



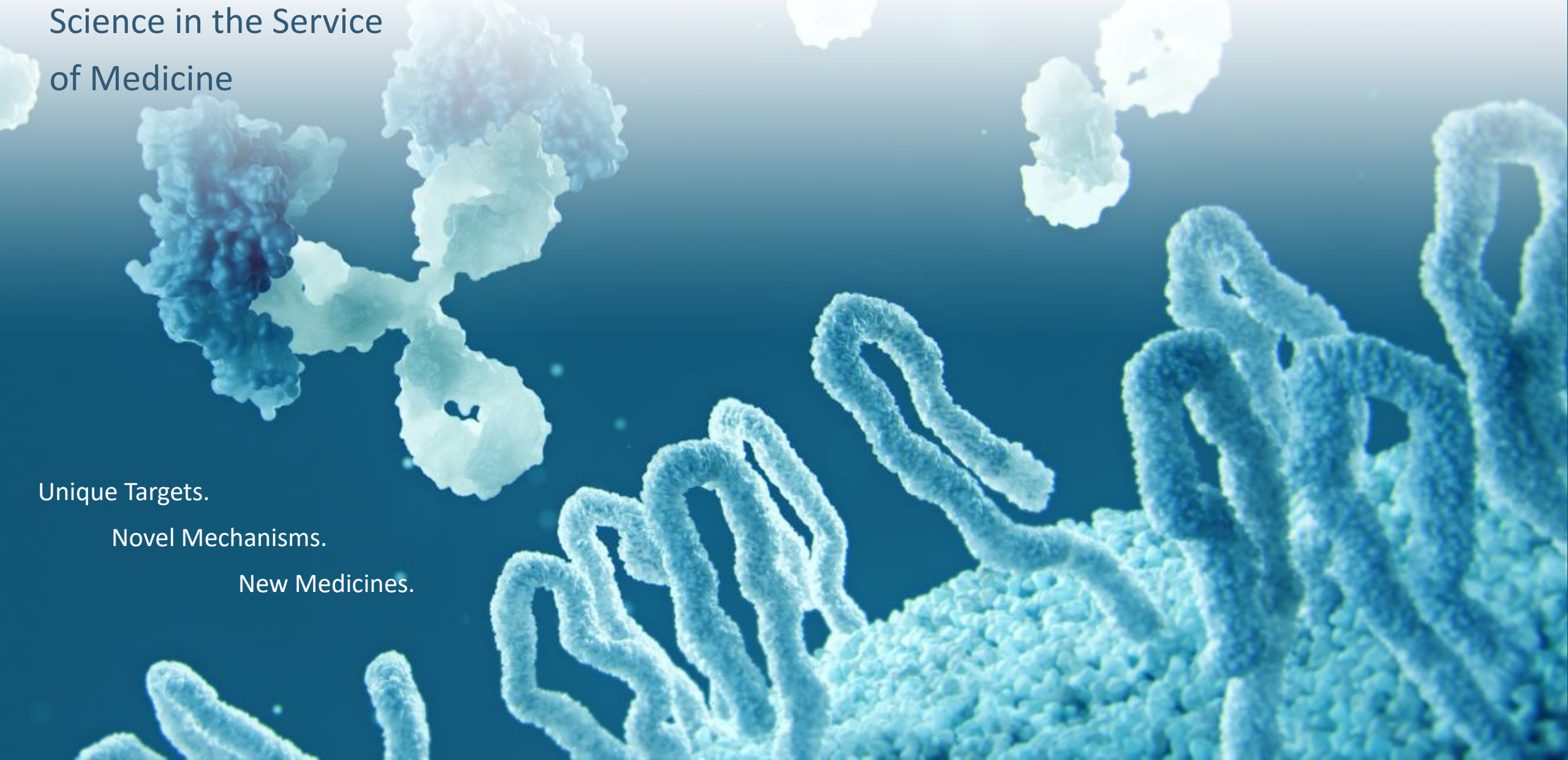
Pepinemab - SEMA4D Antibody: Potential Treatment for Neurodegenerative Disease

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Novel Mechanisms.

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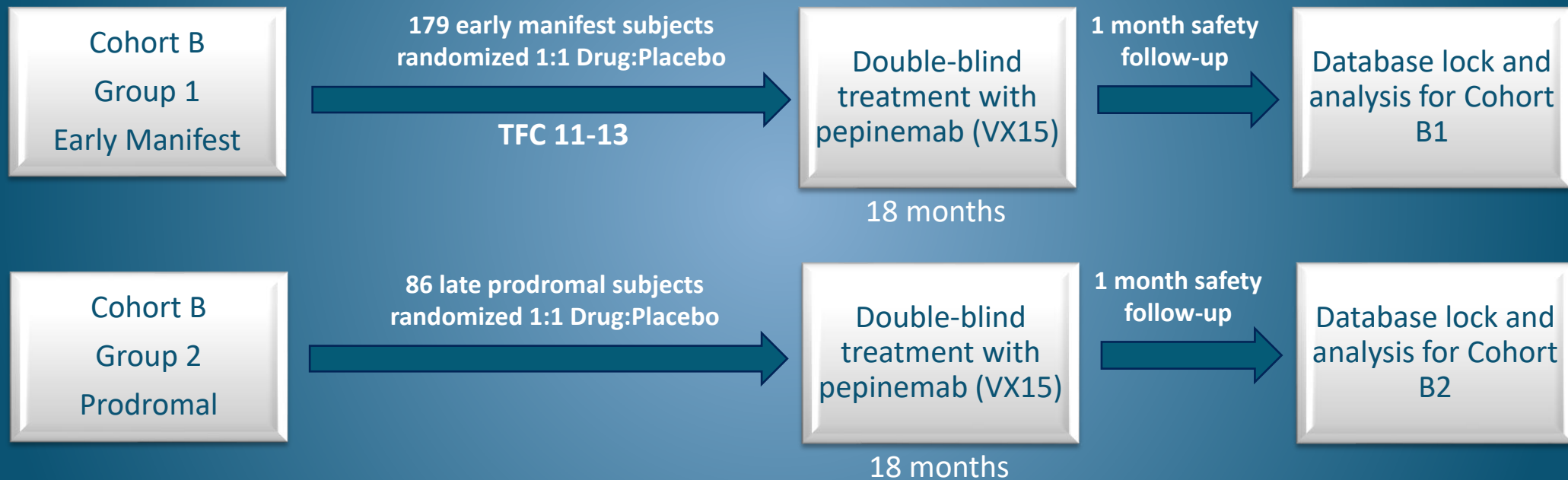
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SIGNAL: randomized placebo controlled trial in subjects with early HD



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

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 Battery: Cohort A, Early Manifest Effect Size

SIGNAL Cohort A: Effect Size of Early Manifest HD-CAB Components

Cognitive Assessment	Effect Size (Cohen's D)
HD-CAB Composite	0.49
OTS	0.45
PTAP	0.38
SDMT	0.10

Effect sizes based on six month slope from baseline to end of Month 6 during the double-blind treatment period in 15 participants with UHDRS-TFC score ≥ 11 and a previous definitive diagnosis of HD.

Cognitive Assessment

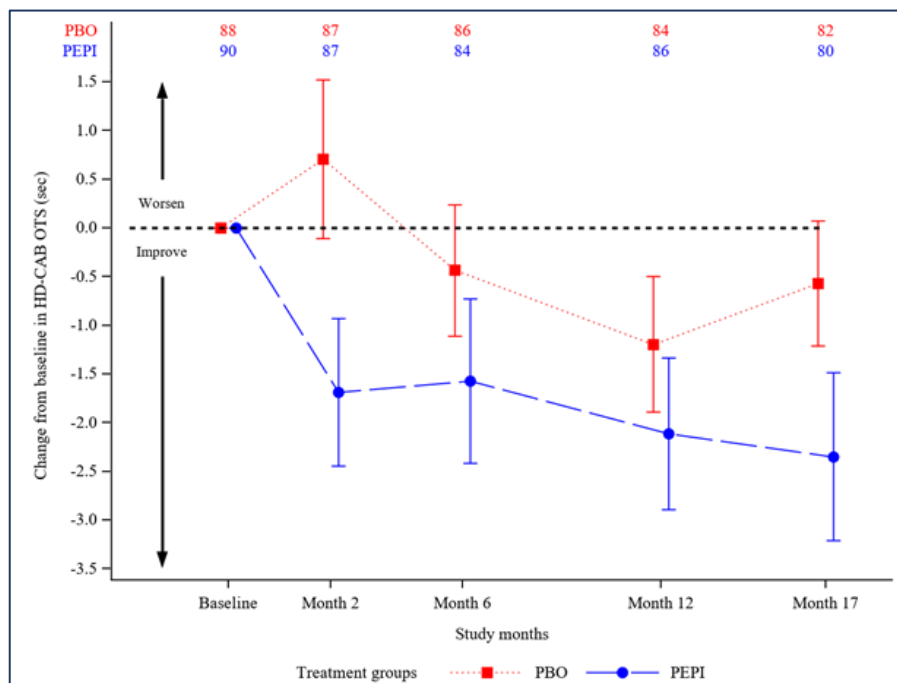
Co-Primary 1a: Test of Planning and Memory

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

1a: One Touch Stockings

Early Manifest HD

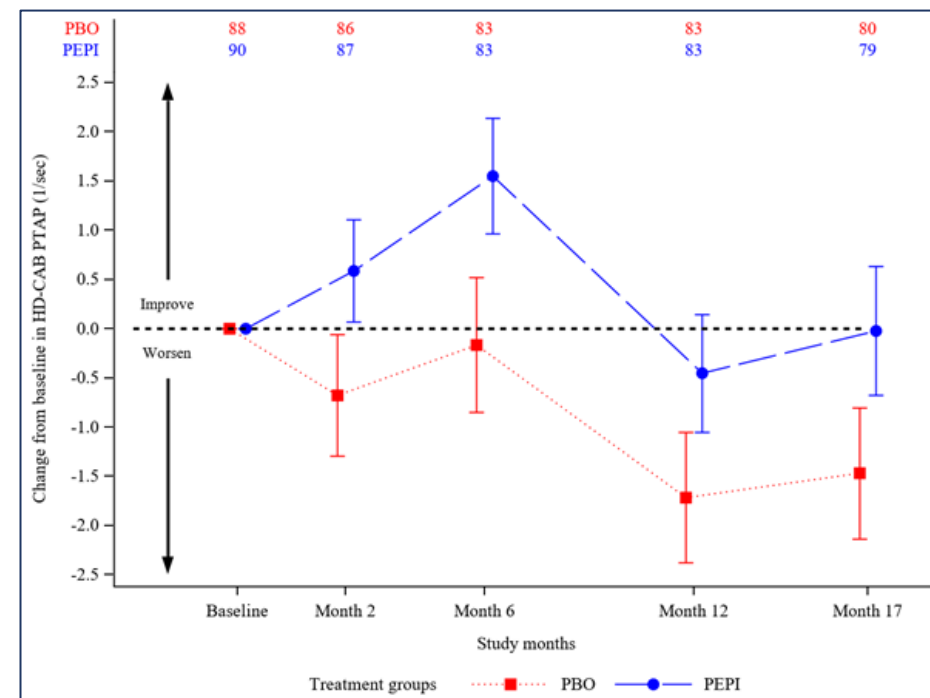
One-sided p-value	Favors PEPI	Success [Critical value]
0.028	Yes	No [0.025] [0.0125]



1b: Paced Finger Tapping Task

Early Manifest HD

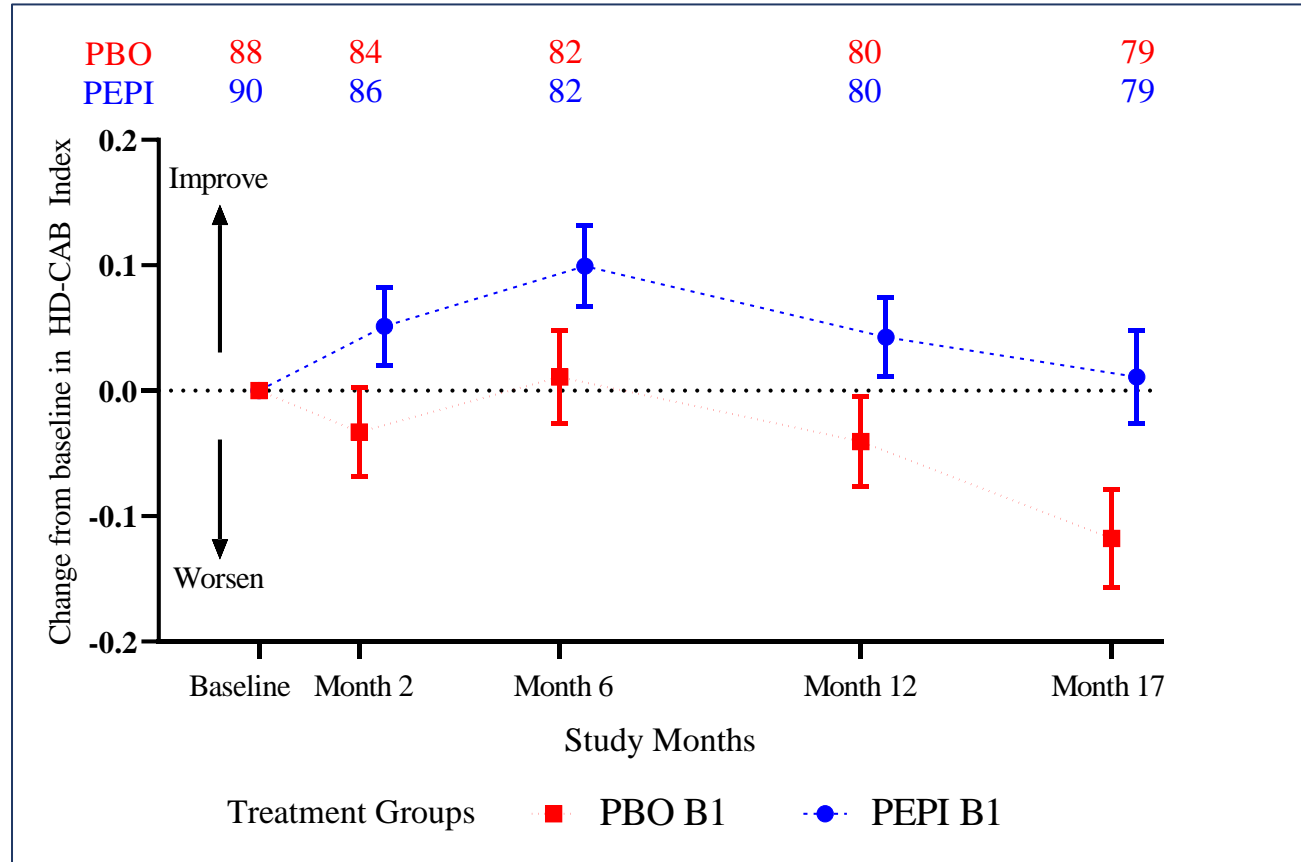
One-sided p-value	Favors PEPI	Success [Critical value]
0.06	Yes	No [0.025] [0.0125]



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

HD-CAB Composite
Index of 6 Cognitive
Assessments

Early manifest HD



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

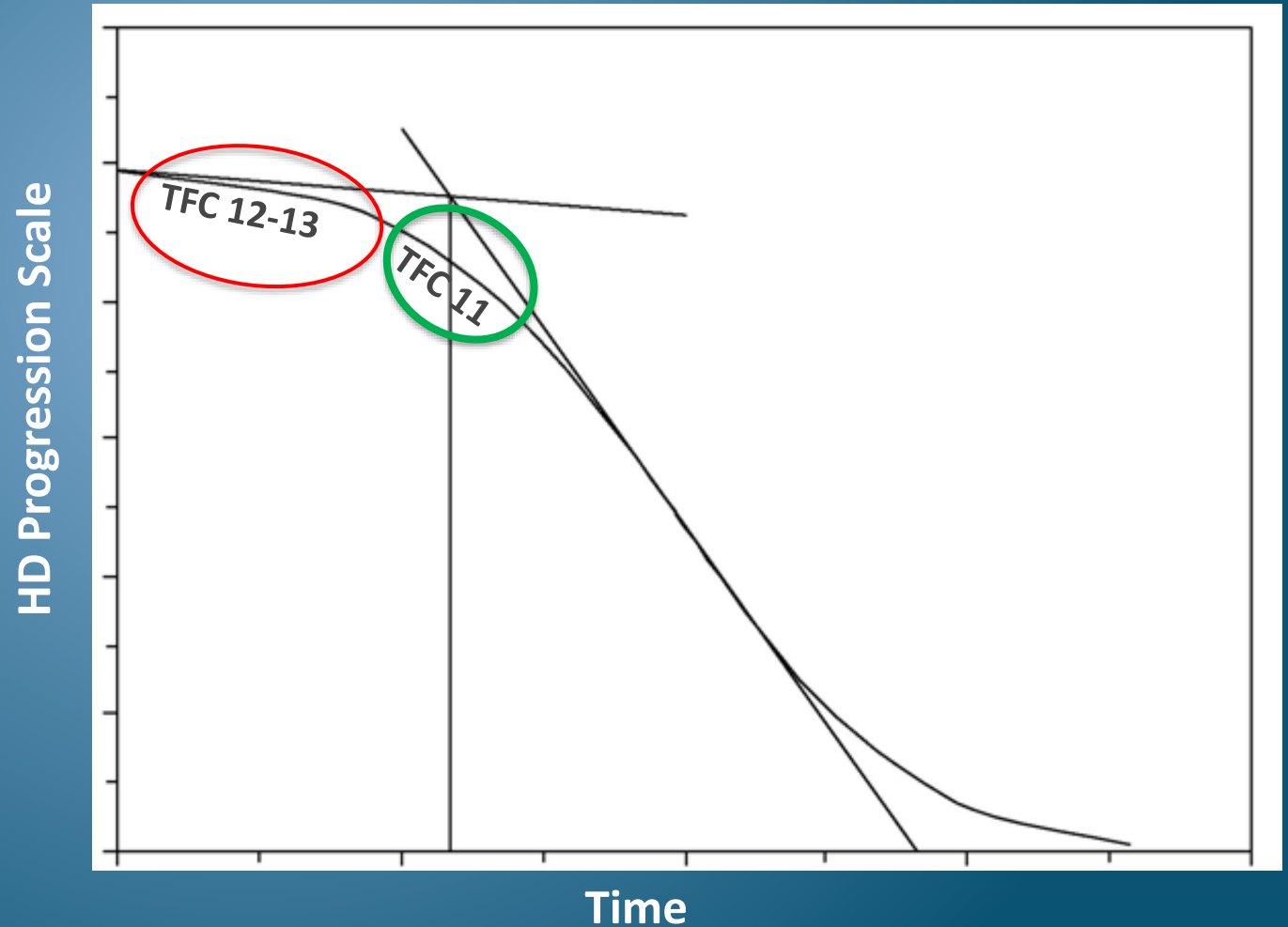
Cognitive Assessment Battery: Post-hoc sensitivity analysis, HD-CAB Composite Score

Full 6-item Composite	P = 0.007 (1-sided)
Omitting OTS	P = 0.018 (1-sided)
Omitting OTS and PTAP	P = 0.046 (1-sided)

- 1) HD-CAB components that assess different cognitive domains need not contribute equally to the Composite Score. Relative contribution is likely dependent on stage of disease.
- 2) The Composite Score is a sensitive measure of the overall direction of change in all six components. This adds information not available from individual scores, and, as shown by sensitivity analysis, allows the Composite to be relatively independent of a single dominant component.

Total Functional Capacity (TFC) and HD disease progression

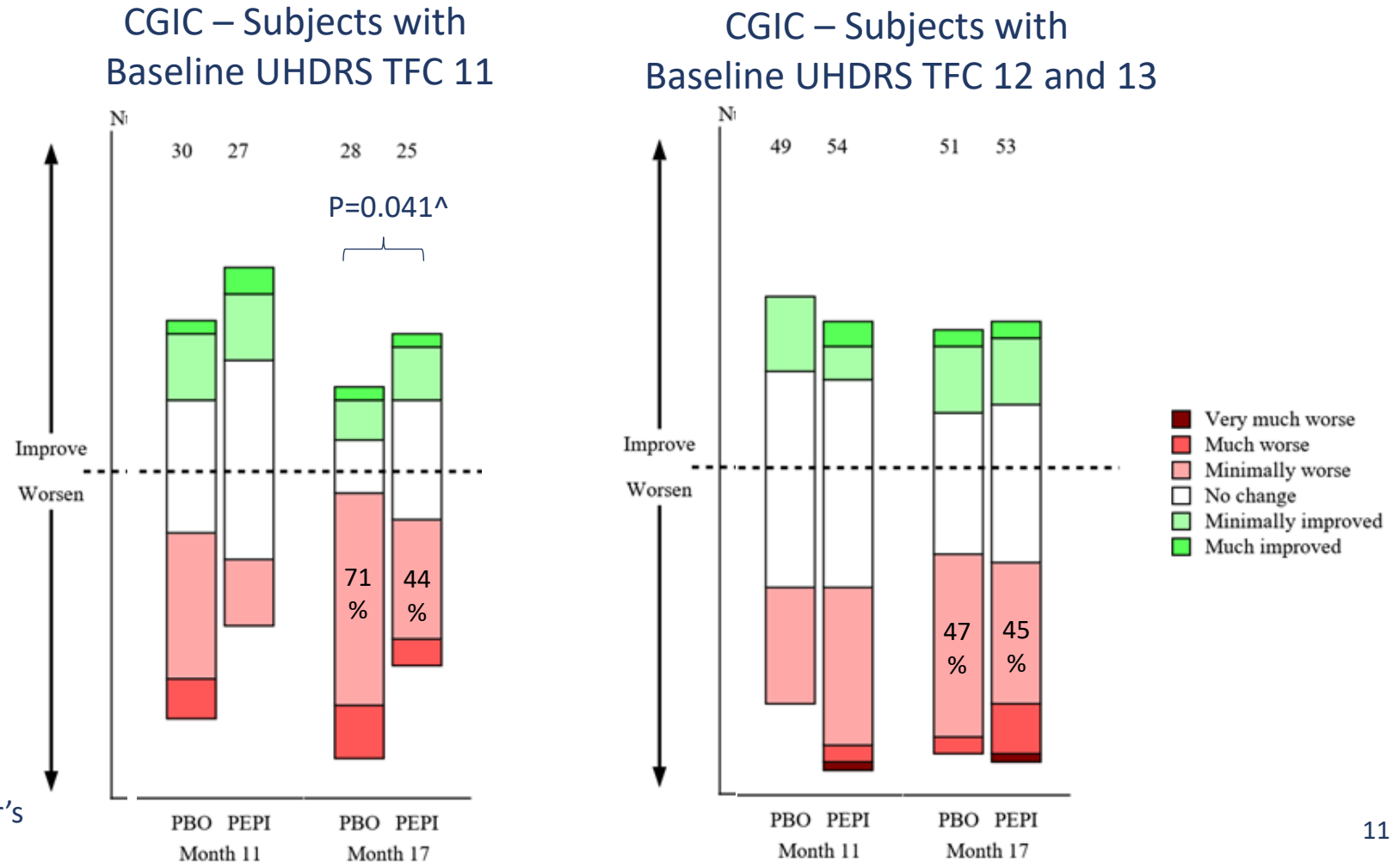
18-month change may be difficult to detect at top of TFC range (TFC 12-13)



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).



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