Abstract 1402

RESULTS OF SIGNAL-AD, A RANDOMIZED PHASE 1B/2 TRIAL EVALUATING SAFETY AND EFFICACY OF THE PEPINEMAB IN AD

Elizabeth Evans[1], Anton Porsteinsson[2], Terrence Fisher[1], Megan Boise[1], Amber Foster[1], John Leonard[1], Vikas Mishra[1], Crystal Mallow[1], Raymond Scott Turner[3], John Huffaker[4], Maurice Zauderer[1]

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Chief Operating Officer

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Advances in AD Drug Development 02
April 5, 2025

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Vaccinex			x	x	x		EE	
			x	x	x		TF	
			x		x		MB, AF, JL, VM, CM	
			x	x	x	x	MZ	

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 Head and Neck cancer, 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.

Pepinemab for treatment of Neurodegenerative Diseases

- **Pepinemab** is a humanized IgG4 **antibody** that
  - blocks Semaphorin 4D (SEMA4D) induced astrocyte reactivity.
  - blocks crosstalk between reactive astrocytes and microglia to inhibit neuroinflammation.
  - preserves vascular integrity in brain.
  - downregulates expression of AD-related proteins in CSF, including GAP-43 and SNAP25 that promote tau spreading and accumulation.

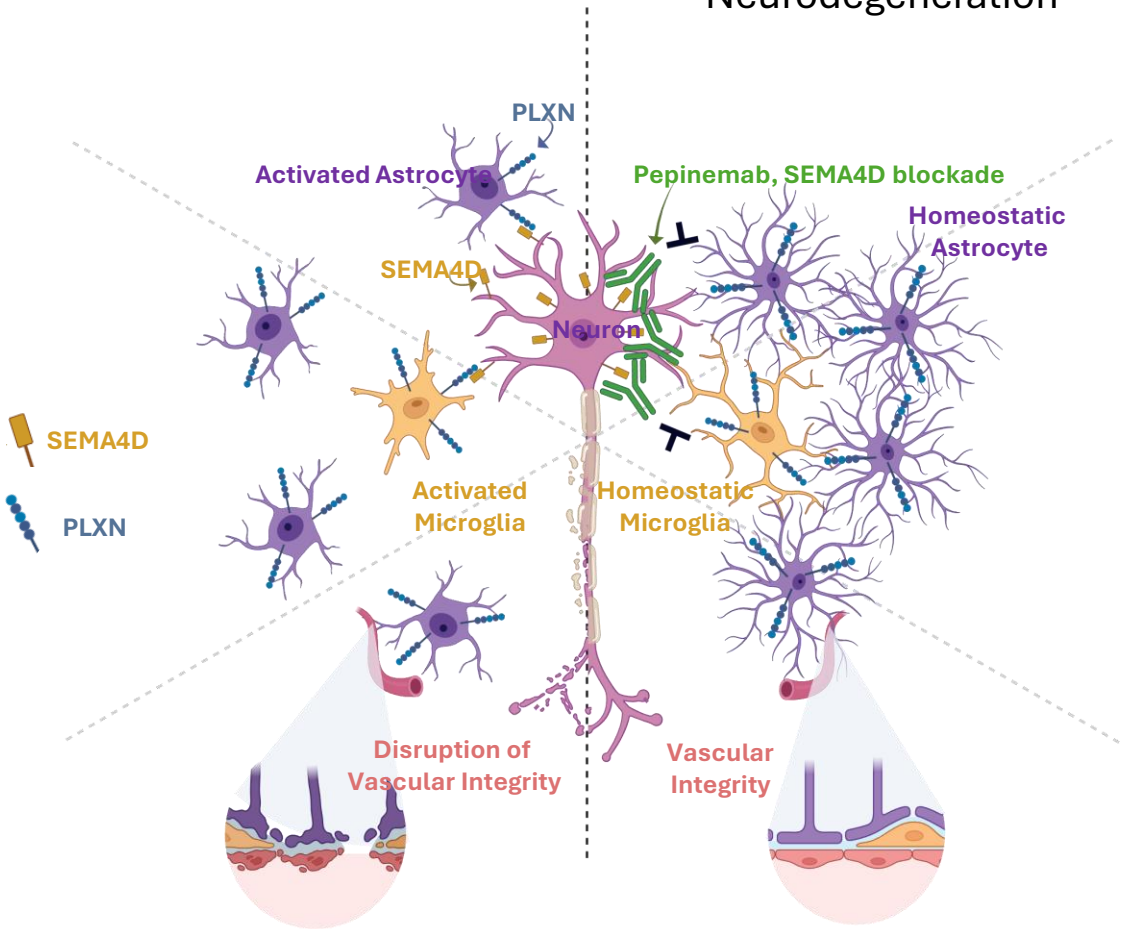
- Pepinemab was **well-tolerated** in multiple clinical trials, including Alzheimer's Disease, Huntington's Disease and Multiple Sclerosis.

- Data from a recently completed SIGNAL-AD study in **early Alzheimer's Disease** and a Phase 2 study in **Huntington's Disease** demonstrated that pepinemab treatment appears to **slow cognitive decline** with favorable effects on **biomarkers** related to disease progression.

Semaphorin 4D and its receptors have been implicated in Alzheimer's Disease and AD-related dementia

Neuroinflammation / Neurodegeneration

Pepinemab to overcome Neuroinflammation / Neurodegeneration



SEMA4D and its receptors, Plexin B1/B2, are upregulated in AD & correlate with amyloid plaque load, tau tangle density, and cognitive decline

- Evans et al. J Nlammation, (2022) 19:200-216
- Mostafavi et al., Nat Neurosci. 2018 Jun;21(6):811-819. (ROS-MAP cohort)
- Yu et al. Ann Neurol. 2018 Jul;84(1):78-88.
- Mathys et al., Nature (2019) 570:332-337
- Grubman et al. 2019 Dec;22(12):2087-2097.

Reactive Astrogliosis

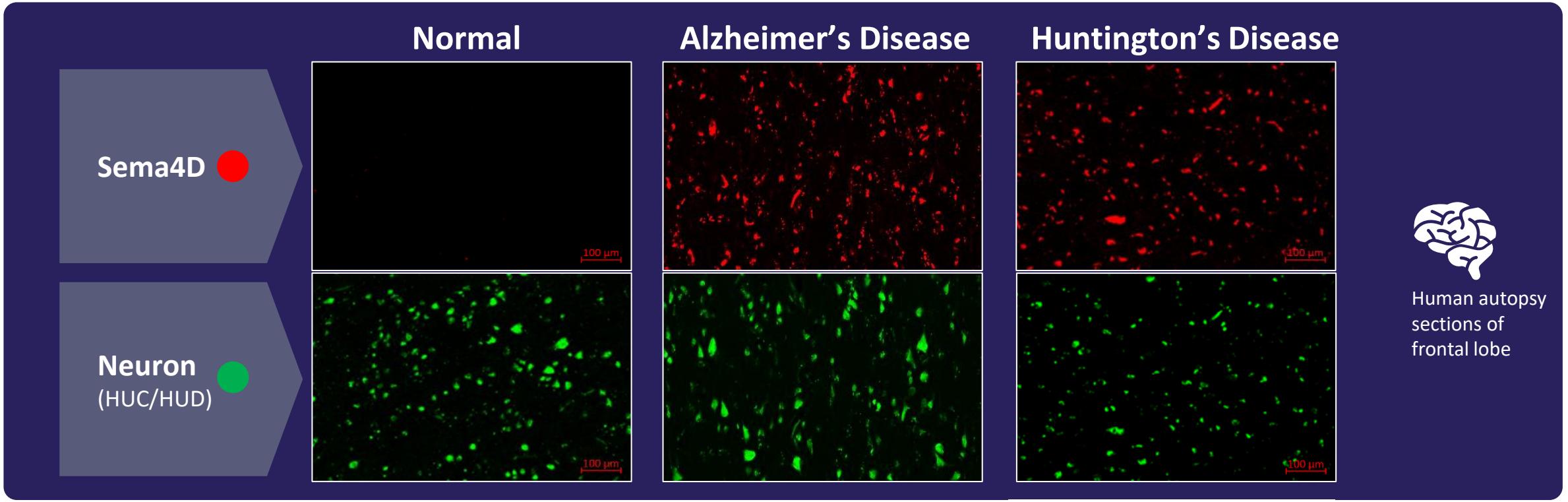
Microglial activation and inflammation

Disruption of vascular integrity

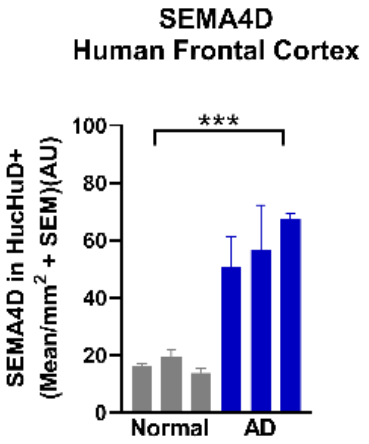
AD models }
BBB }

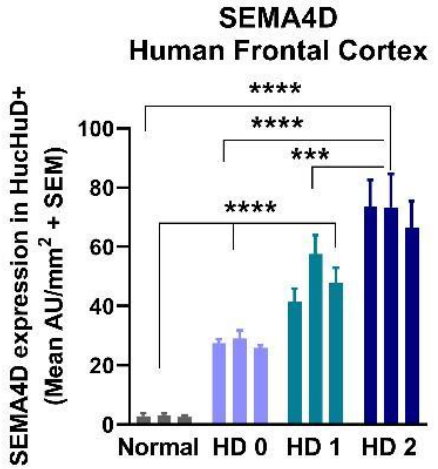
- Evans et al. J Neuroinflammation, (2022) 19:200-216
- Huang et al. Nat Neurosci (2024) 27, 1489–1504
- Mega Vascular Cognitive Impairment and Dementia (MEGAVCID), Alzheimer's & Dementia (2024)
- Smith et al. Neurobiology of Disease (2015) 73:254-268

SEMA4D IS UPREGULATED IN NEURONS DURING DISEASE PROGRESSION



SEMA4D in neurons





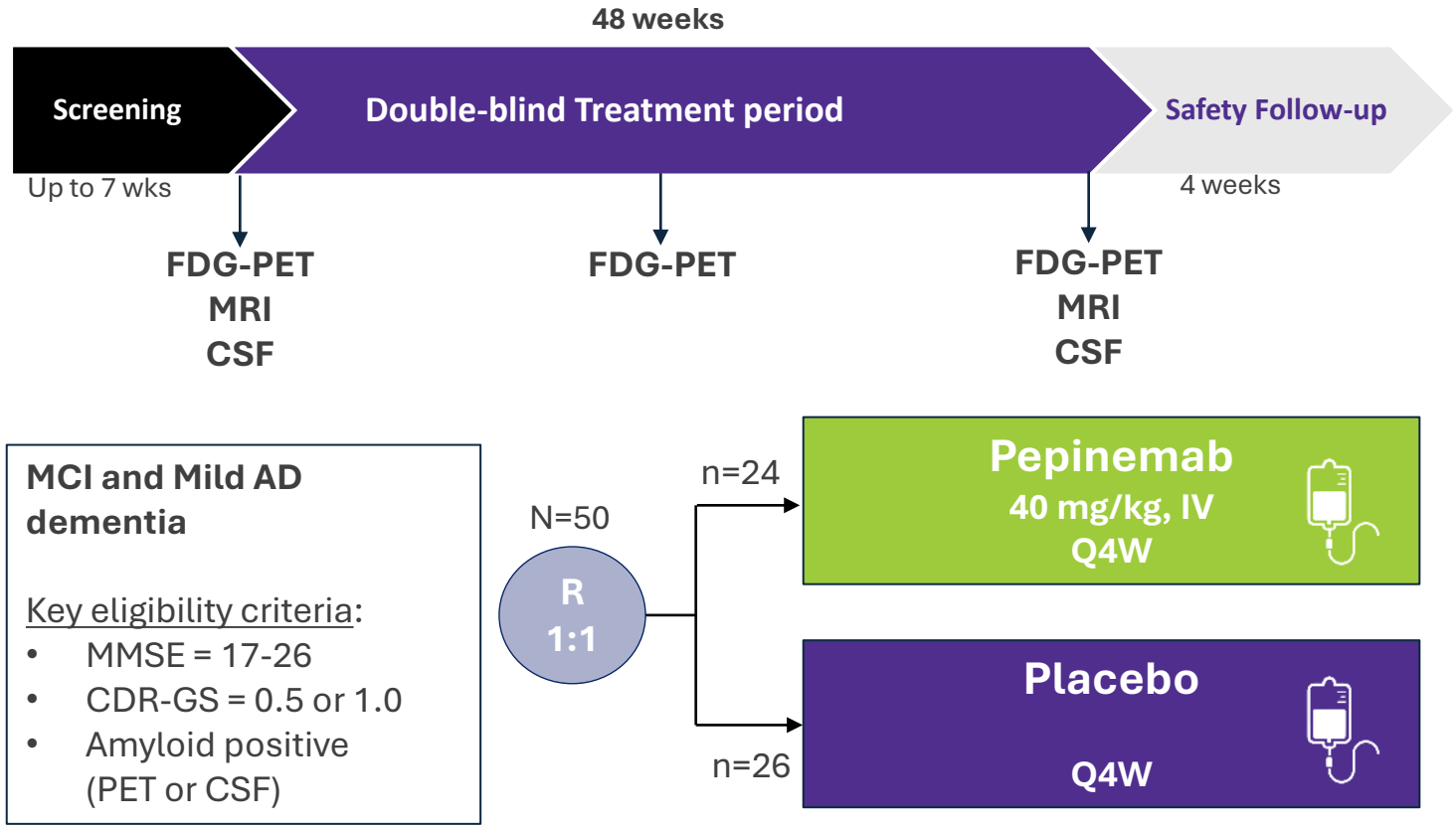
Evans, E. et al., J Neuroinflammation, 2022

ALZHEIMER'S DISEASE

Phase 1b/2 Trial Design

NCT04381468
SIGNAL-AD

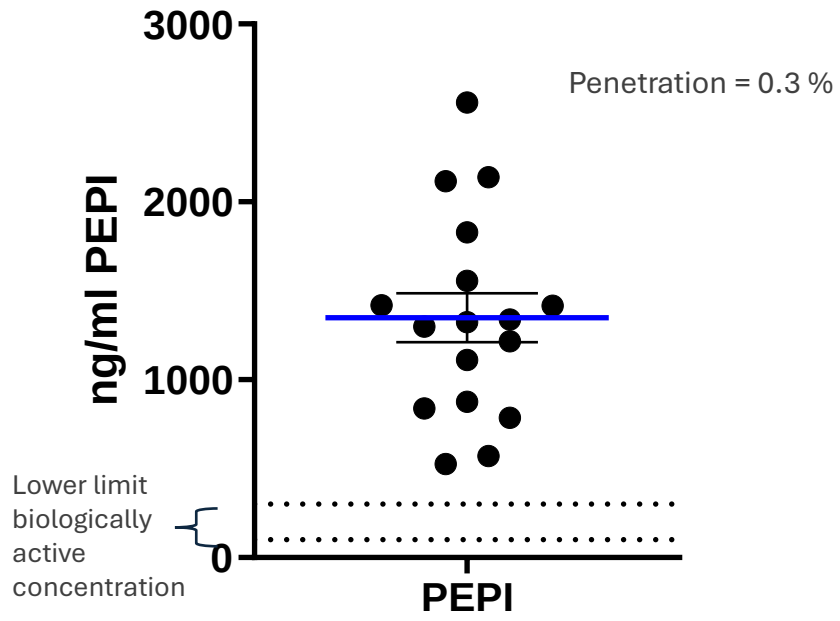
Funding by alzheimer's association® Alzheimer's Drug Discovery Foundation



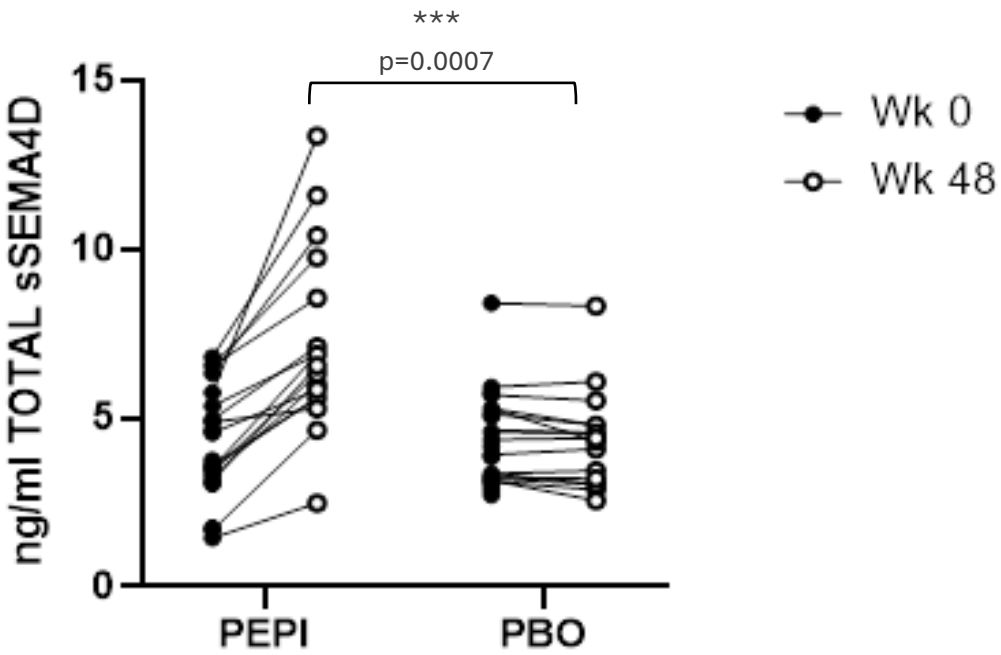
Objectives:	
Primary	**Safety and Tolerability**
Secondaries	• Cognitive and Functional measures: Change in CDR-SB, iADRS, ADAS-Cog13 • Change in FDG-PET SUVR at Week 48 • Biomarker analysis
Exploratory	• **Pre-specified subgroup analysis: including MMSE 22-26/17-21** • PK/PD

Pepinemab is detected at expected levels and binds to target (SEMA4D) in CSF

Subjects dosed with pepinemab contain ≥ saturating levels of drug (100-300 ng/ml) in CSF



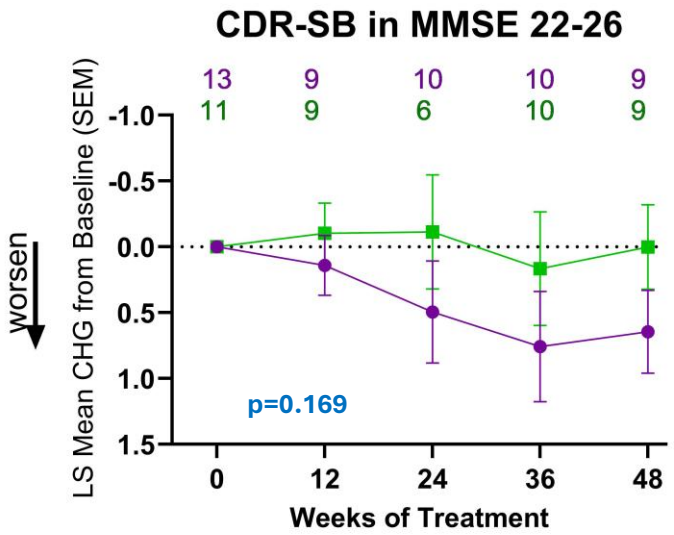
sSEMA4D:PEPI complexes in CSF of subjects dosed with pepinemab – suggesting target engagement

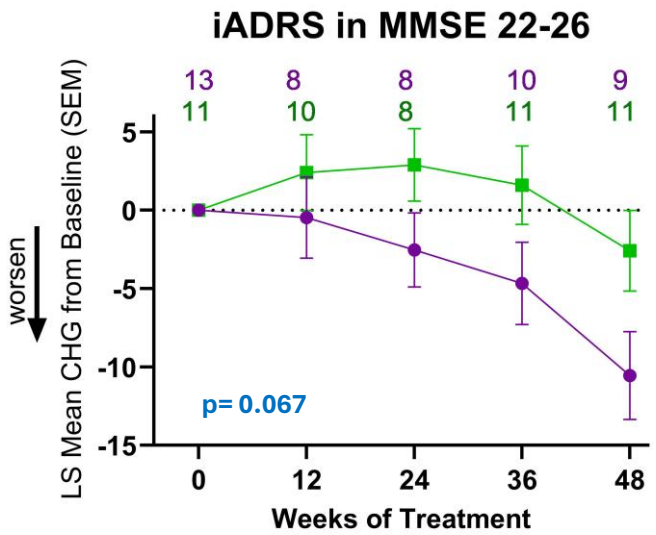


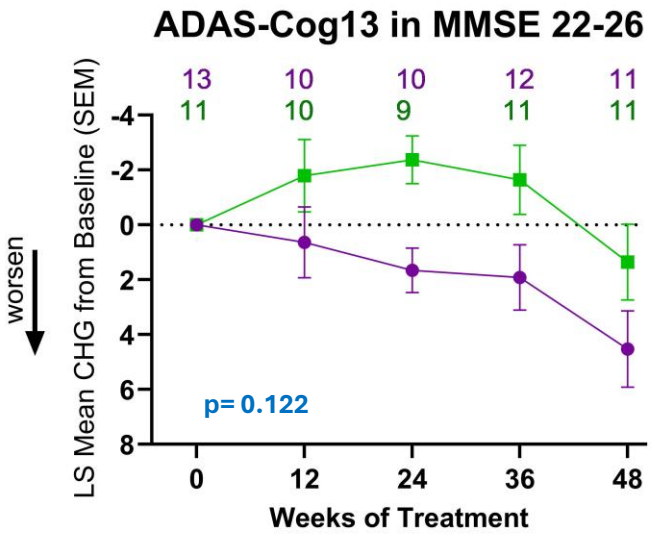
Pepinemab, SEMA4D blocking antibody, improved assessments of cognition and function in Alzheimer's Disease

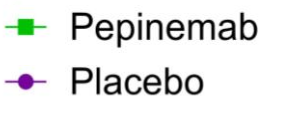
MMSE 22-26 subgroup

NCT04381468
SIGNAL-AD









% slowing by pepinemab at week 48

99%

76%

70%

CDR-SB
% slowing
29% donanemab
27% lecanemab

Huntington's disease Phase 2 trial

NCT02481674

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01919-8

Check for updates

OPEN

Pepinemab antibody blockade of SEMA4D in early Huntington's disease: a randomized, placebo-controlled, phase 2 trial

Andrew Feigin[1], Elizabeth E. Evans[2], Terrence L. Fisher[2], John E. Leonard[2], Ernest S. Smith[2], Alisha Reader[2], Vikas Mishra[2], Richard Manber[3], Kimberly A. Walters[4], Lisa Kowarski[4], David Oakes[5], Eric Siemers[6], Karl D. Kieburtz[5], Maurice Zauderer[2]✉ and the Huntington Study Group SIGNAL investigators*

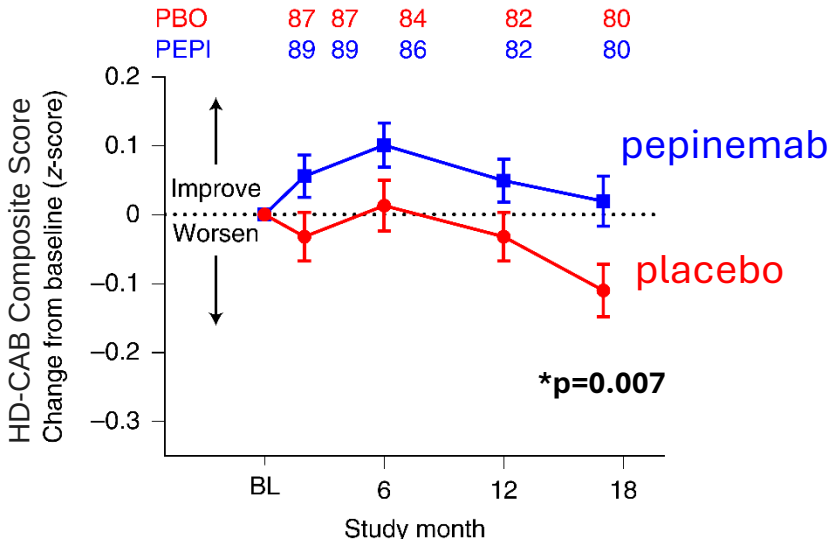
Pepinemab-induced Cognitive Change in Early Huntington's Disease patients, TFC 11-13

HD Cognitive Assessment Battery (HD-CAB)

NCT02481674 SIGNAL

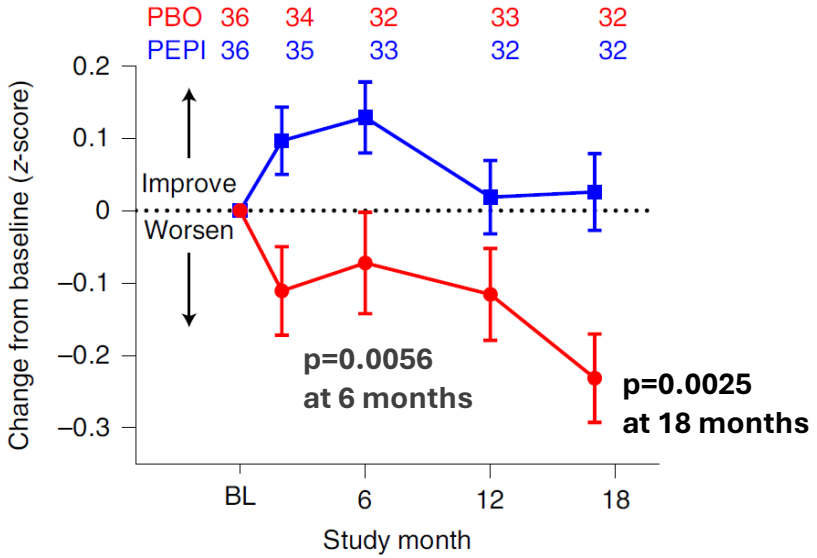
Pepinemab treatment effect is most evident in patients with early signs of cognitive deficits (MoCA <26)

Early Manifest HD:
Intent to treat population (mITT)



Pre-specified exploratory analysis

MoCA <26, Early Manifest

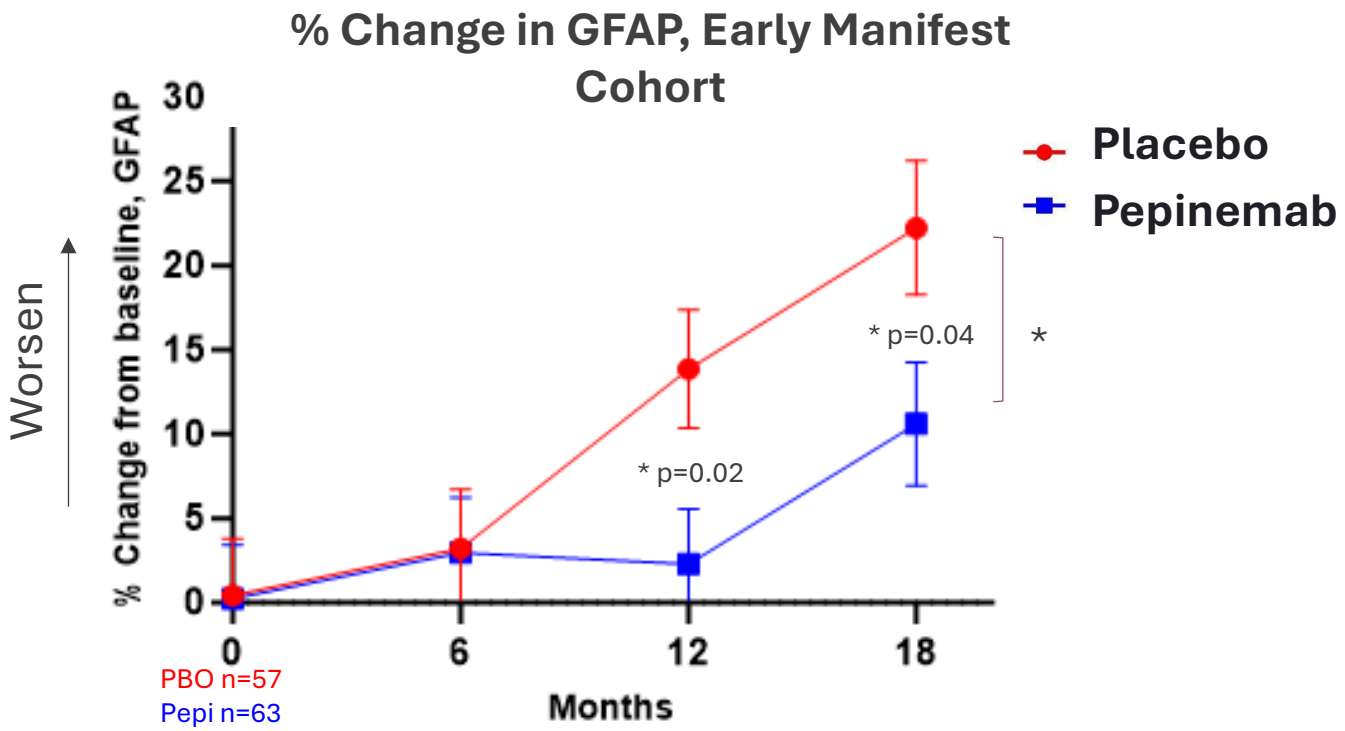


Post-hoc analysis: Montreal Cognitive Assessment (MoCA) subgroups

Feigin, A., Evans, E.E., Fisher, T.L. et al.
Nature Medicine (2022), 28: 2183-2193

Pepinemab treatment reduced levels of GFAP inflammatory biomarker in blood of Early HD patients

NCT02481674 SIGNAL



* % change from baseline over time was analyzed via MMRM after adjusting for baseline value and age. P values represent t-tests for significant difference (PEPI-PBO) at each timepoint.

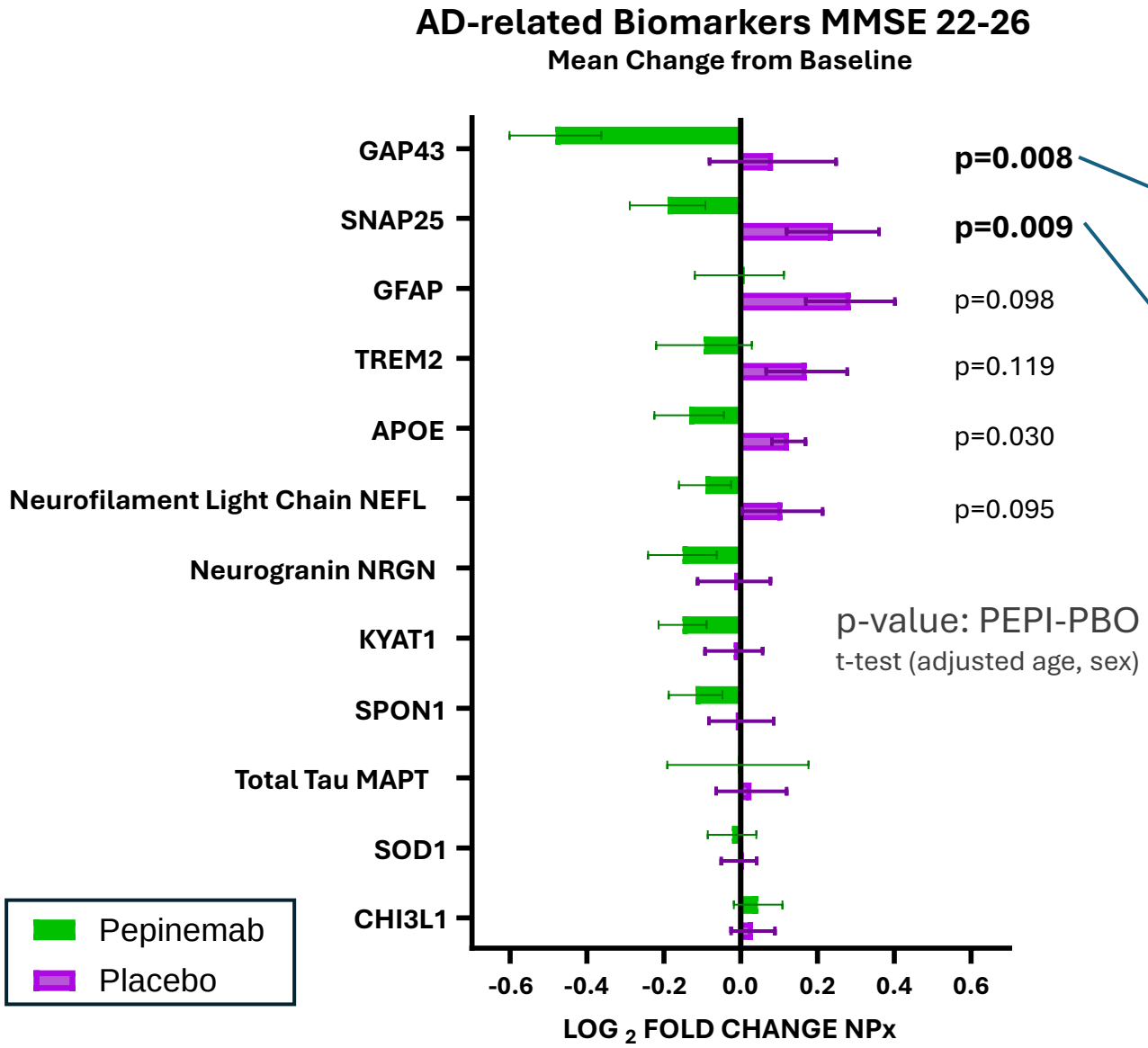
Pepinemab reduced plasma GFAP in SIGNAL-HD

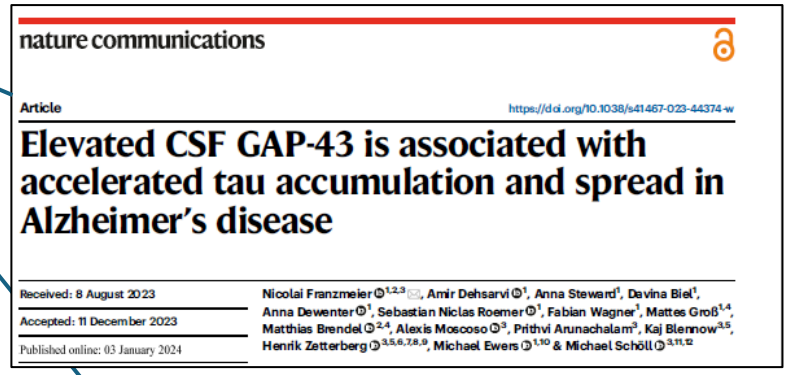
Glial Fibrillary Acidic Protein (GFAP) is a biomarker of neuroinflammation and reactive/dysfunctional astrocytes

Feigin AS, Evans EE, Fisher TL, and Zauderer M. ***Pepinemab: a SEMA4D antagonist for treatment of Huntington's and other neurodegenerative diseases.*** *Expert Opinion on Inv Drugs, 2025*

Pepinemab reduced levels of AD-related proteins associated with tau pathology in patients with mild dementia

NCT04381468
SIGNAL-AD




nature communications

Article

https://doi.org/10.1038/s41467-023-44374-w

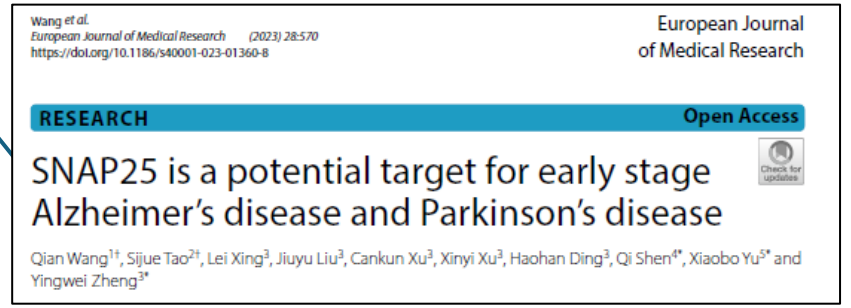
Elevated CSF GAP-43 is associated with accelerated tau accumulation and spread in Alzheimer's disease

Received: 8 August 2023

Accepted: 11 December 2023

Published online: 03 January 2024

Nicolai Franzmeier, Amir Dehsarvi, Anna Steward, Davina Biel, Anna Dewenter, Sebastian Niclas Roemer, Fabian Wagner, Mattes Groß, Matthias Brendel, Alexis Moscoso, Prithvi Arunachalam, Kaj Blennow, Henrik Zetterberg, Michael Ewers & Michael Schöll


Wang et al.
European Journal of Medical Research (2023) 28:570
https://doi.org/10.1186/s40001-023-01360-8

European Journal of Medical Research

RESEARCH

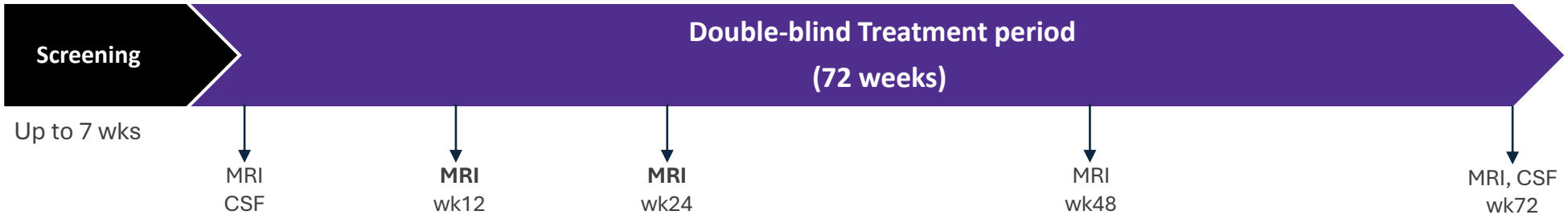
Open Access

SNAP25 is a potential target for early stage Alzheimer's disease and Parkinson's disease

Qian Wang, Sijue Tao, Lei Xing, Jiuyu Liu, Cankun Xu, Xinyi Xu, Haohan Ding, Qi Shen, Xiaobo Yu and Yingwei Zheng

ALZHEIMER'S DISEASE

Planned Phase 2 Trial Design



MCI and Mild AD dementia

Key eligibility criteria:

- **MMSE = 22-28**
- CDR-GS = 0.5 or 1.0
- Amyloid positive (PET or CSF)

n=250

R 1:1

Pepinemab
40 mg/kg, IV
Q4W

Placebo
Q4W

Objectives:

Primary	**Safety and Tolerability** **Target engagement**
Secondaries	Cognitive and Functional measures: Change in CDR-SB, iADRS, ADAS-Cog13
Exploratory	• Biomarkers: plasma GFAP and pTau-217 • PK/PD

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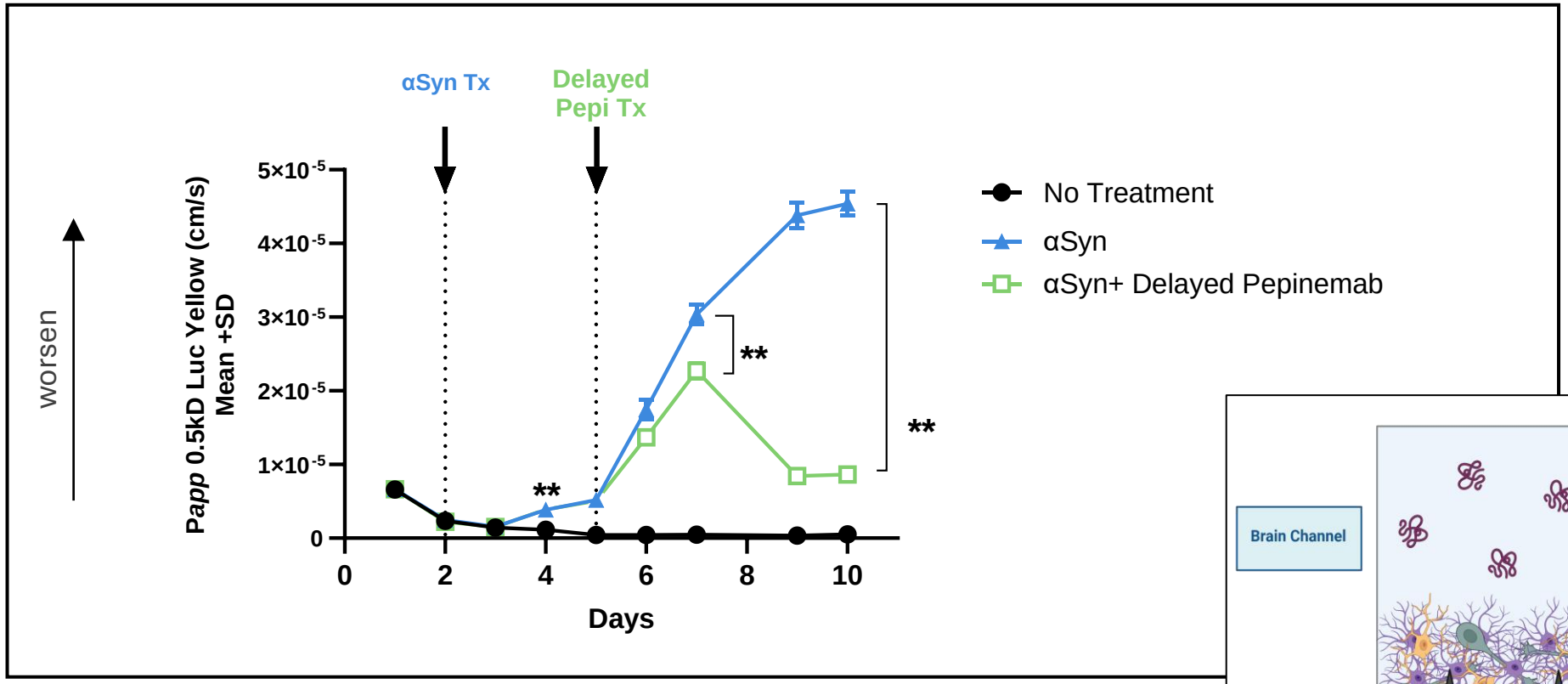
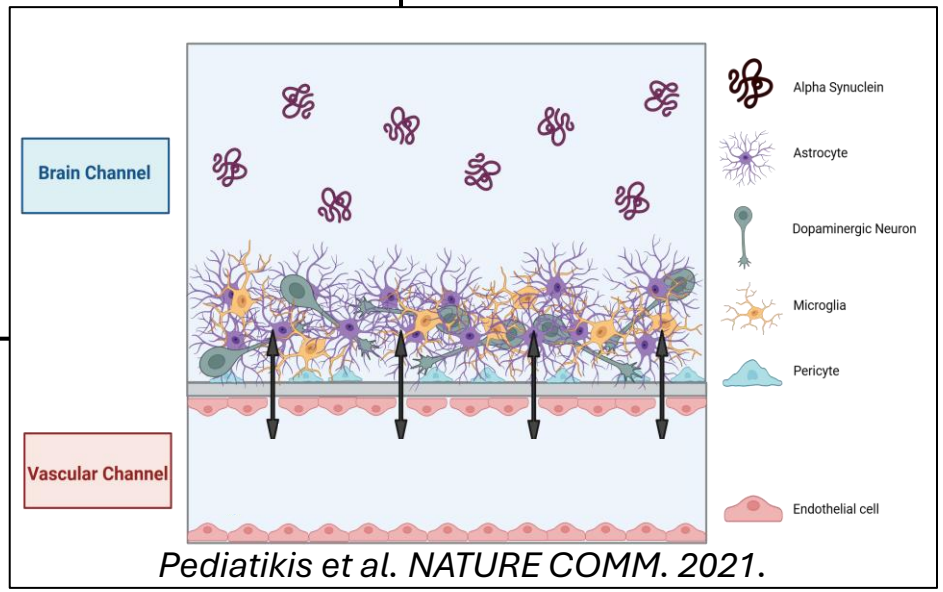
- Pepinemab has broad application in neurologic indications in which inflammation and vascular integrity contributes to disease pathology.

Pepinemab reversed damaging effects of toxic α-Synuclein aggregates on vascular integrity

3D “Brain chip” model





Pediatikis et al. NATURE COMM. 2021.

aSyn fibrils added to brain parenchymal channel
Pepinemab and Control Ig added to vascular channel

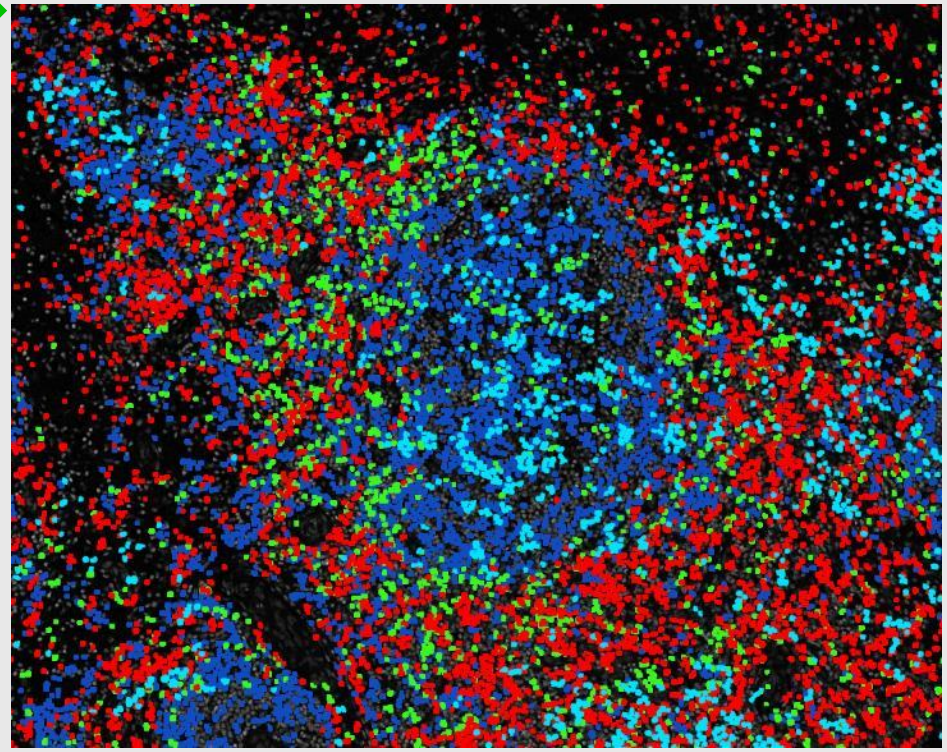
Tertiary Lymphoid Structures (TLS) in Cancer are robust immune Communication centers

PEPINEMAB

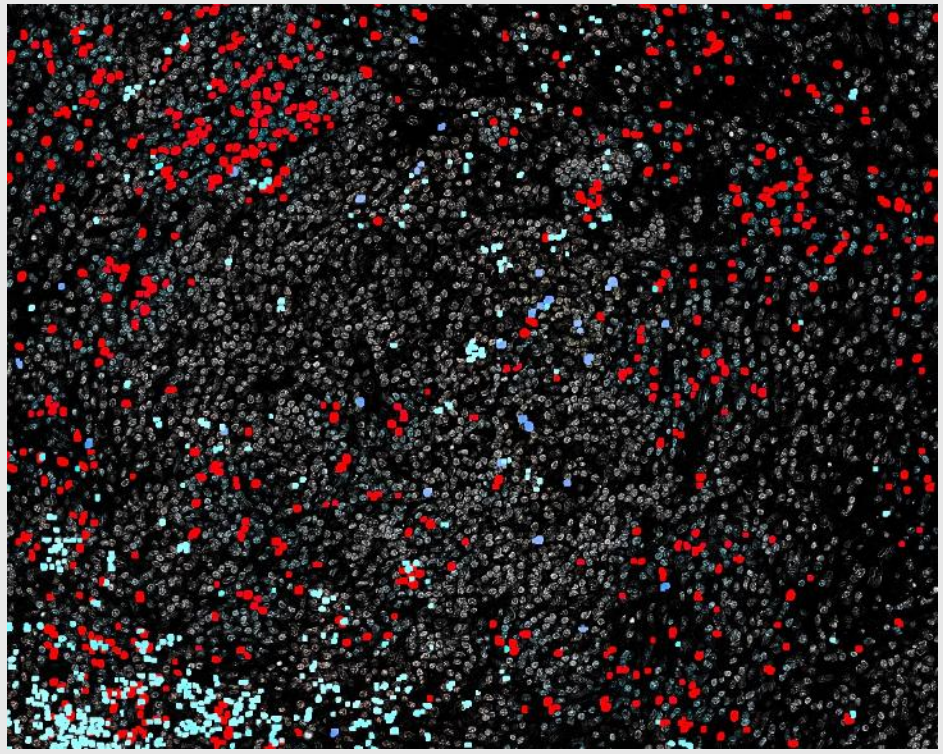
induces formation of highly organized and mature tertiary lymphoid structures (TLS)

Presence of mature TLS is associated with improved clinical outcomes in multiple indications

Pepinemab + Nivolumab



Nivolumab (PD-1 inhibitor)



DC
All CD11c+

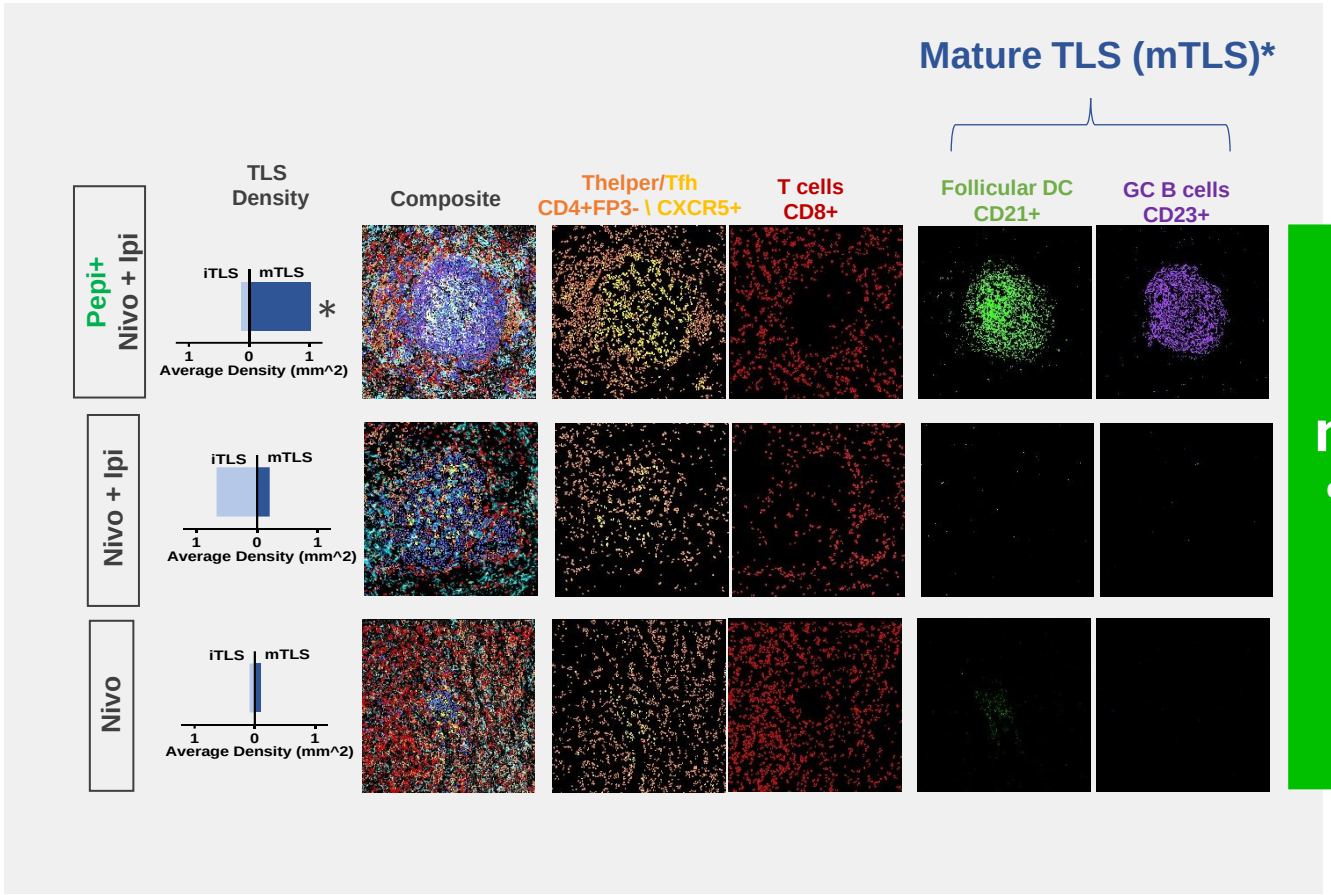
CD8 T cell
CD8+

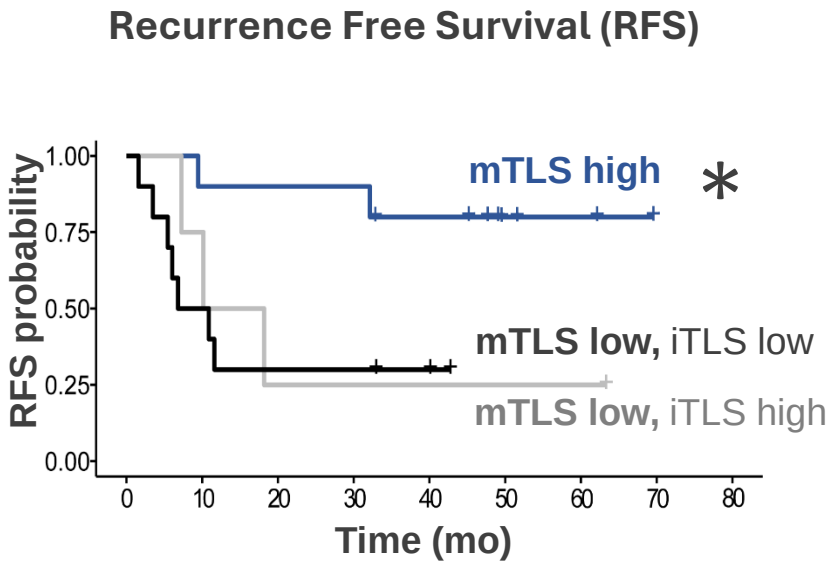
CD4 T helper cell
CD4+FoxP3-

B cells
CD20+

Neoadjuvant trial in Stage III Melanoma. in collaboration with Emory University (NCT03769155)

Pepinemab restores communication between DC and lymphocytes in tumors, resulting in prolonged survival





***High Endothelial Venules are also characteristic of mTLS**

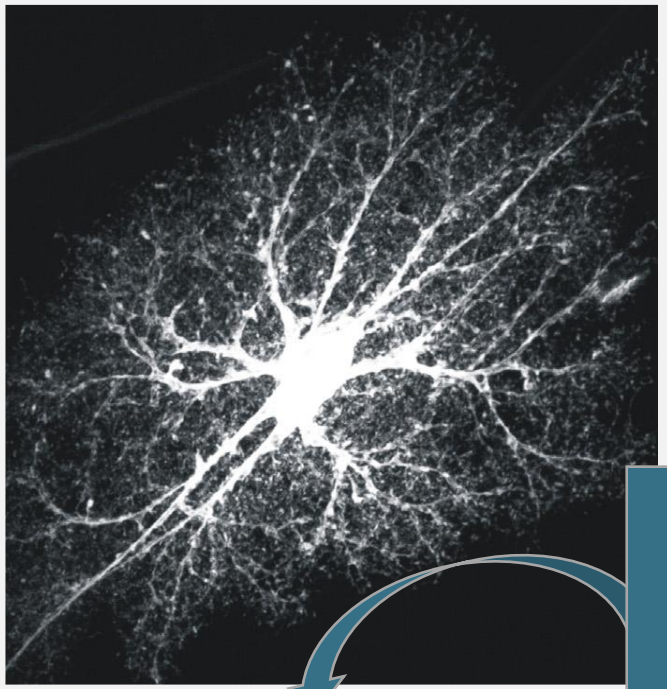
Neoadjuvant trial in Stage III Melanoma. collaboration with Emory University (NCT03769155) and with Jennifer Wargo at MD Anderson Cancer Center (MDACC)
Multiplex IHC and quantification within pathologist-defined Tumor Area

SEMA4D regulates cellular morphology, gene expression and communication in both the nervous and immune systems

Astrocytes in brain and Dendritic Cells in immune system express PlexinB1/B2 receptors and *change form and function* in response to SEMA4D expression caused by damage and disease, “SEMA4D Reactive Regulators”

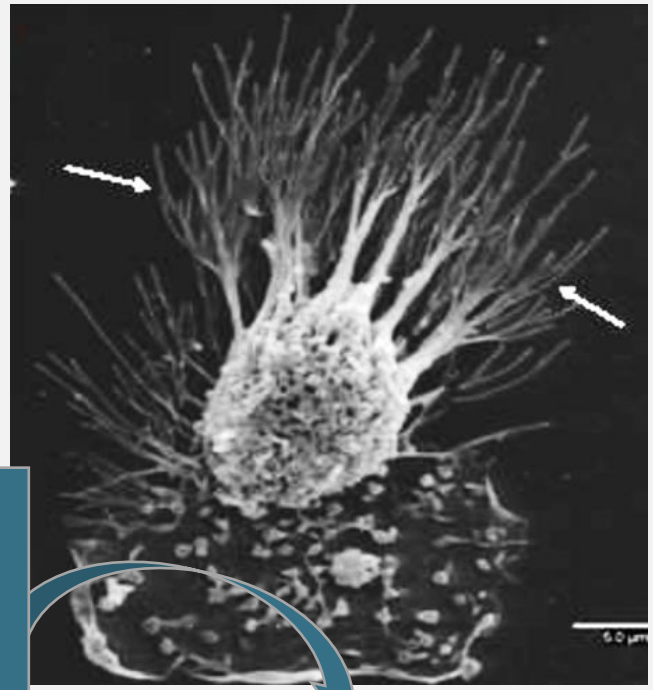
Healthy Astrocyte

Reaches out to touch and interact with other brain cells: neurons, microglia, pericytes, endothelial cells



Mature Dendritic Cell

Facilitates interactions with other immune cells: T and B lymphocytes, macrophage, endothelial cells



As a result of damage/disease, SEMA4D is expressed by

Stressed or Damaged Neurons

Activated T cells

eevans@vaccinex.com

Thanks and Gratitude

Participants, caregivers and their families!

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SIGNAL-AD

alzheimer's association®

Alzheimer's Drug Discovery Foundation

SIGNAL-AD study investigators and staff

Vaccinex Clinical Development and Research Teams:

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Terry Fisher PhD, Sr VP Clinical Development
John Leonard PhD, Megan Boise, Amber Foster, Yelena Lerman PhD, Vikas Mishra PhD, Leslie Balch, Kari Viggiani, Elaine Gersz, Crystal Mallow, Malgorazata Gil Moore, Renee Kirk, Alan Howell

WCG Clinical Services/Statistics Collaborative Initiative, IXICO, UMC, Amsterdam Neuroscience, Signant Health

Please reach out!
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Vaccinex Selected References, Neurology

1. Feigin AS, Evans EE , Fisher TL, Leonard JE, Reader A, Wittes J, Oakes D, Smith ES, Zauderer M, and the Huntington Study Group SIGNAL investigators. **Pepinemab antibody blockade of SEMA4D in patients with early Huntington's Disease: a randomized, placebo-controlled, Phase 2 trial.** Nature Medicine, 2022 Aug 8;1-11. https://www.nature.com/articles/s41591-022-01919-8
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ALZHEIMER'S DISEASE

Abbreviated Demographics and Baseline Characteristics

Topline Demographics, Number (%) of Patients	Pepinemab 40 mg/kg (N=24)	Placebo (N=26)	All Patients (N=50)
Age (years)			
Mean (SD)	72.4 (7.23)	72.1 (7.69)	72.3 (7.40)
Min, Max	55, 82	55, 83	55, 83
Sex [n (%)]			
Male	6 (25.0)	15 (57.7)	21 (42.0)
Female	18 (75.0)	11 (42.3)	29 (58.0)
Race [n (%)]			
White	20 (83.3)	23 (88.5)	43 (86.0)
Non-White	4 (16.7)	3 (11.5)	7 (14.0)
Baseline Mini Mental State Examination (MMSE)			
Mean (SD)	21.8 (4.31)	21.2 (3.20)	21.5 (3.75)
Min, Max	13.0, 29.0	14.0, 26.0	13.0, 29.0
Baseline Clinical Dementia Rating – Sum of Boxes (CDR-SB)			
Mean (SD)	3.9 (1.66)	4.8 (2.13)	4.4 (1.94)
Range(min, max)	1.0, 8.0	2.0, 11.0	1.0, 11.0
Baseline Clinical Dementia Rating – Global Score (CDR-GS)			
0.5	14 (58.3)	11 (42.3)	25 (50.0)
1.0	10 (41.7)	13 (50.0)	23 (46.0)
Baseline APOE-4 Carrier Status [n (%)]			
Non-carrier	9 (37.5)	6 (23.1)	15 (30.0)
Heterozygous	9 (37.5)	15 (57.7)	24 (48.0)
Homozygous	6 (25.0)	5 (19.2)	11 (22.0)
Duration of Disease (years)			
Mean (SD)	1.9 (1.83)	1.3 (1.28)	1.5 (1.57)
Min, Max	0.2, 8.7	0.0, 4.5	0.0, 8.7

ALZHEIMER'S DISEASE

Safety and Tolerability

Topline Safety Results, Number (%) of Patients	Pepinemab 40 mg/kg (N=24)	Placebo (N=26)	All Patients (N=50)
	n (%)	n (%)	n (%)
TEAE	21 (87.5)	23 (88.5)	44 (88.0)
Serious TEAE	1 (4.2)	7 (26.9)	8 (16.0)
TEAE with CTCAE Grade ≥ 3	2 (8.3)	4 (15.4)	6 (12.0)
TEAE Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAE Related to Treatment	0 (0.0)	0 (0.0)	0 (0.0)
TEAE Related to Treatment	12 (50.0)	5 (19.2)	17 (34.0)
TEAE Leading to Treatment Discontinuation	0 (0.0)	1 (3.8)	1 (2.0)
TEAE of Special Interest (TEAESI)	3 (12.5)	0 (0.0)	3 (6.0)
Amyloid-related imaging abnormalities			
ARIA-E	0 (0.0)	0 (0.0)	0 (0.0)
ARIA-H	2 (8.3)*	0 (0.0)	2 (4.0)
	*1 patient at screening		
Any abnormal post-baseline value(s)			
Laboratory: Hematology	19 (79.2)	22 (84.6)	41 (82.0)
Laboratory: Chemistry	24 (100.0)	26 (100.0)	50 (100.0)