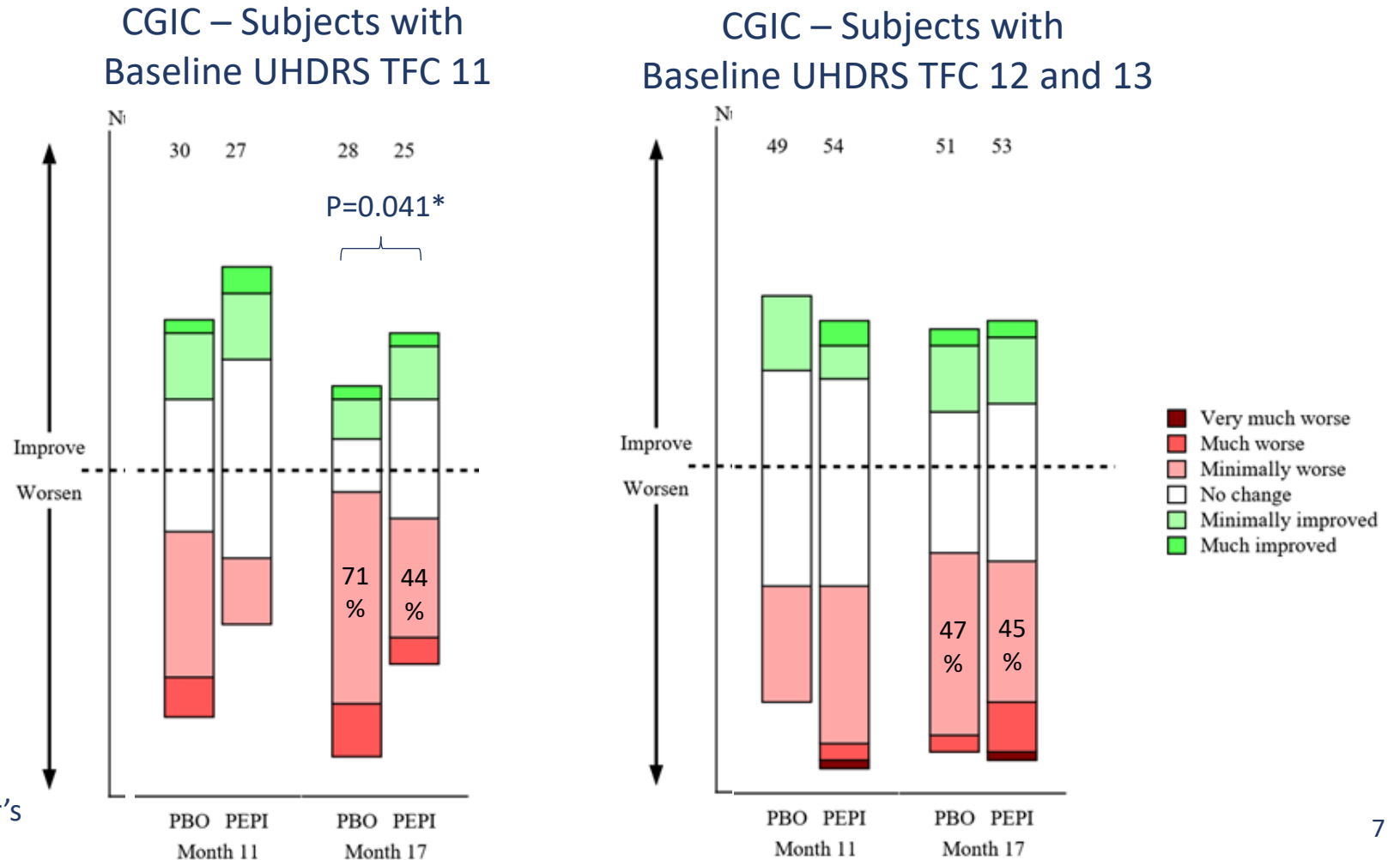
MMRM analysis of HD-CAB Month 17 change from baseline in Early Manifest (B1) and Prodromal (B2) Subjects

CGIC

Post-hoc Subgroup Analysis – Early Manifest HD

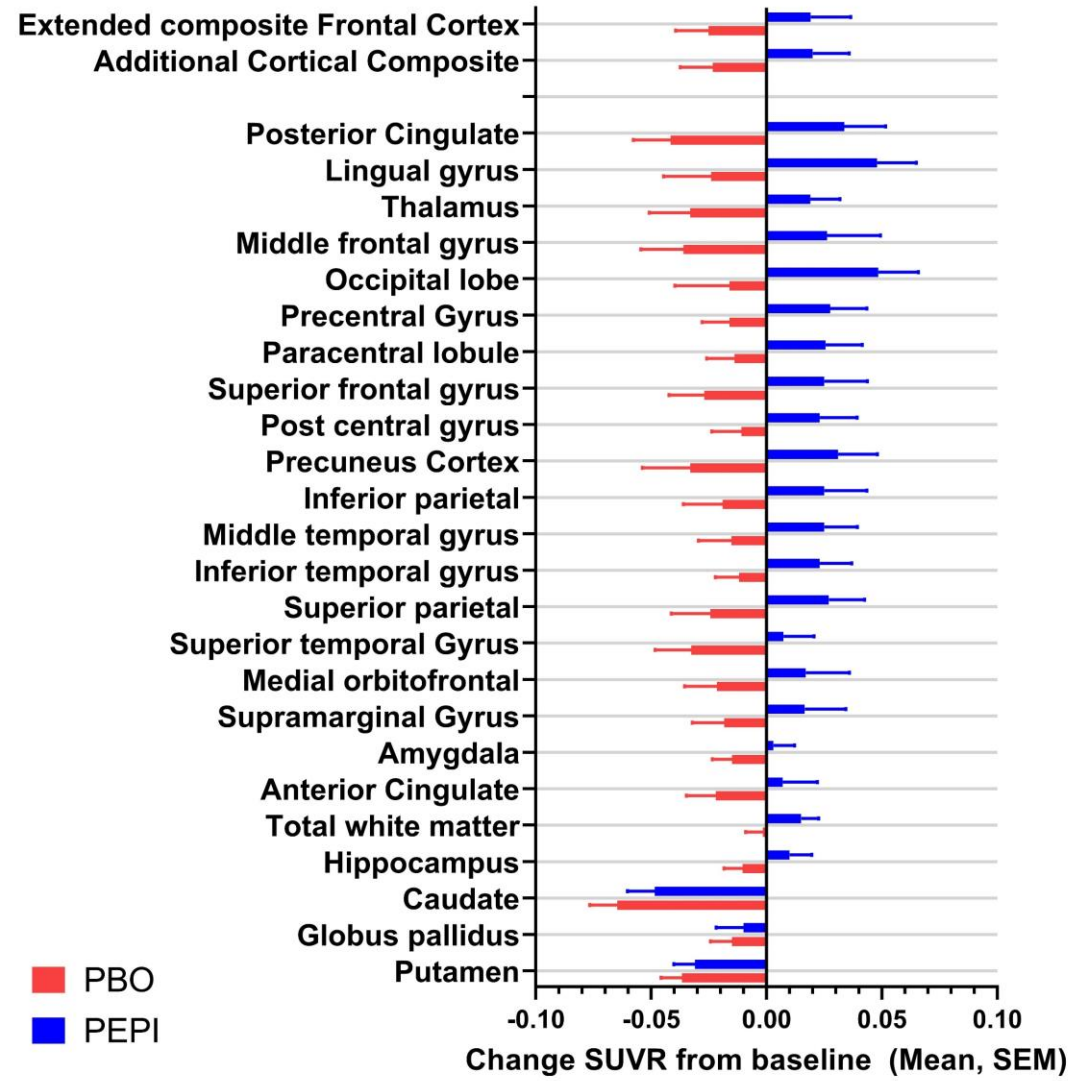
Subjects were less likely to experience decline in CGIC following treatment with pepinemab compared to placebo.

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

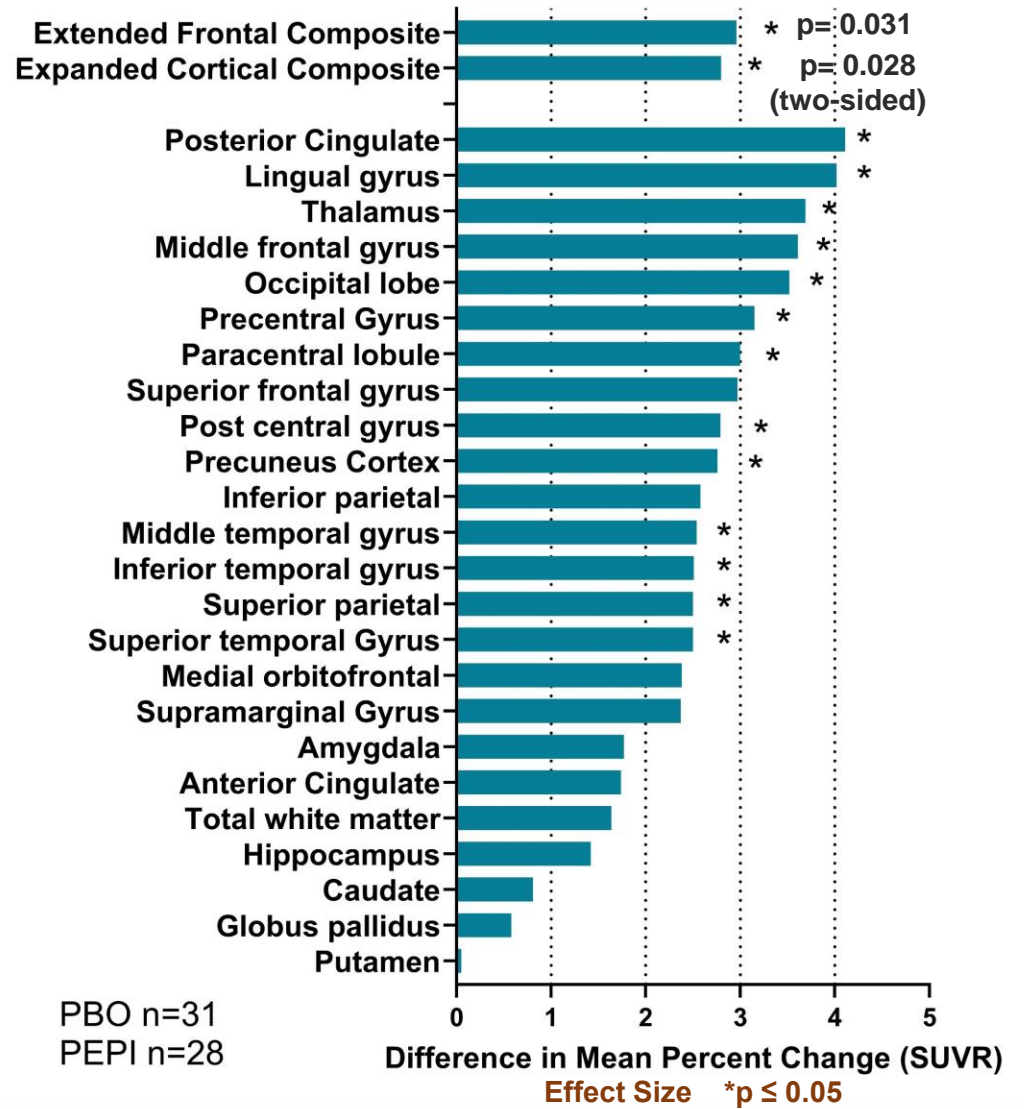


*nominal one-sided p-value, Fisher's exact test for worsening score

**FDG-PET Change SUVR
Early Manifest at visit 18**



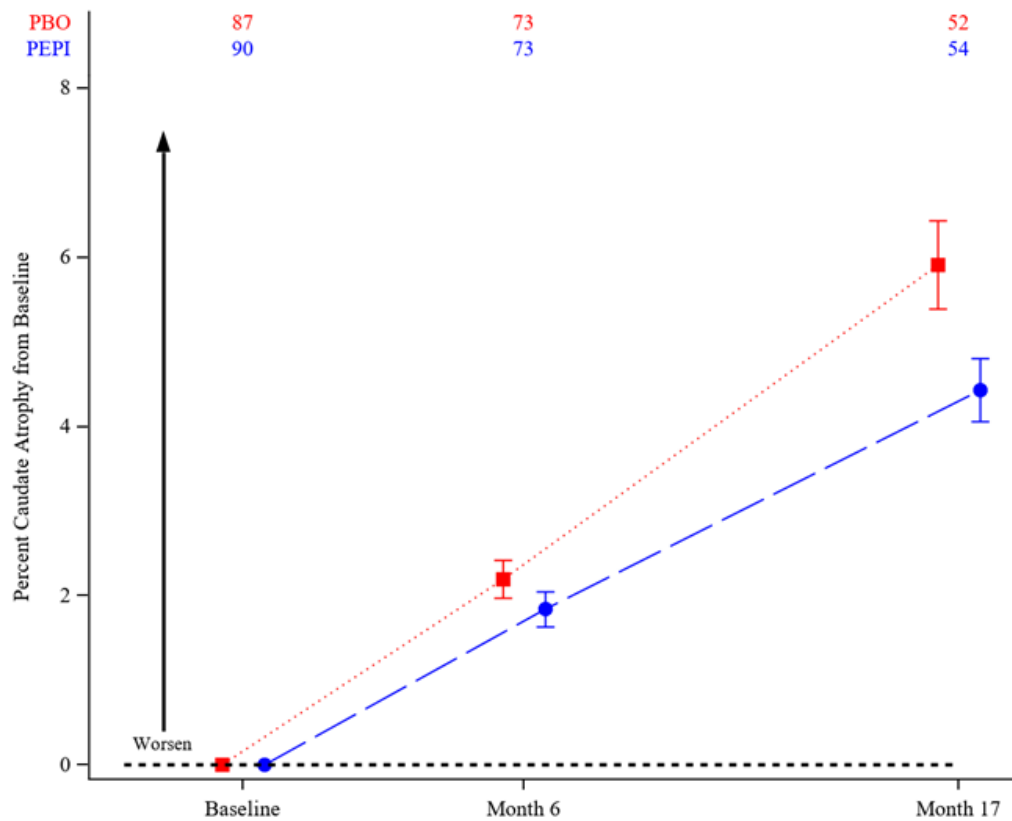
**FDG-PET Difference in % Change SUVR (PEPI-PBO)
Early Manifest at Visit18**



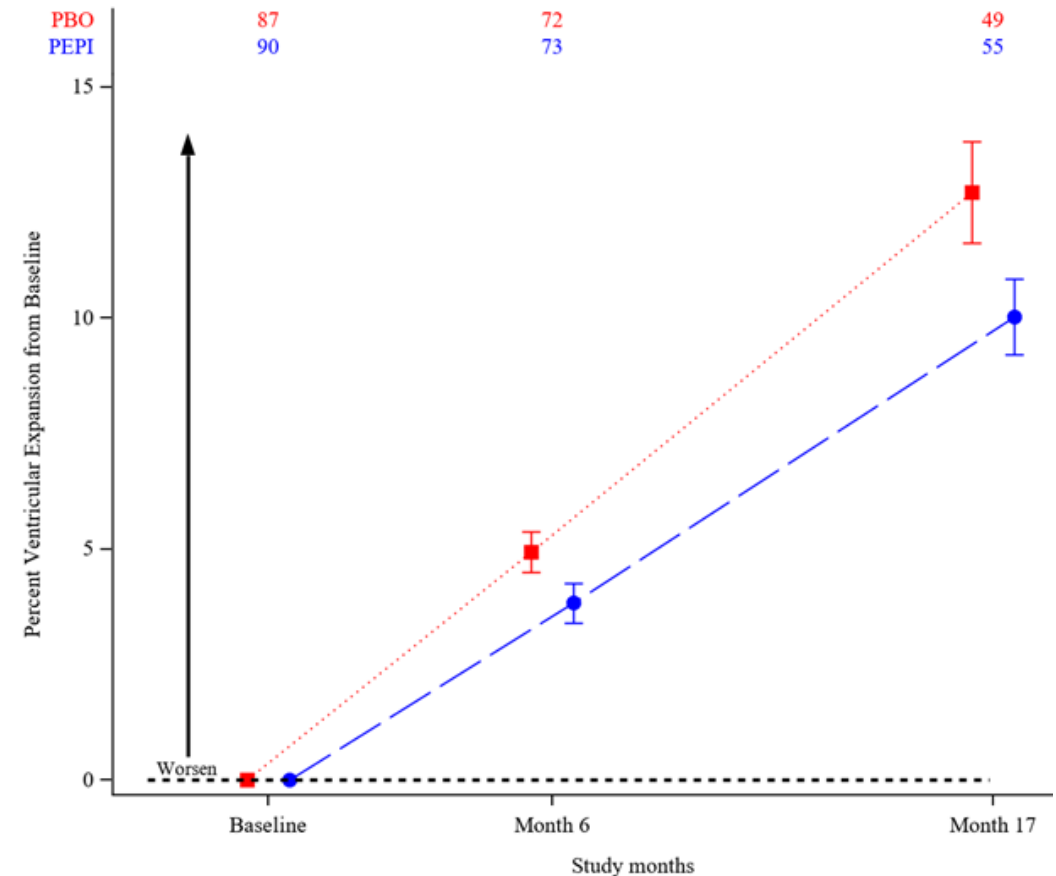
volumetric MRI analysis – Boundary Shift Integral

Pre-specified exploratory endpoint

CBSI (caudate atrophy) Early Manifest (B1)

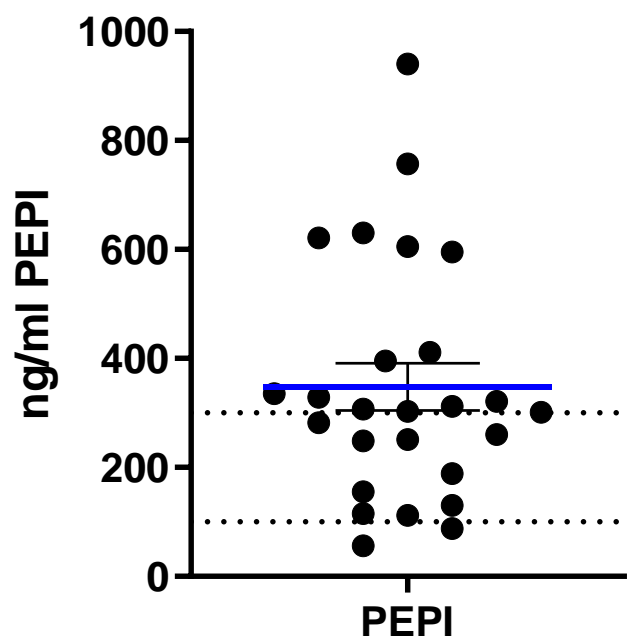


VBSI (ventricular expansion) Early Manifest (B1)

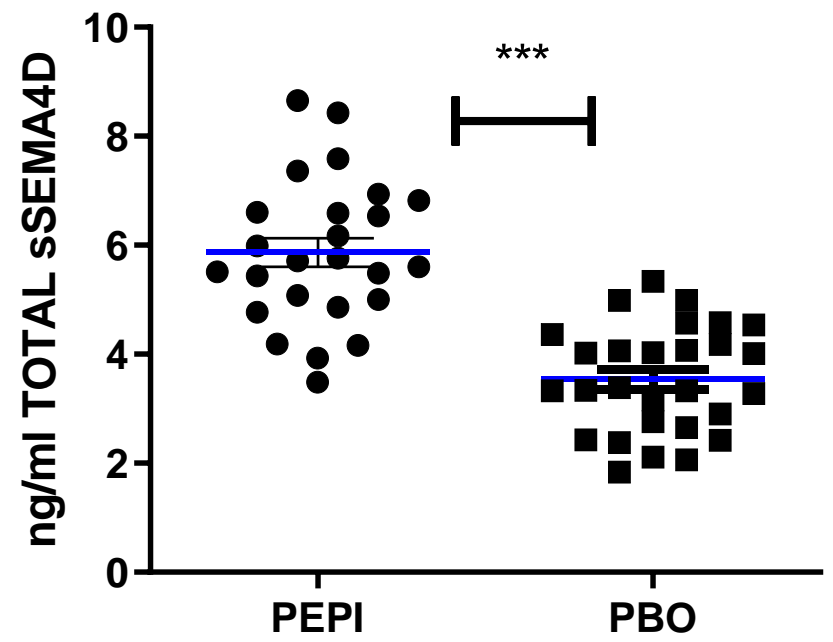


Pepinemab and sSEMA4D levels in cerebrospinal fluid (CSF)

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



Pepinemab : sSEMA4D complex increases in subjects dosed with pepinemab – suggesting target engagement



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
- A Phase 3 trial of pepinemab in HD is in the protocol design stage