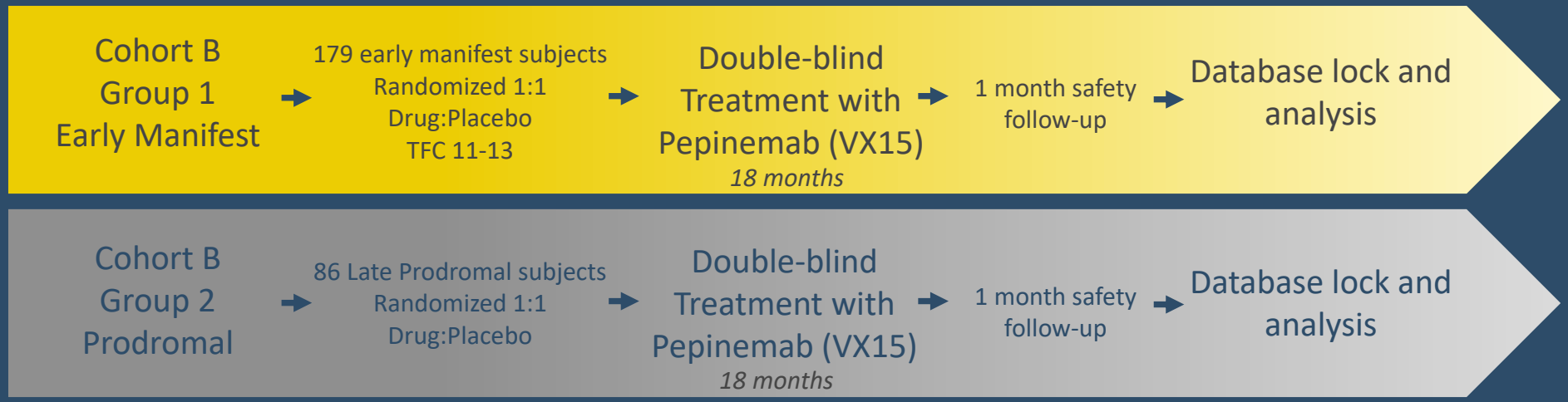
Pepinemab – Anti-SEMA4D Antibody Treatment for Huntington's Disease

■ Unique Targets ■ Novel Mechanisms ■ New Medicines

SIGNAL: RANDOMIZED PLACEBO-CONTROLLED TRIAL IN SUBJECTS WITH EARLY HD



Key Study Objectives

Safety and tolerability

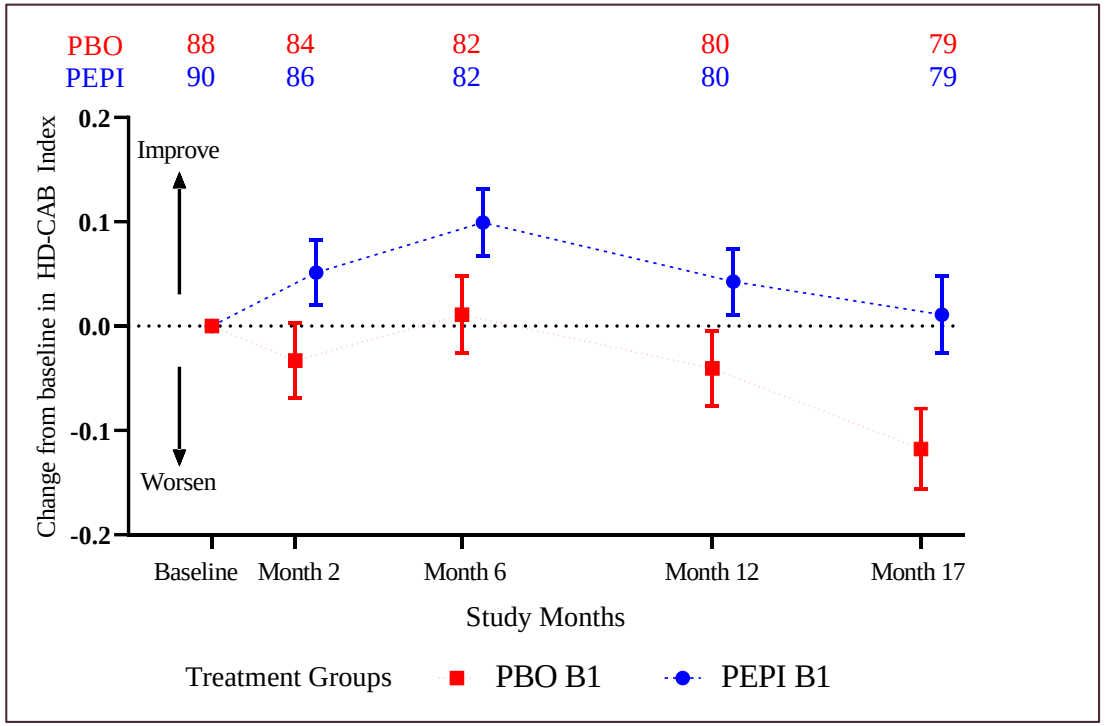
Co-primary endpoints: HD-CAB and Clinical global impression of change (CGIC)

Secondary and Exploratory including Brain imaging measures

COGNITIVE ASSESSMENT BATTERY (HD-CAB)

Early Manifest HD: Intent to treat population (mITT)

HD-CAB Composite Index of 6 Cognitive Assessments



HD-CAB Composite Index:

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

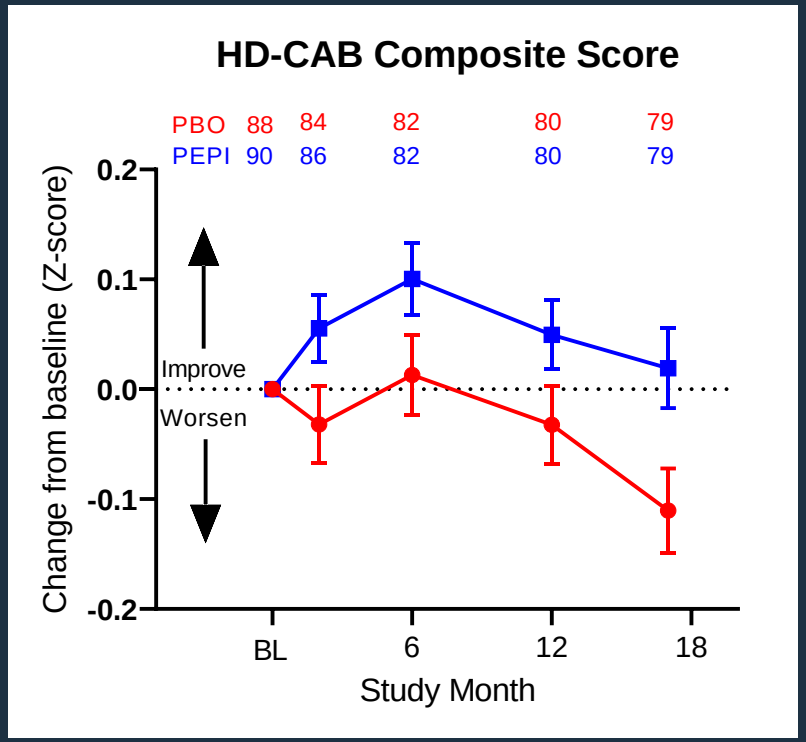
Co-Primary: Two-item HD Cognitive Assessment

LS Mean Difference Estimate (95% CI)	One-sided p-value	Favors PEPI	Critical value
OTS: -1.98 (-4.00, 0.05)	**0.028**	**Yes**	**Yes [0.025]**
PTAP: 1.43 (-0.37, 3.23)	**0.060**		

HD-CAB STRATIFIED BY BASELINE MoCA

(Montreal Cognitive Assessment, Post-hoc Subgroup Analysis)

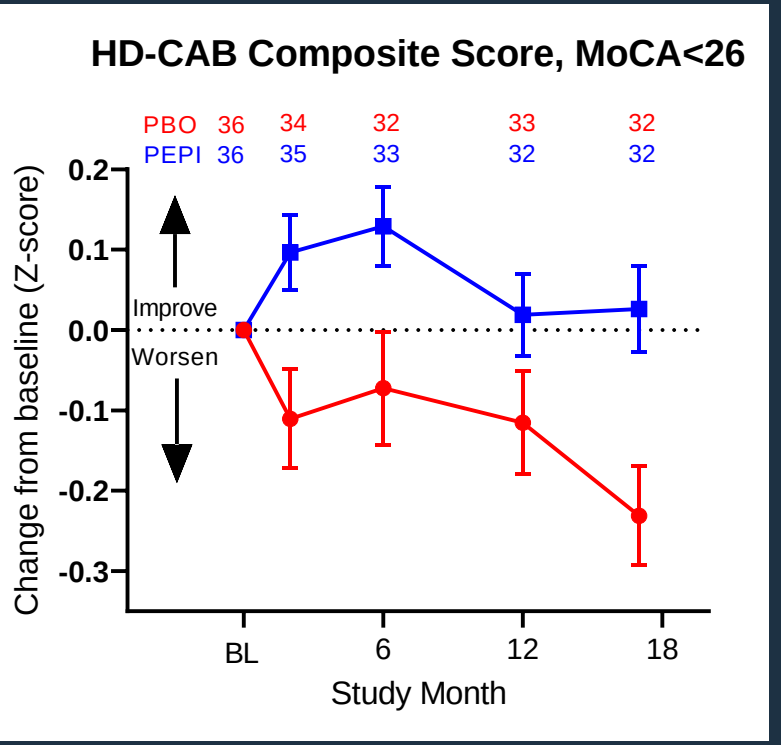
mITT



LS Mean Estimate (SE), month 17

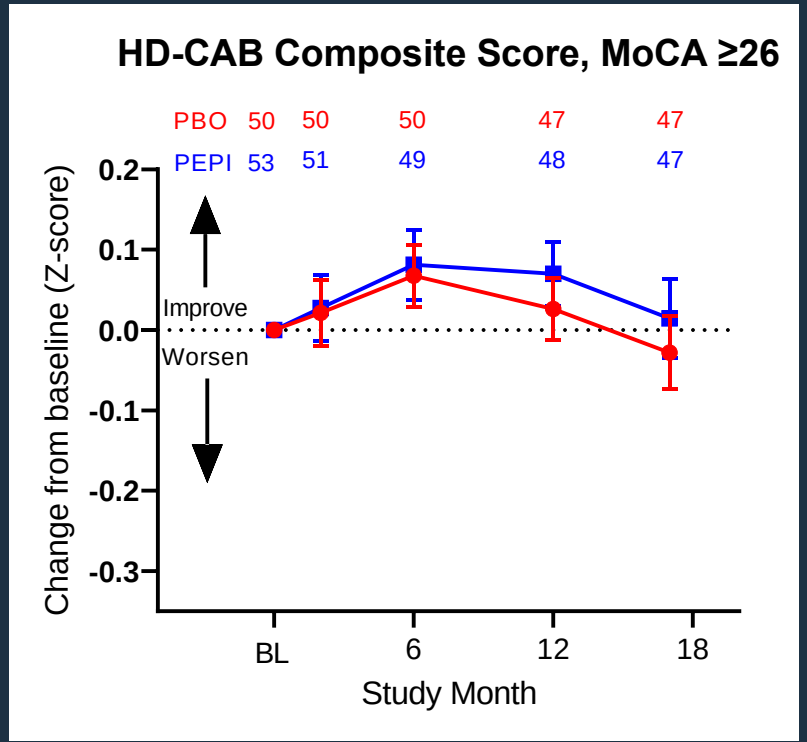
mITT: 0.13 (0.05), **p=0.007**

MoCA < 26



MoCA <26: 0.24 (0.08), **p=0.0025**

MoCA ≥ 26



MoCA ≥26: 0.06 (0.06), **p=0.197**

Stratification by MoCA has different impact on different cognitive domains

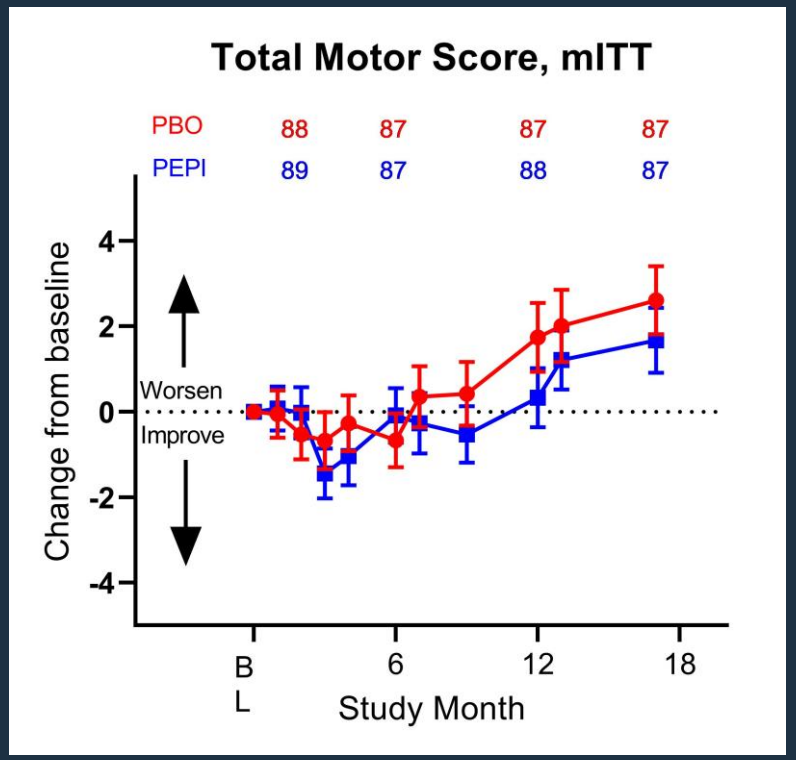
Population		LS mean difference (SE) PEPI-PBO month 17			p-value		
		HD-CAB	OTS	PTAP	HD-CAB	OTS	PTAP
MoCA<26	n=32	0.244 (0.08)	-1.872 (1.44)	1.89 (1.10)	0.0025	0.099	0.044
MoCA≥26	n=47	0.055 (0.06)	-1.730 (1.34)	1.086 (1.32)			
Total mITT	n=79				0.007	0.028	0.060

The larger the difference between LSQ mean difference (PEPI-PBO) in subgroup MoCA<26 and MoCA≥26, the greater the assymetric distribution between the two subgroups and the greater the impact of stratification on p-values. In the absence of asymmetry, stratification has a negative impact on p=value because it makes group size smaller. Hence, OTS, which measures executive function, a cognitive domain that appears to decline earlier in disease progression than PTAP, which measures processing speed, has a p-value that increases with stratification whereas the PTAP p-value declines (improves significance). This is particularly striking for the HD-CAB Composite at month 6.

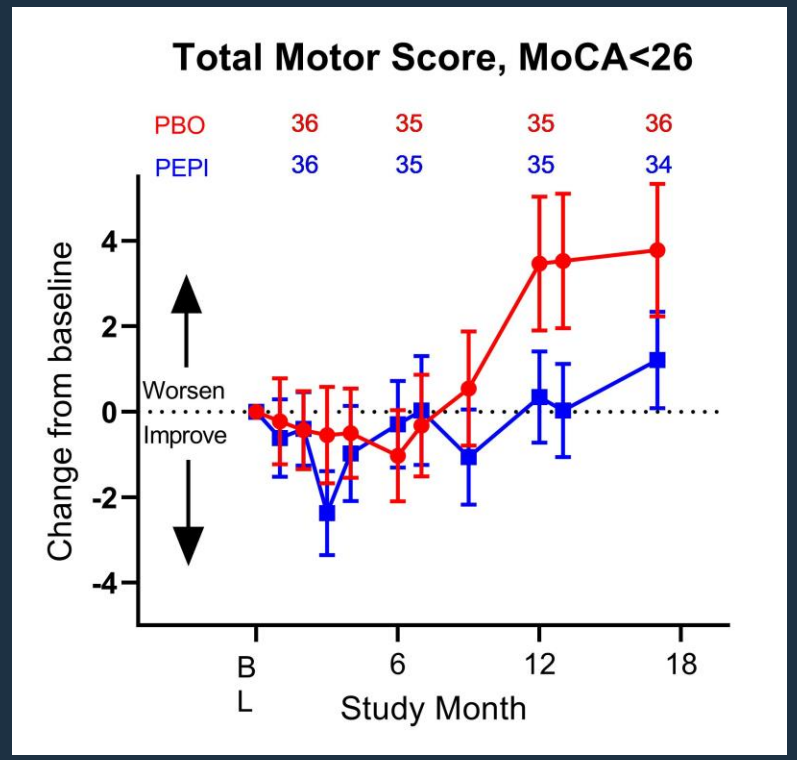
TOTAL MOTOR SCORE (TMS) STRATIFIED BY BASELINE MoCA

(Montreal Cognitive Assessment, Post-hoc Subgroup Analysis)

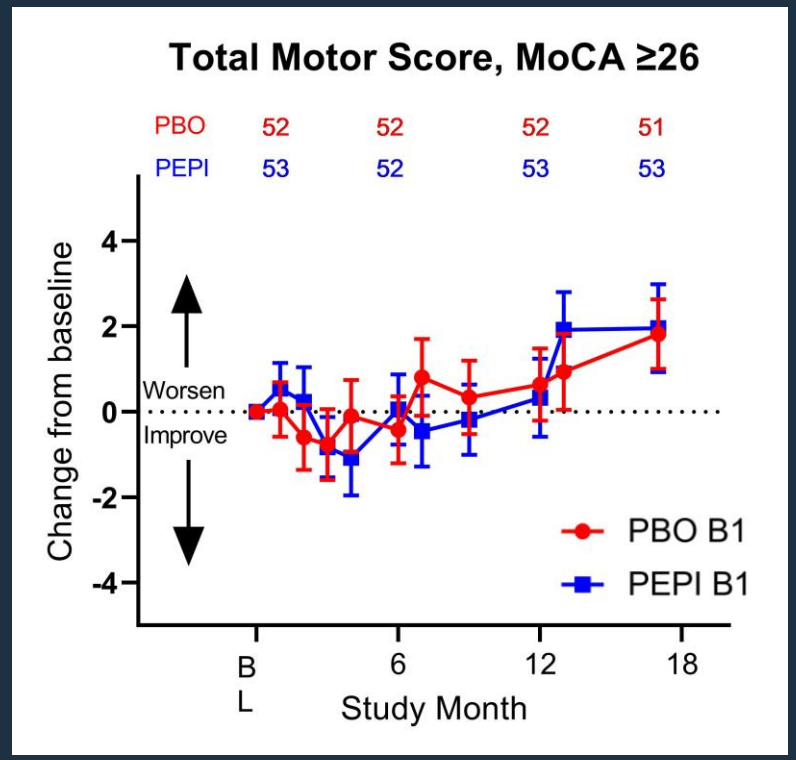
mITT



MoCA < 26

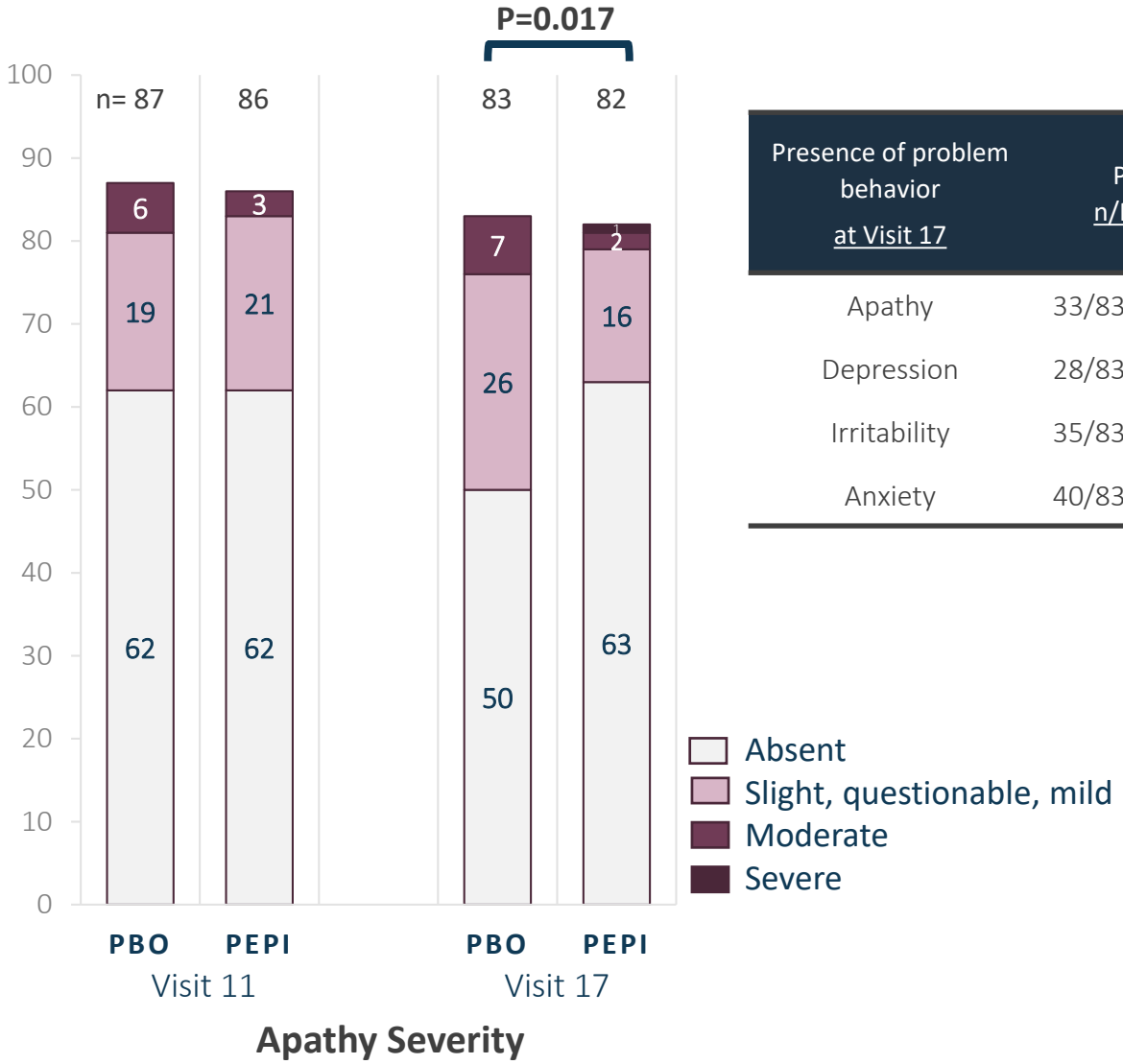


MoCA ≥ 26



PEPINEMAB-RELATED IMPROVEMENT IN PBA-s APATHY SEVERITY SCORE

Several HD studies suggest that among behavioral measures apathy severity correlates best with disease progression and correlates with cognition



Presence of problem behavior at Visit 17	PBO n/N (%)	PEPI n/N (%)	One-Sided p-value (+ Favors PEPI)
Apathy	33/83 (39.76)	19/82 (23.17)	**0.017 (+)**
Depression	28/83 (33.73)	16/82 (19.51)	0.030 (+)
Irritability	35/83 (42.17)	32/82 (39.02)	0.41 (+)
Anxiety	40/83 (48.19)	40/82 (48.78)	0.60 (-)

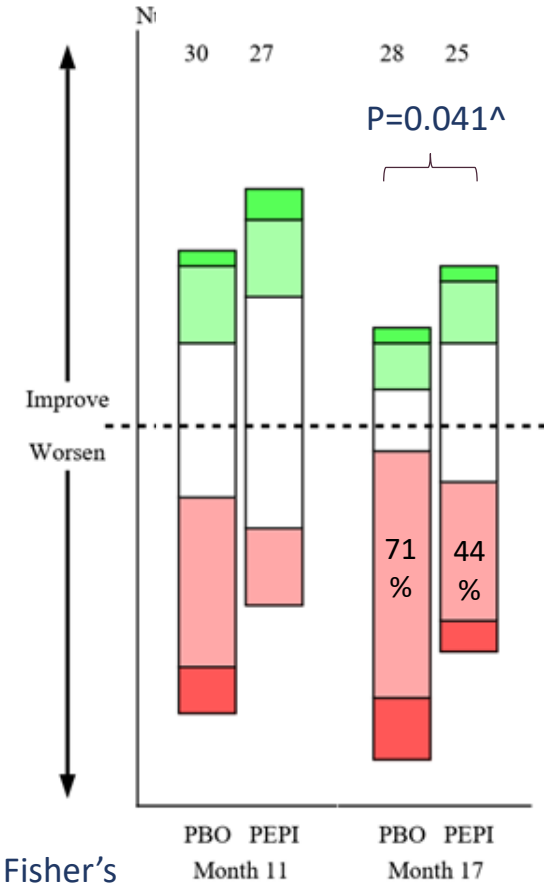
CO-PRIMARY 2: CGIC

Post-hoc Subgroup Analysis, Early Manifest HD

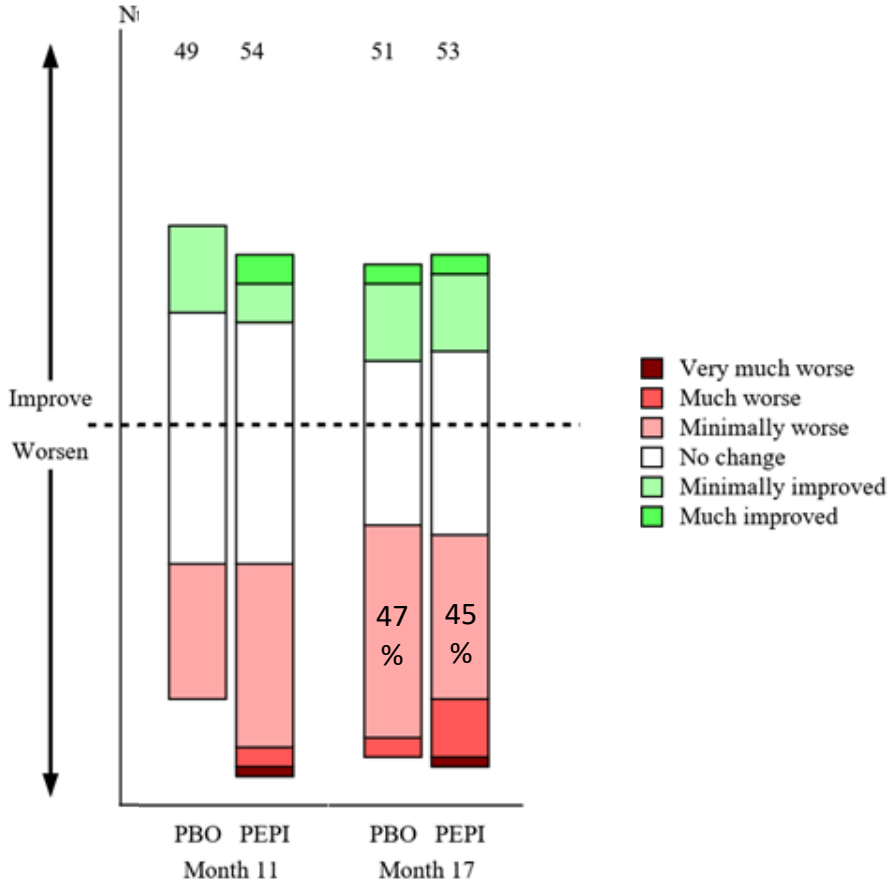
Subjects were less likely to experience decline in CGIC following treatment with pepinemab compared to placebo.

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

CGIC – Subjects with Baseline UHDRS TFC 11



CGIC – Subjects with Baseline UHDRS TFC 12 and 13

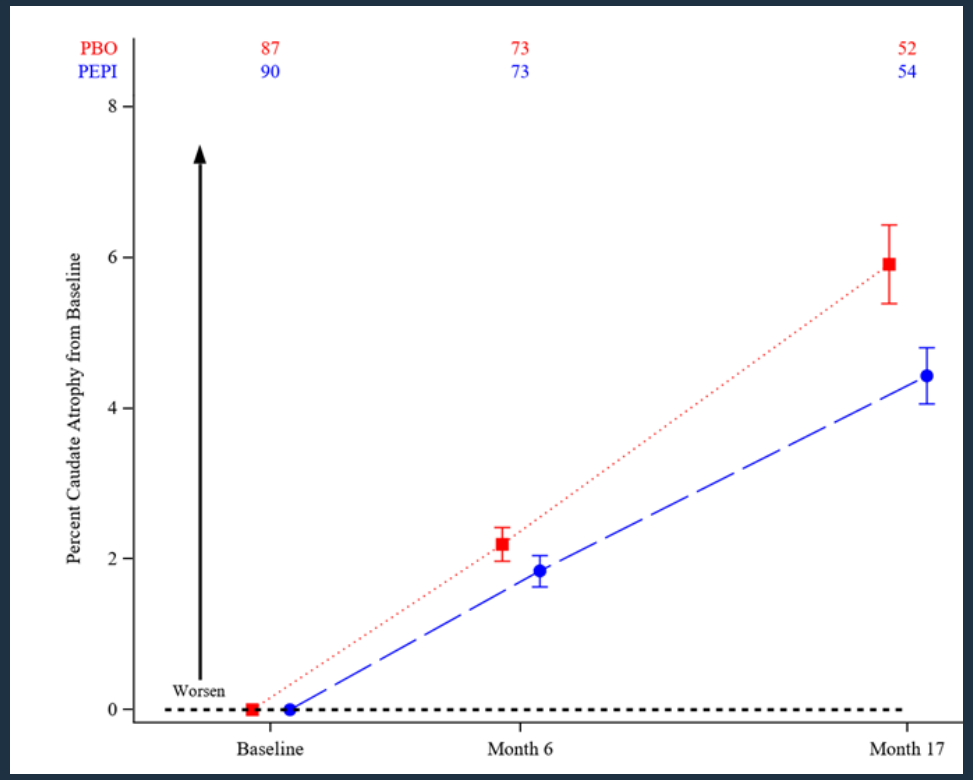


^nominal one-sided p-value, Fisher's exact test for worsening score

PEPINEMAB REDUCES BRAIN ATROPHY

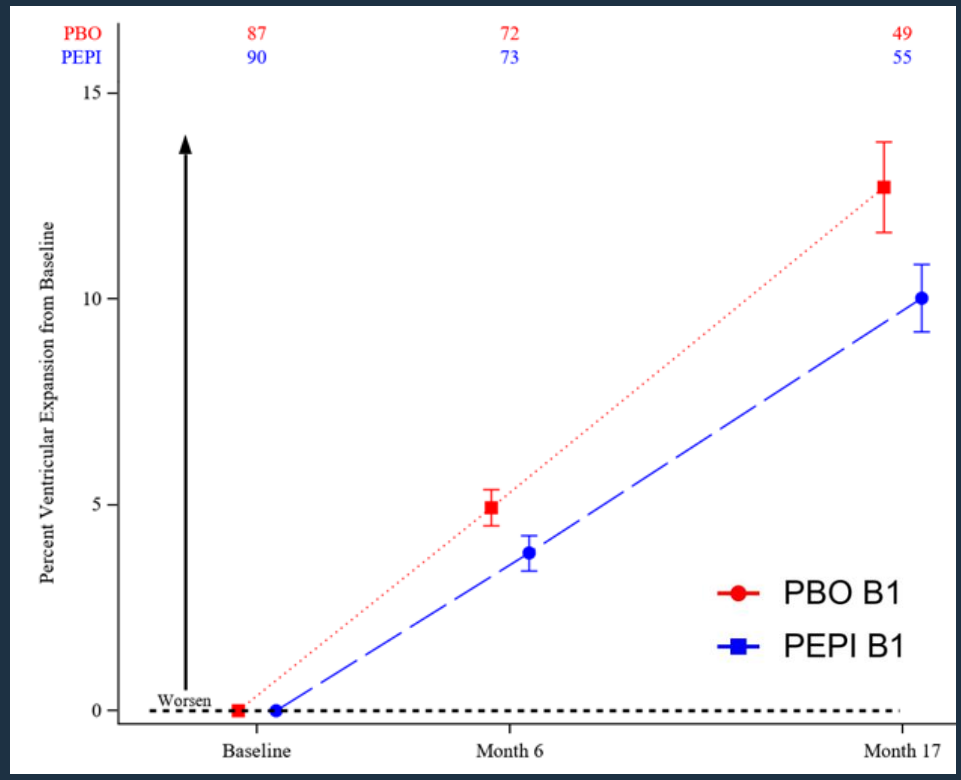
Volumetric MRI– Boundary Shift Integral Analysis
Early Manifest HD

CBSI (caudate atrophy)



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

VBSI (ventricular expansion)

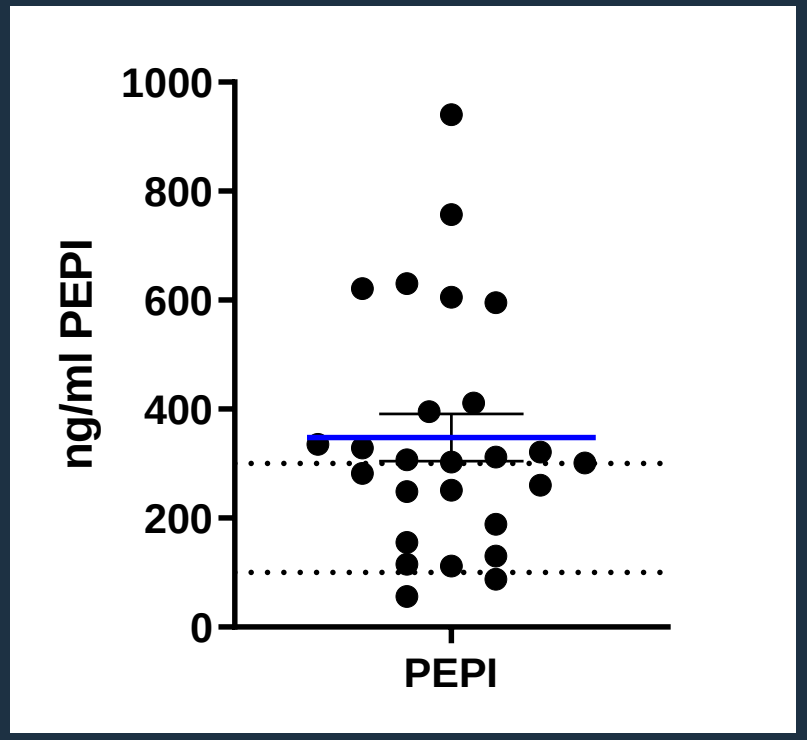


VBSI:-2.47 (-5.04, 0.10);
p = 0.060

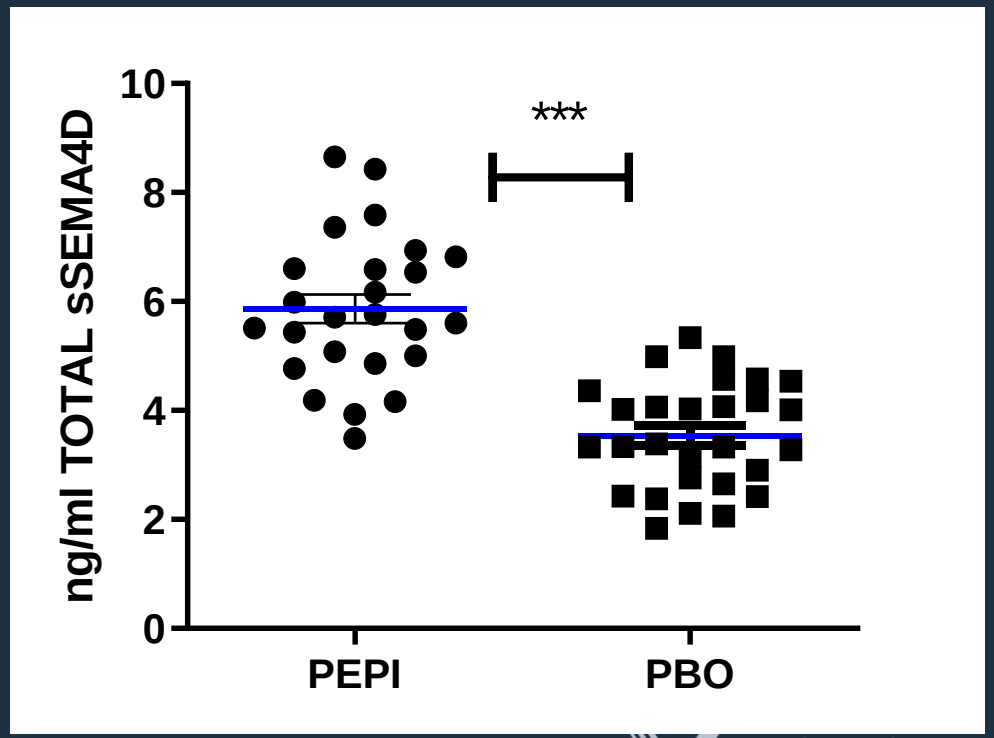
PEPINEMAB IS DETECTED AT PROJECTED LEVELS IN CSF

PK/PD

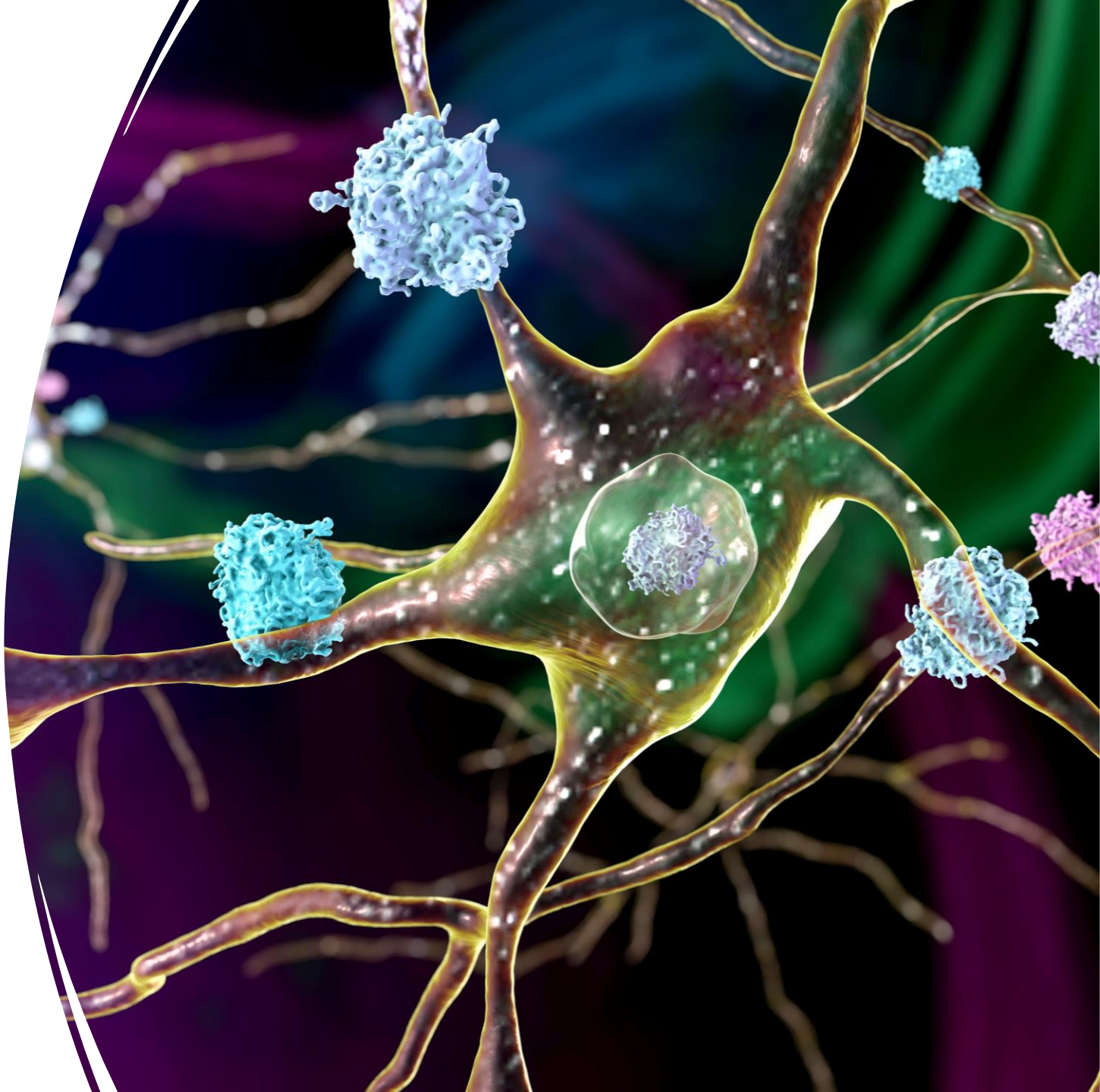
Most subjects dosed with pepinemab have at least saturating levels (100-300 ng/ml) in CSF



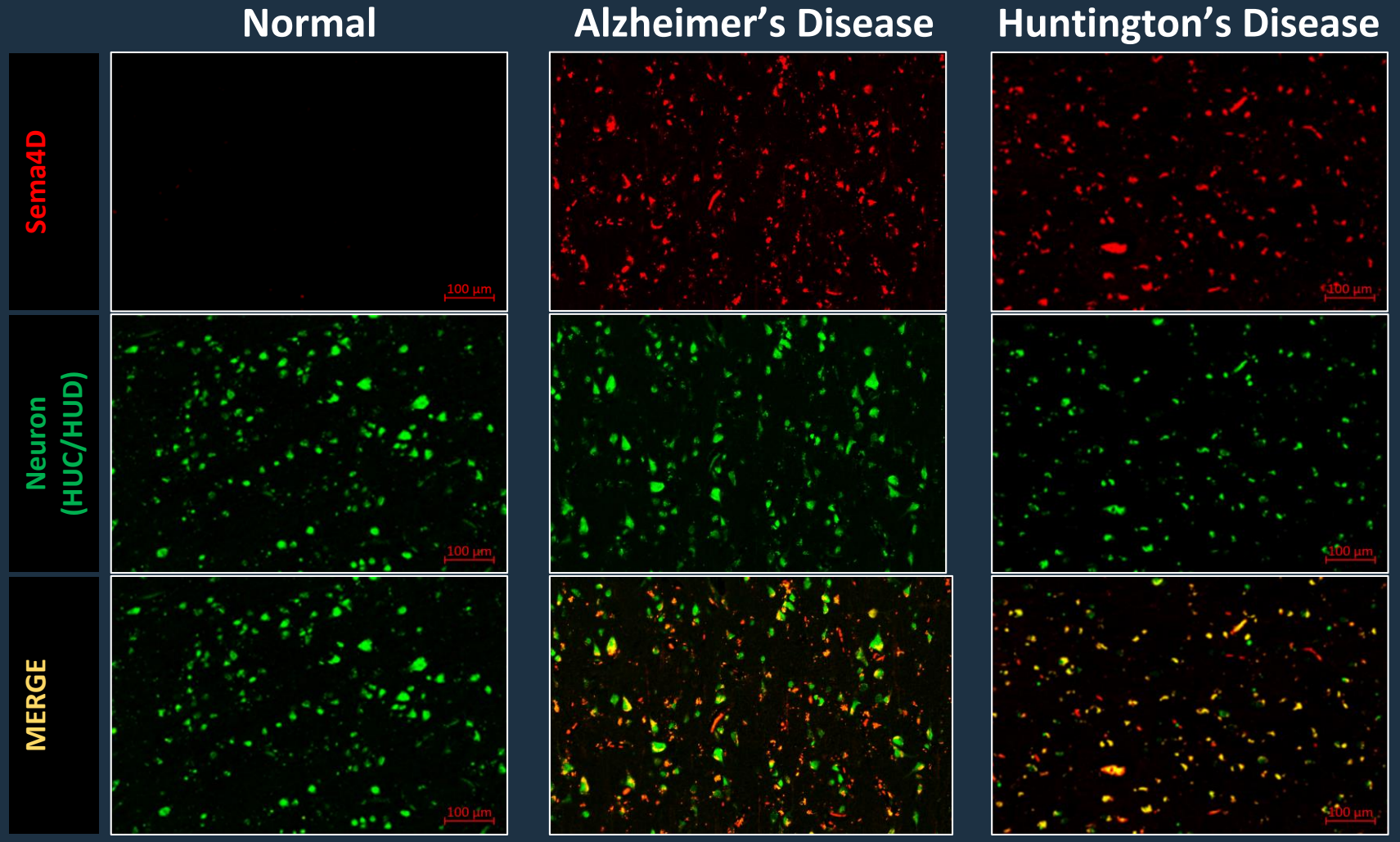
sSEMA4D increases in subjects dosed with pepinemab – suggesting target engagement



MECHANISM OF ACTION STUDIES



SEMA4D is upregulated in neurons during disease progression



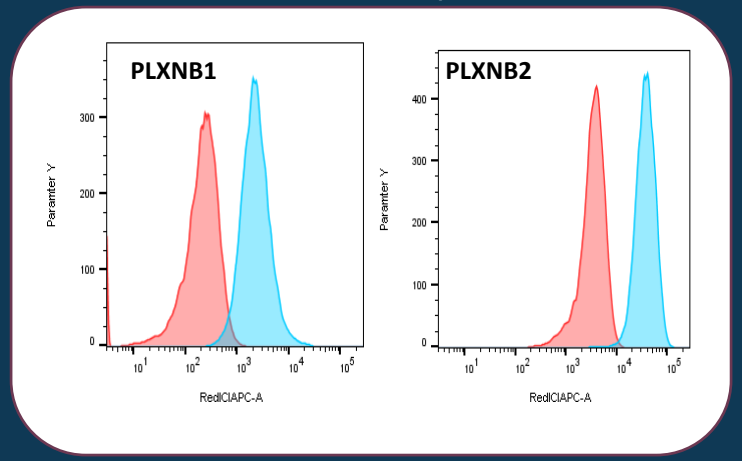
Human autopsy sections of frontal lobe

SEMA4D:PLXN-B1/B2 signaling

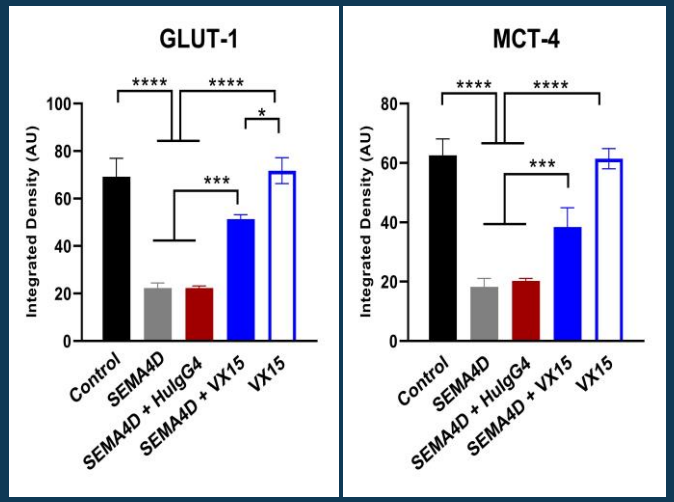
Astrocytes regulate energy substrates

Purified human astrocyte cultures

Plexin-receptors



rSEMA4D ± anti-SEMA4D



GLUT-1 glucose transporter

MCT-4 lactose transporter

SEMA4D antibody blockade inhibits microglial activation and improves disease phenotype in preclinical models

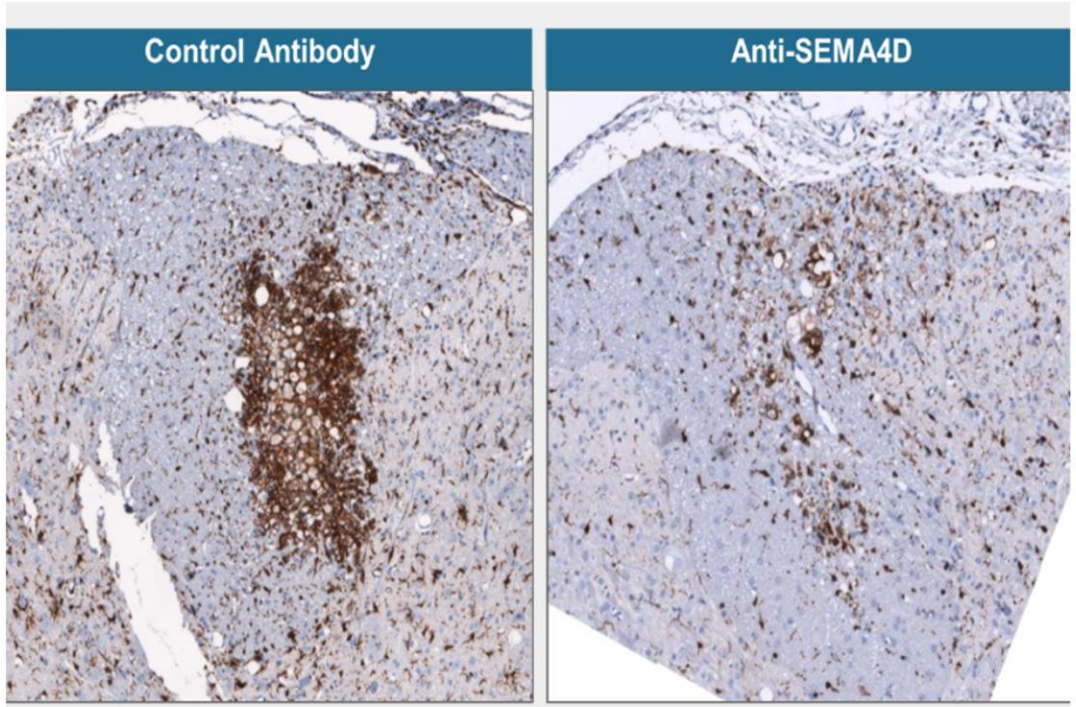
SEMA4D compromises blood–brain barrier, activates microglia, and inhibits remyelination in neurodegenerative disease

Ernest S. Smith [a], Alan Jonason [a], Christine Reilly [a], Janaki Veeraraghavan [a], Terrence Fisher [a], Michael Doherty [a], Ekaterina Klimatcheva [a], Crystal Mallow [a], Chad Cornelius [a], John E. Leonard [a], Nicola Marchi [b], Damir Janigro [b], Azeb Tadesse Argaw [c], Trinh Pham [c], Jennifer Seils [a], Holm Bussler [a], Sebold Torno [a], Renee Kirk [a], Alan Howell [a], Elizabeth E. Evans [a], Mark Paris [a], William J. Bowers [a], Gareth John [c], Maurice Zauderer [a,*]

[a] Vaccinex, Inc., Rochester, NY 14620, USA

2014 Neurobiology of Disease

SEMA4D blocking antibody prevents activation of murine Iba-1+ microglia at the site of demyelinated lesions in spinal cord.



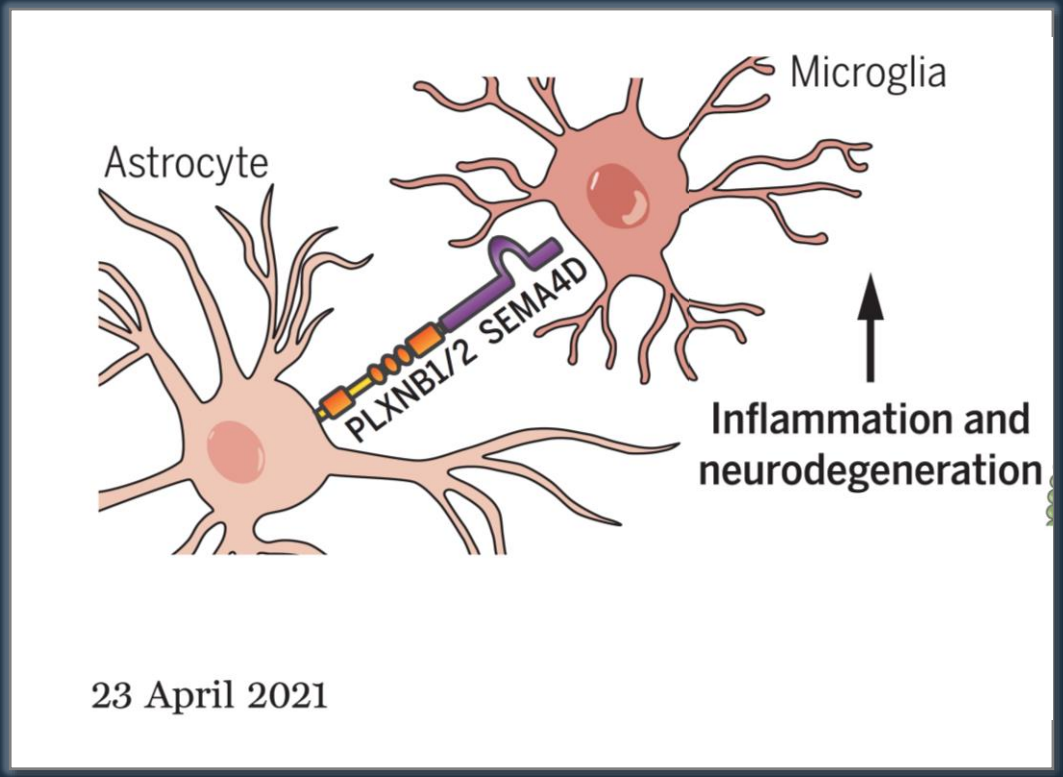
SEMA4D:PLXN-B1/B2 signaling
Cellular cross-talk in CNS

RESEARCH ARTICLE

NEUROSCIENCE

Barcoded viral tracing of single-cell interactions in central nervous system inflammation

Iain C. Clark[1,2]†, Cristina Gutiérrez-Vázquez[1]†, Michael A. Wheeler[1,3]†, Zhaorong Li[1,3], Veit Rothhammer[1,4], Mathias Linnerbauer[1,4], Liliana M. Sanmarco[1], Lydia Guo[1], Manon Blain[5], Stephanie E. J. Zandee[6], Chun-Cheih Chao[1], Katelyn V. Batterman[7], Marius Schwabenland[8], Peter Lotfy[1,3], Amalia Tejeda-Velarde[1]‡, Patrick Hewson[1], Carolina Manganeli Polonio[1], Michael W. Shultis[1], Yasmin Salem[1], Emily C. Tjon[1], Pedro H. Fonseca-Castro[1], Davis M. Borucki[1], Kalil Alves de Lima[1], Agustin Plasencia[1], Adam R. Abate[9,10], Douglas L. Rosene[7], Kevin J. Hodgetts[1], Marco Prinz[8,11,12], Jack P. Antel[5], Alexandre Prat[6], Francisco J. Quintana[1,3]*



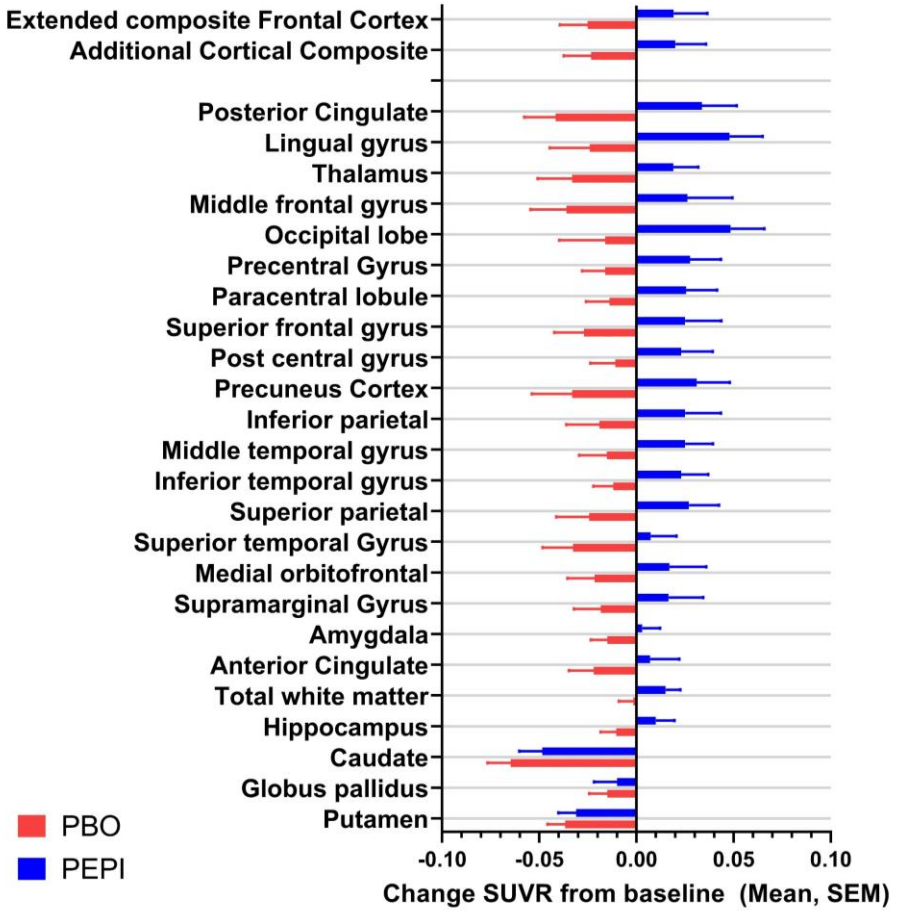
"we detected the activation of proinflammatory signatures and chemokine-mediated signaling in microglia connected to astrocytes displaying a high proinflammatory phenotype."

FDG-PET CORRELATES WITH COGNITIVE FUNCTION

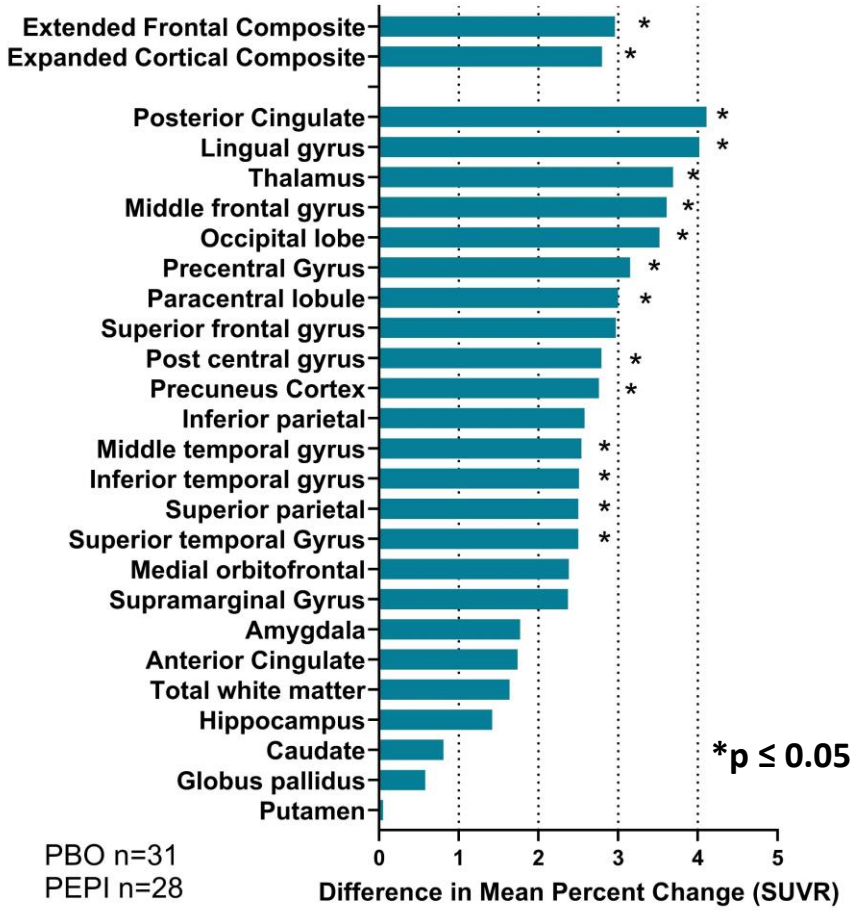
Early Manifest HD

Pepinemab treatment reverses loss of metabolic activity

FDG-PET Change SUVR
Early Manifest at Visit 18



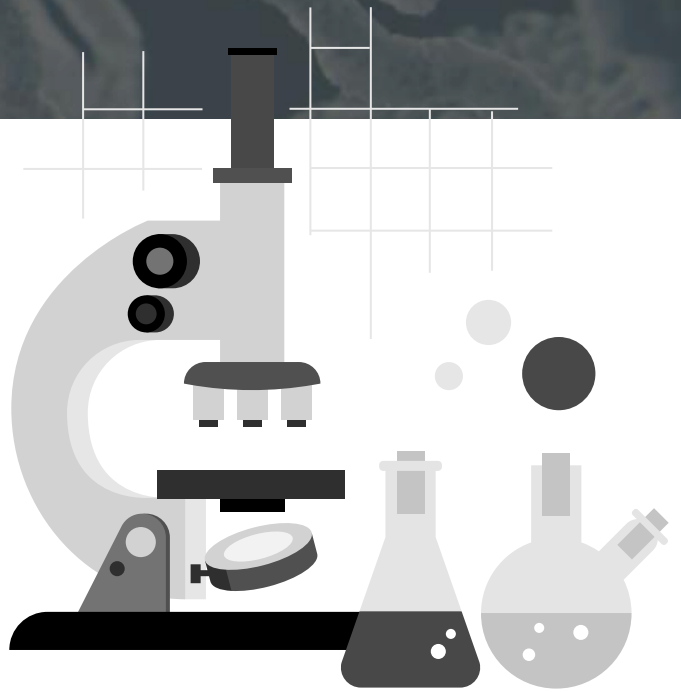
FDG-PET Difference in % Change SUVR (PEPI-PBO)
Early Manifest at Visit 18



Appendix

VACCINEX

Science in the Service of Medicine



DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Category	Cohort B1		Cohort B2	
	PBO N=88	PEPI N=91	PBO N=45	PEPI N=41
Age (years)	47.5 (10.6)	50.0 (11.4)	42.7 (10.8)	47.3 (10.8)
Sex, n (%)				
Female	48 (55)	44 (48)	27 (60)	23 (56)
Male	40 (45)	47 (52)	18 (40)	18 (44)
Race, n (%)				
White	82 (93)	88 (97)	45 (100)	40 (98)
Black or African American	2 (2)	0	0	1 (2)
Asian	1 (1)	1 (1)	0	0
Multiple	0	1 (1)	0	0
Other	3 (3)	1 (1)	0	0
Ethnicity, n (%)				
Not Hispanic or Latino	84 (95)	87 (96)	45 (100)	40 (98)
Hispanic or Latino	4 (5)	4 (4)	0	1 (2)
Education (years)	15.5 (2.3)	14.7 (2.2)	15.7 (2.7)	15.4 (2.6)
Weight (kg)	75.5 (16.2)	79.9 (22.4)	79.6 (15.3)	83.9 (20.3)
Height (cm)	170.5 (9.5)	171.8 (10.3)	170.8 (9.9)	169.7 (9.6)
BMI (kg/m^2)	26.0 (5.6)	26.8 (6.0)	27.3 (5.0)	29.2 (7.1)
Time since HD symptom onset (years)	4.7 (3.7)	5.8 (4.9)	3.3 (4.3)	3.8 (4.2)
Time since clinical HD diagnosis (years) [a,b]	2.9 (3.2)	2.5 (2.6)	NA	NA
CAG repeat length	44.1 (3.8)	43.5 (3.1)	42.8 (2.3)	42.4 (2.7)
CAP score [c]	469.9 (95.9)	466.3 (84.6)	374.4 (72.4)	403.6 (98.1)

Abbreviations: CAG, cytosine, adenine, and guanine; CAP, CAG/age product; DCL, Diagnostic Confidence Level; HD, Huntington disease; HD-CAB, Huntington's Disease Cognitive Assessment Battery; ITI, inter-tap interval; ITT, intent-to-treat; NA, Not applicable; OTS, One Touch Stockings of Cambridge; PBO, placebo; PEPI, pepinemab; PTAP, Paced Tapping; SD, standard deviation; Tap-Speed, speeded index finger tapping; TFC, Total Functional Capacity; UHDRS, Unified Huntington's Disease Rating Scale.

Note(s): Column header counts and denominators are the number of subjects in the ITT population. The sample sizes are the number of subjects in the ITT population with non-missing data.

a) Cohort B2 clinical HD diagnosis data has been excluded from this table.

b) Only the year of clinical HD diagnosis is reported on the case report form; to calculate time since HD diagnosis, the month and day of HD diagnosis is imputed to January 1.

c) CAP score=age × (CAG repeat length33.66). The relevant inclusion criterion requires a CAP score>200.

d) Score ranging from 0 to 13; higher scores indicate better functioning.

e) Time to a correct response (averaged over all trials per visit); lower values indicate better performance.

f) Tapping consistency measured as the reciprocal of the average standard deviation of the ITI durations (over all trials per visit); higher scores indicate better performance.

g) Calculated from observed value at baseline

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

(Continued)

Category	Cohort B1		Cohort B2	
	PBO N=88	PEPI N=91	PBO N=45	PEPI N=41
UHDRS-DCL at baseline, n (%)				
0, 1—Normal or non-specific signs	0	0	0	0
2—May be HD signs (50%-89% confident)	0	1 (1%)	28 (62%)	25 (61%)
3—Likely HD signs (90%-98% confident)	1 (1%)	1 (1%)	15 (33%)	13 (32%)
4—Unequivocal (>99% confident)	87 (99%)	89 (98%)	2 (4%)	3 (7%)
UHDRS-TFC at screening [d]	12.0 (0.9)	12.0 (0.8)	12.7 (0.6)	12.5 (0.8)
TFC 11 stratified subgroup	11.0 (0)	11.0 (0)	--	--
TFC 12-13 stratified subgroup	12.67 (0.47)	12.41 (0.50)	--	--
UHDRS-TFC at screening, n (%) [d]				
TFC 11	33 (38%)	29 (32%)	4 (9%)	7 (17%)
TFC 12	18 (20%)	37 (41%)	7 (16%)	5 (12%)
TFC 13	37 (42%)	25 (27%)	34 (76%)	29 (71%)
MoCA score	26.02 (2.04)	26.14 (2.30)	26.84 (2.17)	27.56 (1.80)
MoCA <26 stratified subgroup	23.97 (0.94)	23.78 (1.07)	--	--
MoCA ≥26 stratified subgroup	27.44 (1.21)	27.72 (1.34	--	--
MoCA at screening, n (%)				
MoCA <26 stratified subgroup	36 (40.9%)	36 (40.0%)	--	--
MoCA ≥26 stratified subgroup	52 (59.1%)	54 (60.0%)	--	--
PBA-s Apathy severity n (%) [g]				
Absent	64 (73%)	67 (75%)		
Slight, questionable, or mild	20 (23%)	20 (22%)		
Moderate	4 (5%)	2 (2%)		
Caudate Brain Volume BSI (mL) [g]	5.13 (1.19)	4.83 (1.19)	5.93 (1.56)	5.92 (1.31)
Ventricular Volume BSI (mL) [g]	32.7 (18.2)	35.2 (21.8)	19.5 (12.1)	21.4 (8.5)

Abbreviations: CAG, cytosine, adenine, and guanine; CAP, CAG/age product; DCL, Diagnostic Confidence Level; HD, Huntington disease; HD-CAB, Huntington's Disease Cognitive Assessment Battery; ITI, inter-tap interval; ITT, intent-to-treat; NA, Not applicable; OTS, One Touch Stockings of Cambridge; PBO, placebo; PEPI, pepinemab; PTAP, Paced Tapping; SD, standard deviation; Tap-Speed, speeded index finger tapping; TFC, Total Functional Capacity; UHDRS, Unified Huntington's Disease Rating Scale.

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g) Calculated from observed value at baseline

Vaccinex Selected References, Neurology

1. Smith ES, Jonason A, Reilly C, Veeraraghavan J, Fisher T, Doherty M, Klimatcheva E, Mallow C, Cornelius C, Leonard JE, Marchi N, Janigro D, Argaw AT, Pham T, Seils J, Bussler H, Torno S, Kirk R, Howell A, Evans EE, Paris M, Bowers WJ, John G, Zauderer M. **SEMA4D compromises blood-brain barrier, activates microglia, and inhibits remyelination in neurodegenerative disease**. Neurobiol Dis. 2014 Oct 18;73C:254-268. doi: 10.1016/j.nbd.2014.10.008. http://www.sciencedirect.com/science/article/pii/S0969996114003015

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