AAN 2022 Annual Meeting

P3: Movement Disorders: Huntington's Disease
Poster 007, Neighborhood 11
Saturday, April 2

Clinical evidence that treatment with pepinemab, a novel regulator of neuroinflammation, may provide cognitive benefit to patients with Huntington's and potentially other neurodegenerative diseases

Elizabeth Evans, Terrence Fisher, Vikas Mishra, Megan Boise, Amber Foster, Ernest Smith, John Leonard, Andrew Feigin, Eric Siemers, Maurice Zauderer

CONTACT: eevans@vaccinex.com

Disclosures

EE, TF, VM, MB, AF, ES, JL, MZ are full time employees at Vaccinex, Inc.

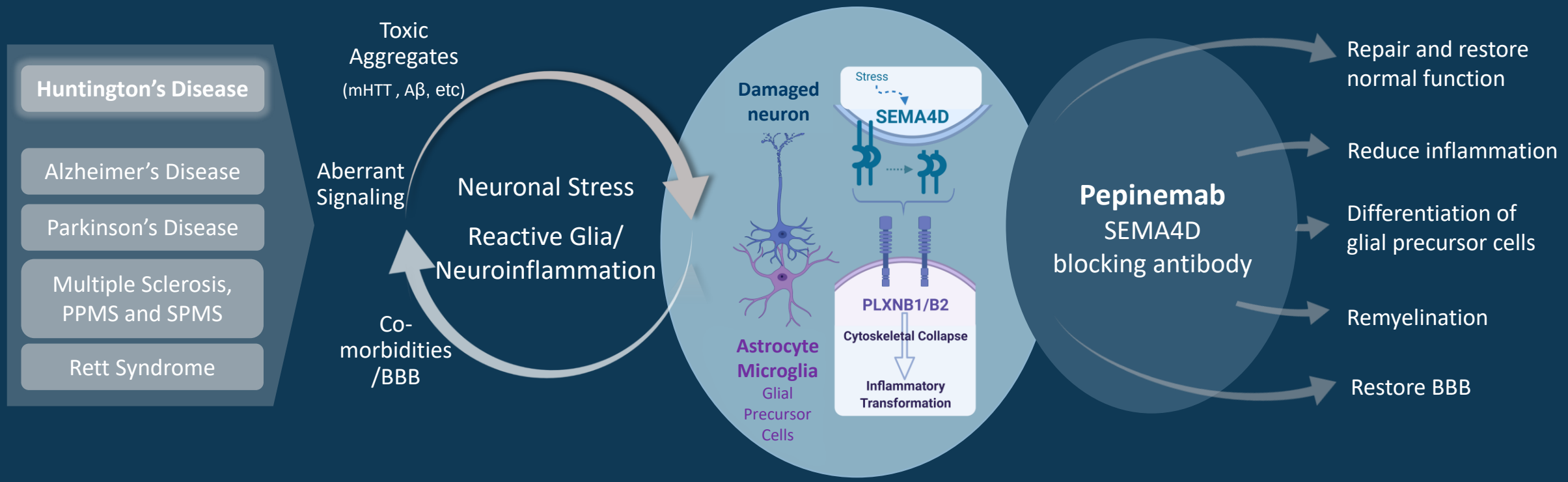
AF and ES have received compensation from employment, consulting and board participation in various companies – see full disclosures in program.

Forward Looking Statements

To the extent that statements contained in this presentation are not descriptions of historical facts regarding Vaccinex, Inc. ("Vaccinex," "we," "us," or "our"), they are forward-looking statements reflecting management's current beliefs and expectations. Such statements include, but are not limited to, statements about the Company's plans, expectations and objectives with respect to the results and timing of clinical trials of pepinemab in various indications, the use and potential benefits of pepinemab in Huntington's and Alzheimer's disease and other indications, and other statements identified by words such as "may," "will," "appears," "expect," "planned," "anticipate," "estimate," "intend," "hypothesis," "potential," "advance," and similar expressions or their negatives (as well as other words and expressions referencing future events, conditions, or circumstances). Forward-looking statements involve substantial risks and uncertainties that could cause the outcome of the Company's research and pre-clinical development programs, clinical development programs, future results, performance, or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, uncertainties inherent in the execution, cost and completion of preclinical and clinical trials, uncertainties related to regulatory approval, the risks related to the Company's dependence on its lead product candidate pepinemab, the ability to leverage its ActivMAb® platform, the impact of the COVID-19 pandemic, and other matters that could affect the Company's development plans or the commercial potential of its product candidates. Except as required by law, the Company assumes no obligation to update these forward-looking statements. For a further discussion of these and other factors that could cause future results to differ materially from any forward-looking statement, see the section titled "Risk Factors" in the Company's periodic reports filed with the Securities and Exchange Commission ("SEC") and the other risks and uncertainties described in the Company's most recent year end Annual Report on Form 10-K and subsequent filings with the SEC.

PROPOSED MECHANISM OF ACTION:

Preclinical and clinical evidence suggests pepinemab may reprogram reactive gliosis in CNS diseases



Preclinical Neurology Models

SEMA4D antibody blockade improves disease phenotype

Anti-semaphorin 4D immunotherapy ameliorates neuropathology and some cognitive impairment in the YAC128 mouse model of Huntington disease

Amber L. Southwell [a], Sonia Franciosi [a], Erika B. Villanueva [a], Yuanyun Xie [a], Laurie A. Winter [b], Janaki Veeraraghavan [b], Alan Jonason [b], Boguslaw Felczak [a], Weining Zhang [a], Vlad Kovalik [a], Sabine Waltl [a], George Hall [a], Mahmoud A. Pouladi [c,d], Ernest S. Smith [b], William J. Bowers [b], Maurice Zauderer [b], Michael R. Hayden [a,*]

2015 Neurobiology of Disease

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

International Journal of Molecular Sciences 2021

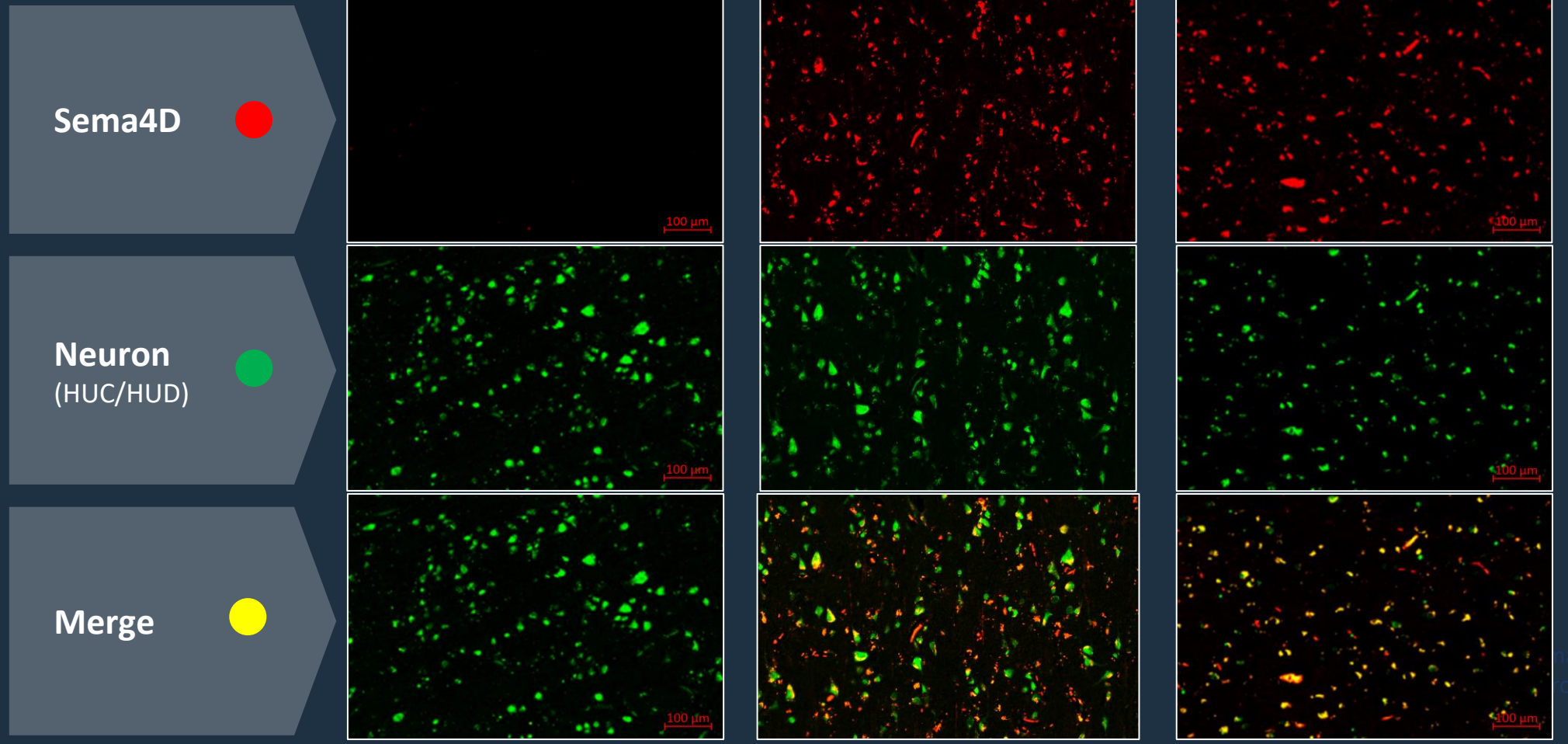
Article

Anti-Semaphorin 4D Rescues Motor, Cognitive, and Respiratory Phenotypes in a Rett Syndrome Mouse Model

Yilin Mao [1,2], Elizabeth E. Evans [3], Vikas Mishra [3], Leslie Balch [3], Allison Eberhardt [3], Maurice Zauderer [3,†] and Wendy A. Gold [1,2,4,5,*,†]

SEMA4D IS UPREGULATED IN NEURONS

Human autopsy brain sections: HD and AD



Human autopsy sections of frontal lobe

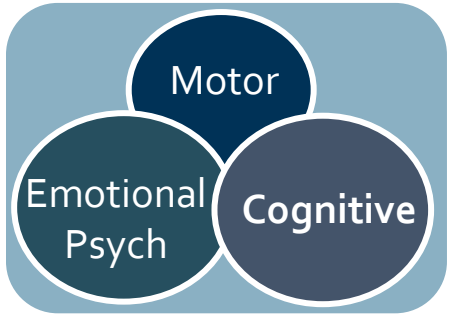
HUNTINGTON'S DISEASE

Genetic Disease
HD is caused by dominant mutation in a single gene.

Unmet need
No approved treatments to alter the course of Huntington's Disease.

~40,000 individuals
with manifest disease in US

>150,000 more
at risk of inheriting mutation



Symptoms
Cognitive impairment = most significant impact on daily life (FDA Voice of the Patient)

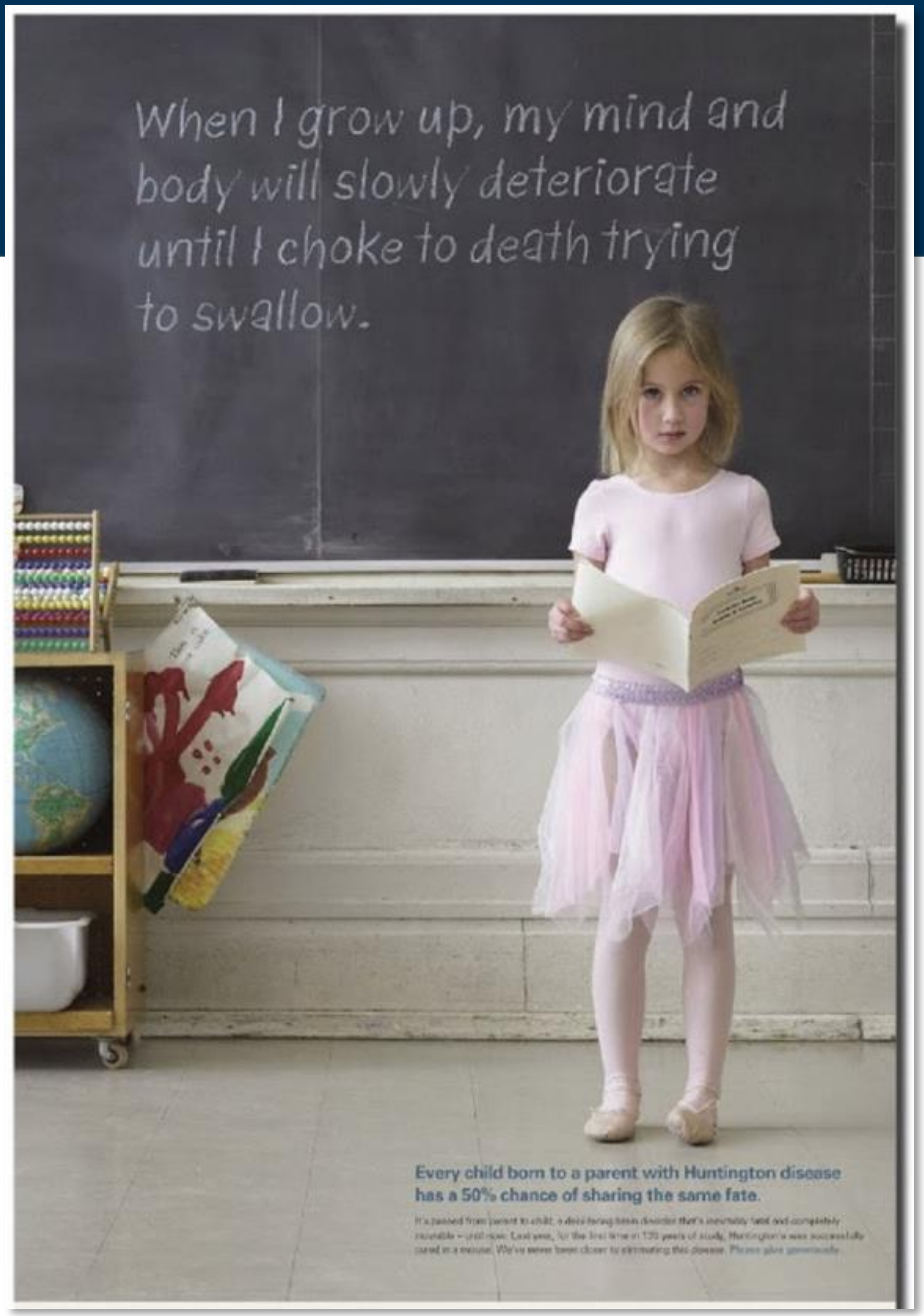


Photo credit: Huntington Society of Canada

HUNTINGTON'S DISEASE

Abbreviated Clinical Trial Design*

SIGNAL

Orphan Disease and Fast Track Designations

Early Manifest HD

placebo
n=88

Monthly X18 months

Safety Follow-up 1 month

Randomized 1:1 Double-blind

pepinemab
n=91

Monthly X18 months

Safety Follow-up 1 month

Data Analysis and Study Objectives

Safety and tolerability

Primary Efficacy Outcomes (mITT)
Cognitive Function
CGIC

Key Exploratory and Biomarker Outcomes
Brain Volume (vMRI)
Metabolic imaging (FDG-PET)

Post-hoc Subgroup Analyses

NCT02481674. *Note 86 subjects with Late Prodromal HD were also included in study

ABBREVIATED SAFETY AND BASELINE CHARACTERISTICS

mITT: Early Manifest HD

Pepinemab (PEPI) SEMA4D blocking antibody is well tolerated

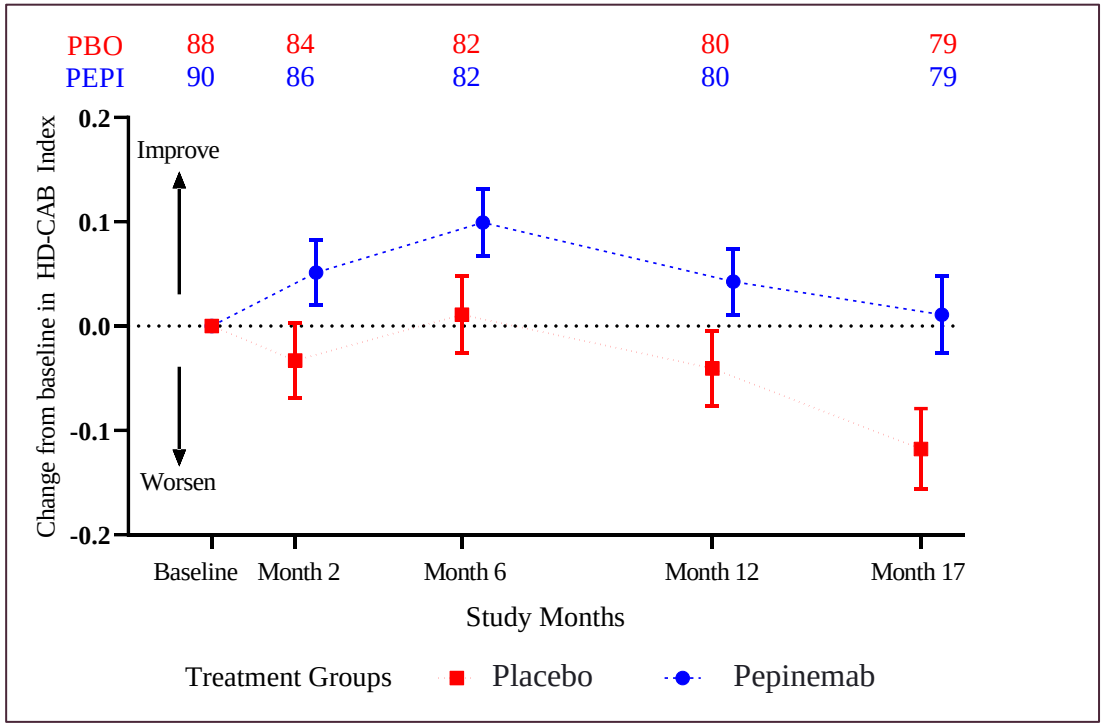
Early Manifest HD	Placebo (n=88)	Pepinemab (n=91)
Discontinued Treatment Early	10	13
Had any SAE (*)	8	4
Had any Grade 3+ AE (*)	14	17
CAG repeat length	44.1	43.5
CAP score**	470	466
UHDRS-DCL at screening DCL-4, Unequivocal HD (>99% confident)	88 (100%)	91 (100%)
UHDRS-TFC at screening, n (%)		
11 12-13	33 (38%) 55 (62%)	29 (32%) 61 (68%)
MoCA score, mean (SE)	26.02 (2.04)	26.14 (2.30)
MoCA <26 subgroup	23.97 (0.94)	23.78 (1.07)
MoCA ≥26 subgroup	27.44 (1.21)	27.72 (1.34)

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

COGNITIVE ASSESSMENT BATTERY (HD-CAB)

mITT Co-Primary and pre-specified Exploratory analysis, Early Manifest HD

HD-CAB Composite Index of 6 Cognitive Assessments



Two-item HD Cognitive Assessment: Pre-specified Co-Primary

LS Mean Difference Estimate (95% CI)	One-sided p-value	Favors Pepinemab	Critical value
OTS: -1.98 (-4.00, 0.05)	**0.028**	**Yes**	**No [0.025]**
PTAP: 1.43 (-0.37, 3.23)	**0.060**		

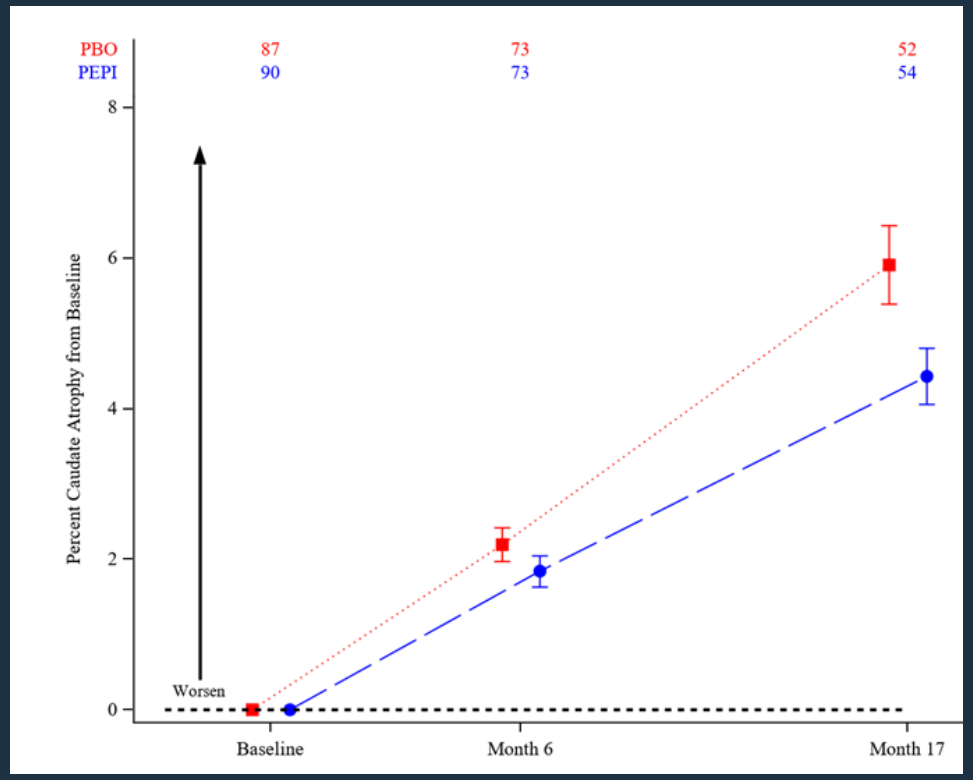
HD-CAB Composite Index: Pre-specified Exploratory

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

PEPINEMAB APPEARS TO REDUCE BRAIN ATROPHY

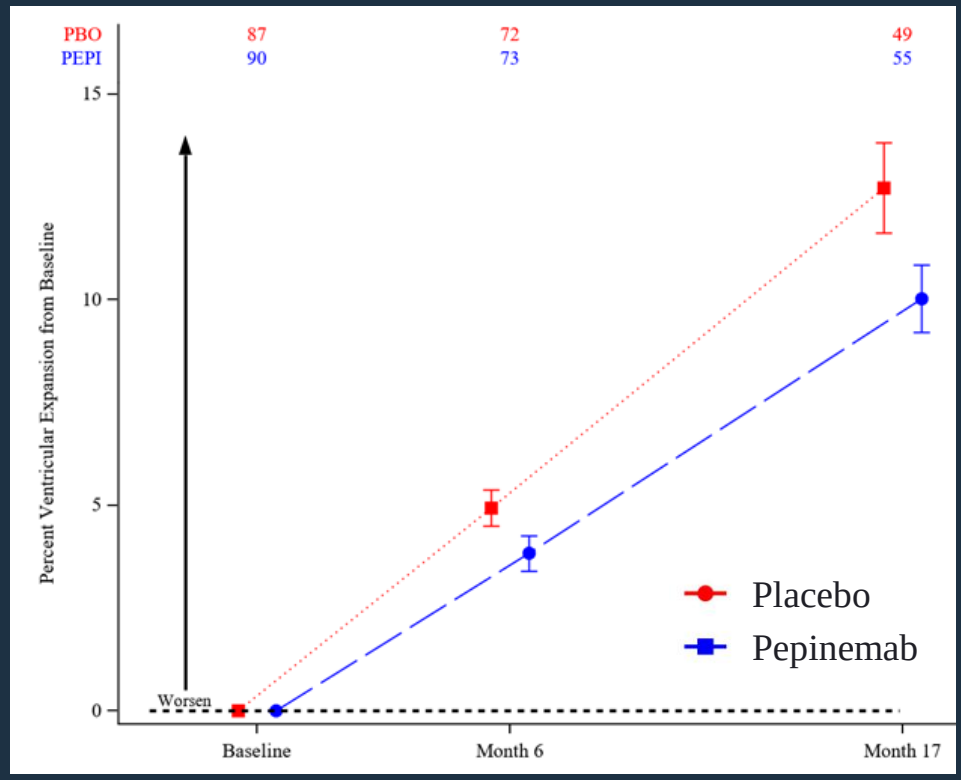
Volumetric MRI– Boundary Shift Integral Analysis (BSI)
Pre-specified Exploratory Endpoint, Early Manifest HD

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

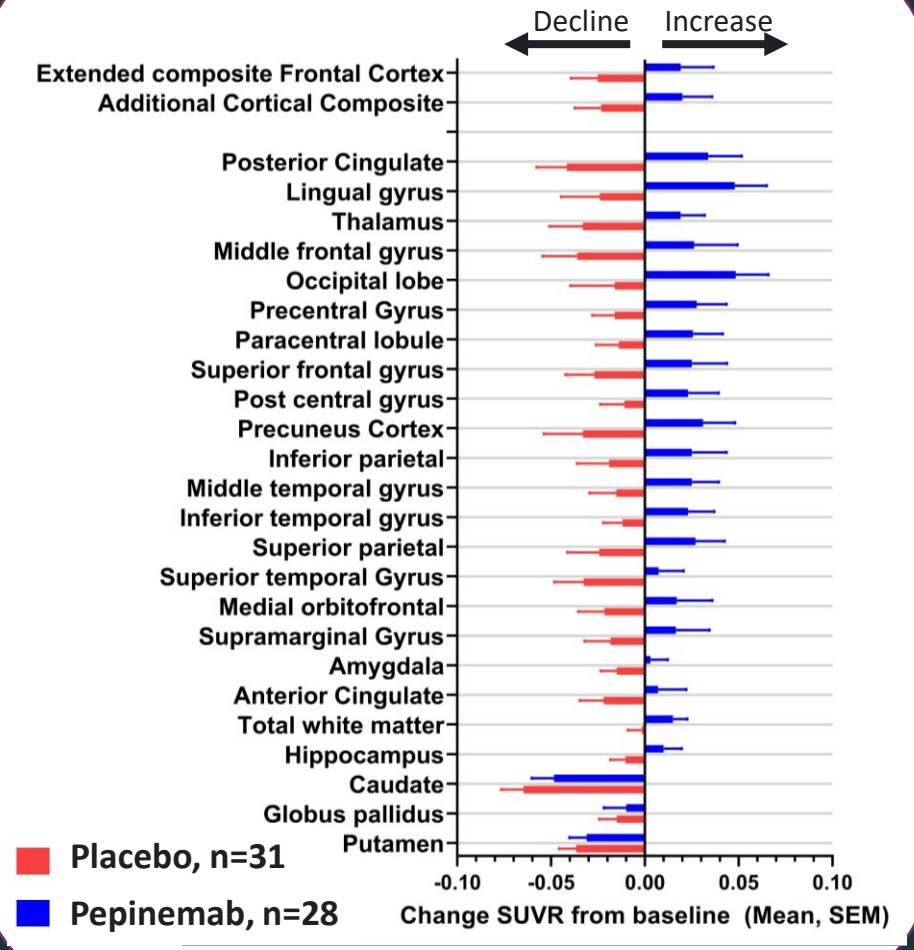
FDG-PET CORRELATES WITH COGNITIVE FUNCTION

Pre-specified Exploratory Endpoint, Early Manifest HD

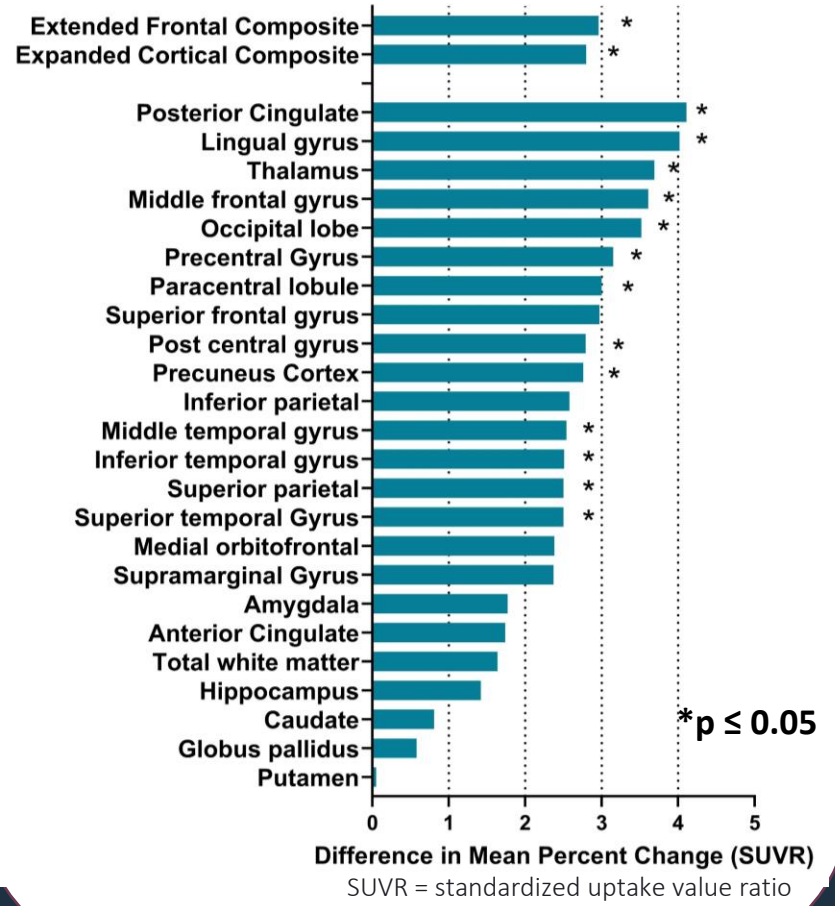
1. FDG-PET measures brain metabolic activity.
2. Decline in FDG-PET is reported to correlate with cognitive impairment in neurodegenerative diseases.

Pepinemab treatment appears to reverse loss of metabolic activity.

Change in FDG-PET at Month 18



Difference (PEPI-PBO) at Month 18



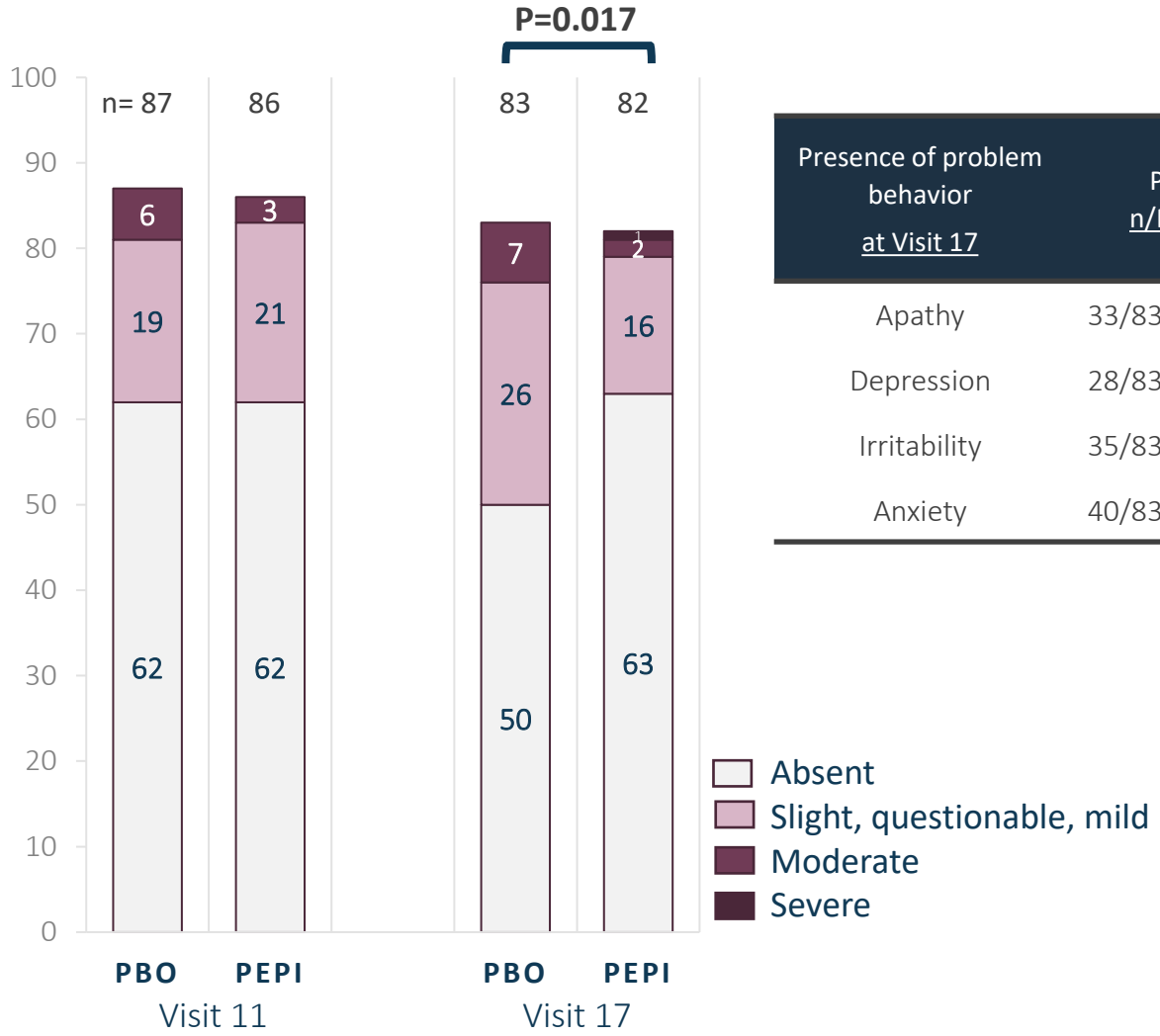
SUVR = standardized uptake value ratio

Problem Behaviors Assessment (PBA-s)

Post-hoc analysis of individual assessments, Early Manifest HD

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

Pepinemab treatment reduced apathy severity



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 (-)

PBO = Placebo
PEPI = Pepinemab

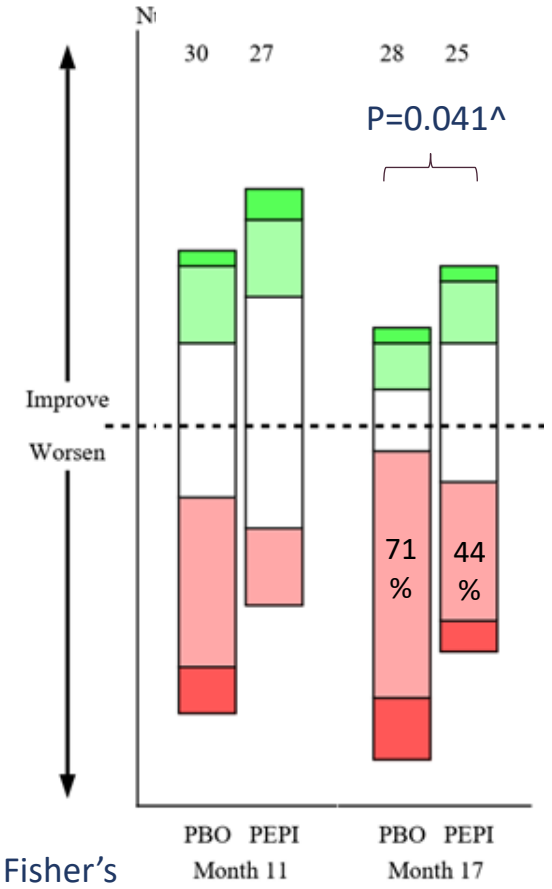
CGIC: Clinical Global Impression of Change

Co-Primary and Post-hoc Subgroup Analysis to inform patient selection

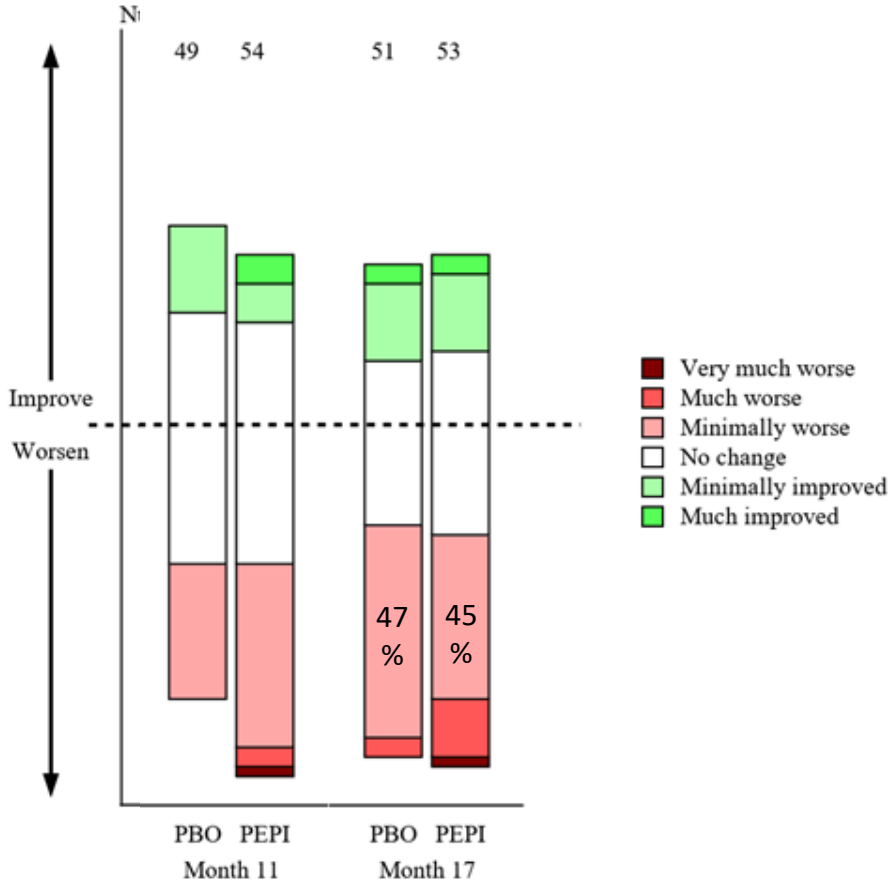
No significant treatment effect observed in the mITT early manifest HD population

A treatment effect was, however, evident in subjects with somewhat more advanced disease (TFC 11) in post-hoc subgroup analysis.

CGIC – Subjects with Baseline UHDRS TFC 11



CGIC – Subjects with Baseline UHDRS TFC 12 and 13

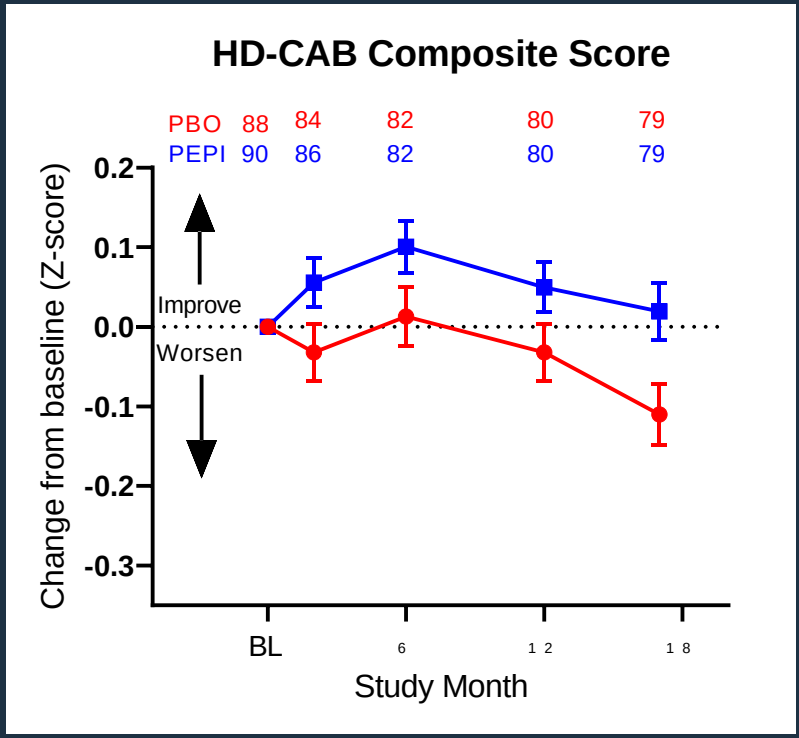


^nominal one-sided p-value, Fisher's exact test for worsening score

HD-CAB STRATIFIED BY BASELINE MoCA

(Montreal Cognitive Assessment) Post-hoc Subgroup Analysis to inform patient selection

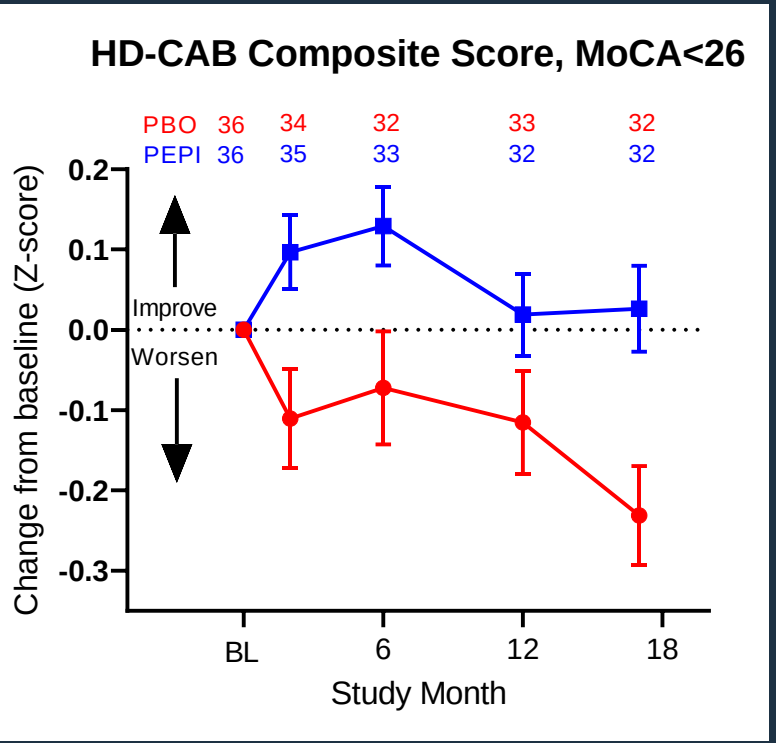
mITT



LS Mean Estimate (SE), month 17

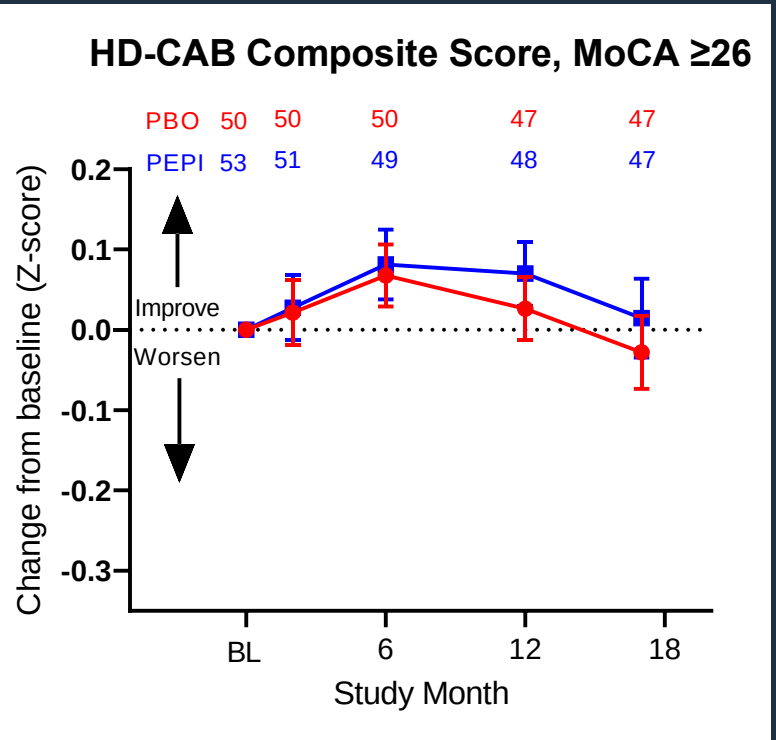
mITT: 0.13 (0.05), **p=0.007**

MoCA < 26



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

MoCA ≥ 26



MoCA ≥26: 0.06 (0.06), **p=0.197**

SIGNAL Phase 2 Trial
Summary, Lessons Learned, Next Steps

Orphan Disease and Fast Track Designations




Proposed Mechanism of Action	Safety and Tolerability	Efficacy Outcomes	Target Engagement
Preclinical data suggests reduced neuroinflammation and restoration of normal glia function **Combination of SEMA4D immunotherapy with ASO improves measures of anxiety and brain atrophy in Hu97/18 HD mice**	**Well tolerated** Intravenous administration	Pre-specified primary efficacy endpoints were not significant. Evidence suggests potential cognitive benefit, i.e. HD-CAB, Apathy, FDG-PET Reduced brain atrophy observed Greatest benefit from treatment was detected in patients with signs of mildly advanced disease	Confirmed drug penetration into CNS at expected level Antigen-antibody complexes detected

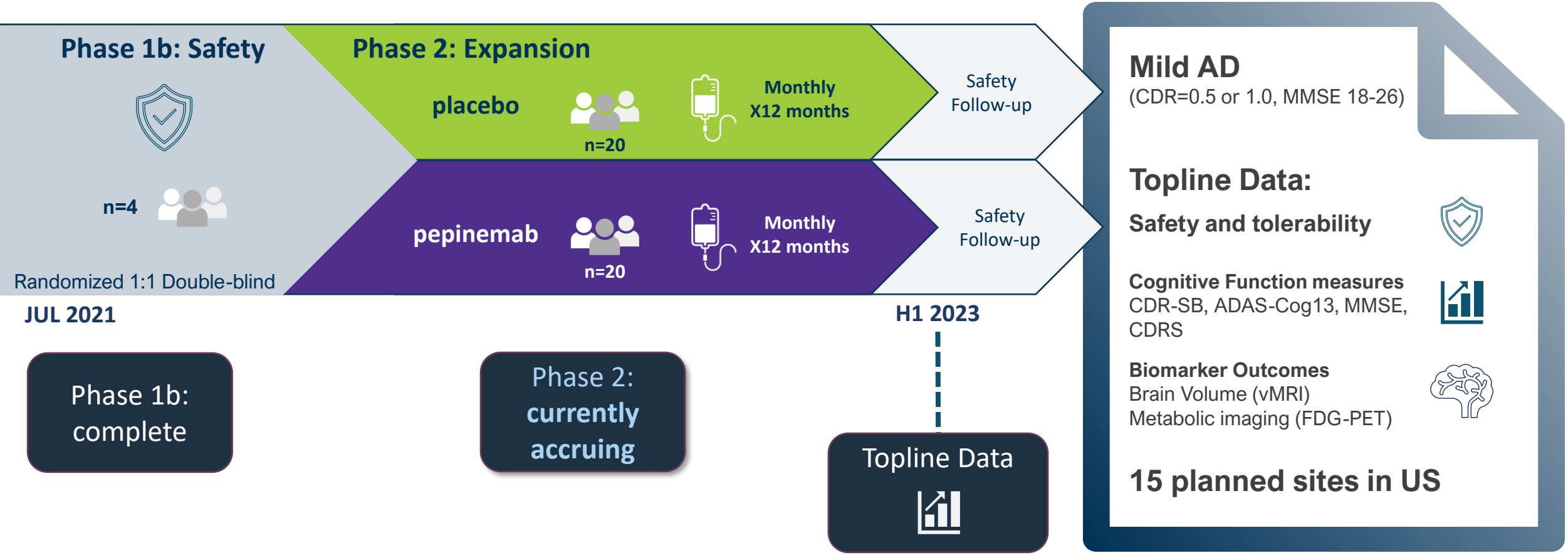
Continued clinical development in Huntington's Disease – potential for Combination Therapy
Initiated phase 1/2a trial in Alzheimer's Disease

ALZHEIMER'S DISEASE

Phase 1b/2 Trial Design

SIGNAL-AD

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



NCT04381468

Signal-AD Site Map