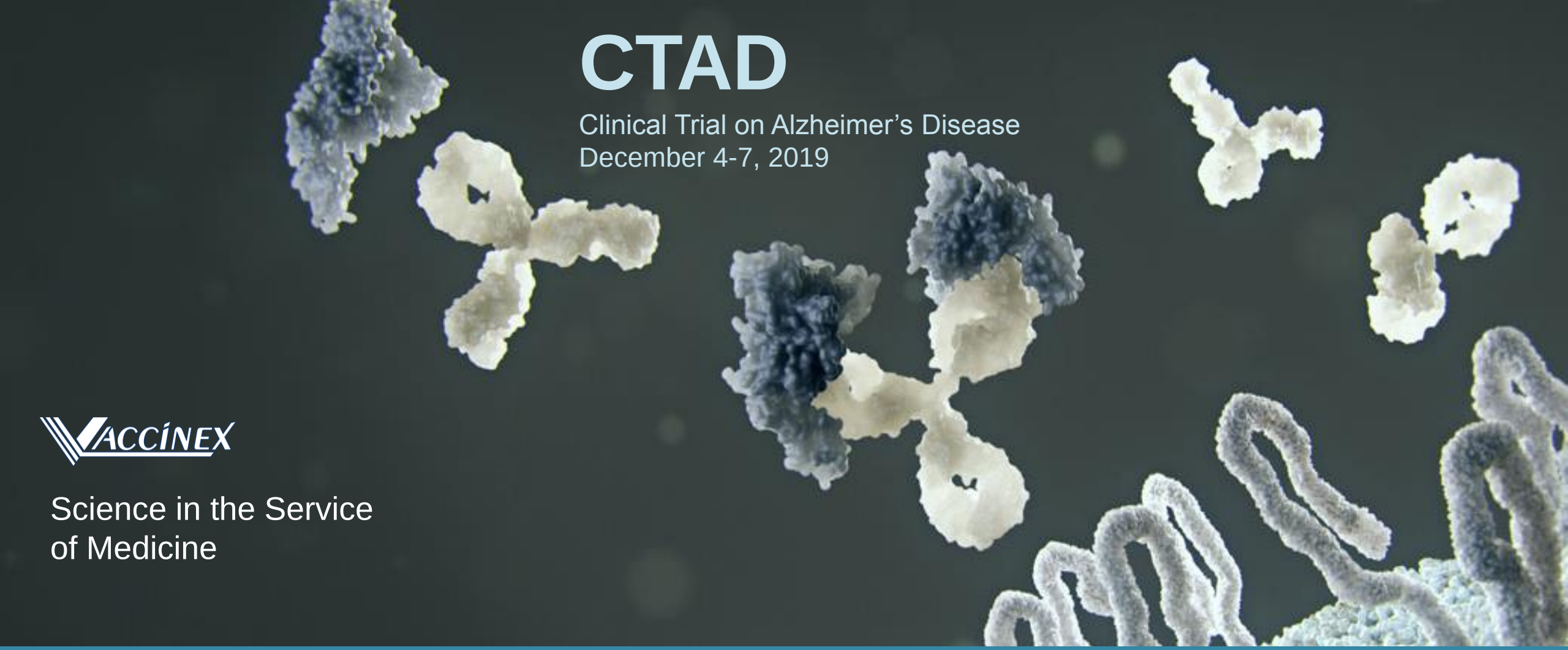


CTAD

Clinical Trial on Alzheimer's Disease
December 4-7, 2019

VACCINEX

Science in the Service
of Medicine

Regulation of glial cell activation and neurodegeneration by anti-semaphorin 4D antibody pepinemab, a potential treatment for Alzheimer's and Huntington's Disease

Elizabeth Evans, VP Preclinical Research

Disclosure Information

12TH CLINICAL TRIALS ON ALZHEIMER'S DISEASE (CTAD)

December 7, 2019

Elizabeth Evans, PhD

I have the following financial relationships to disclose:

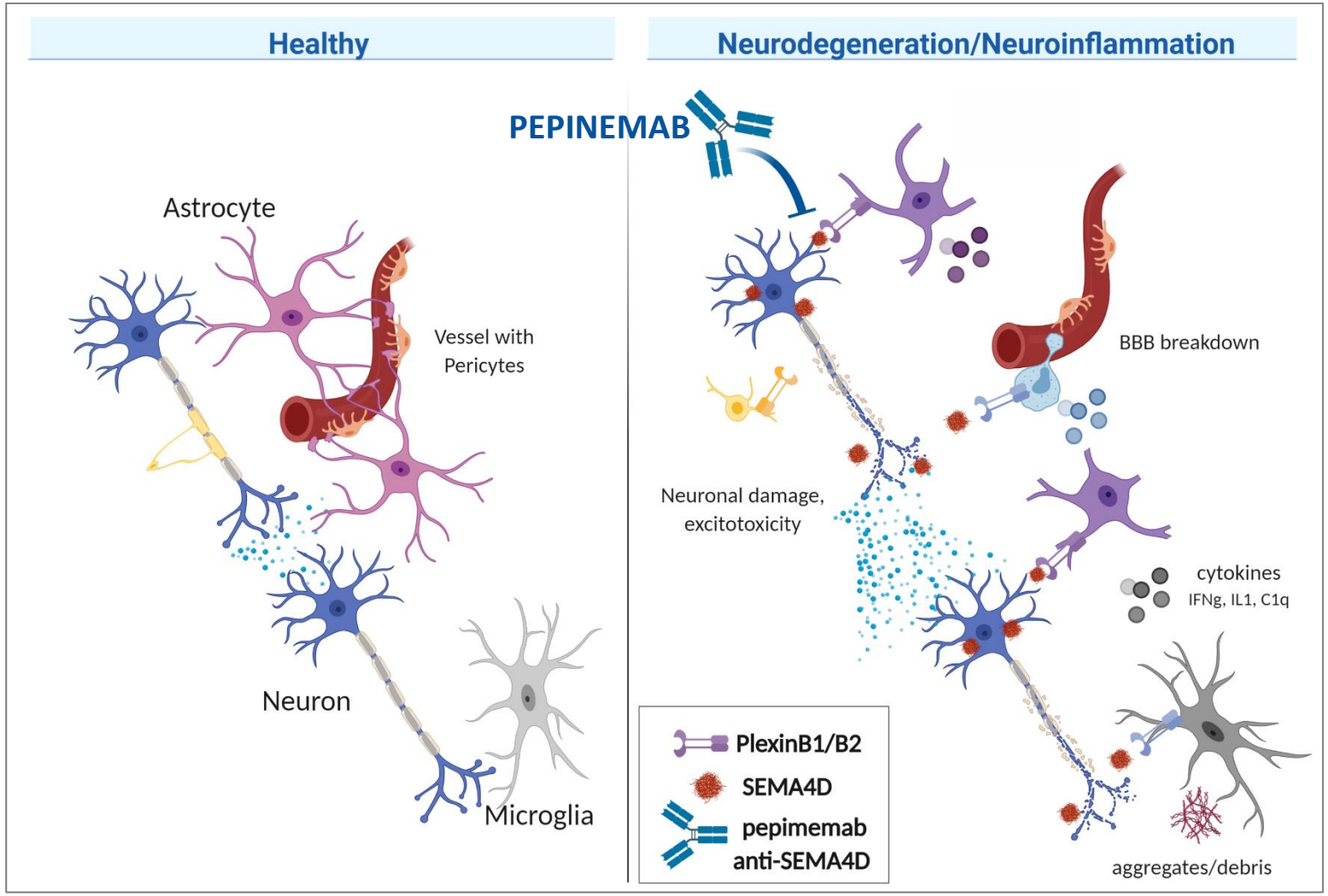
Employee and shareholder of: Vaccinex, Inc

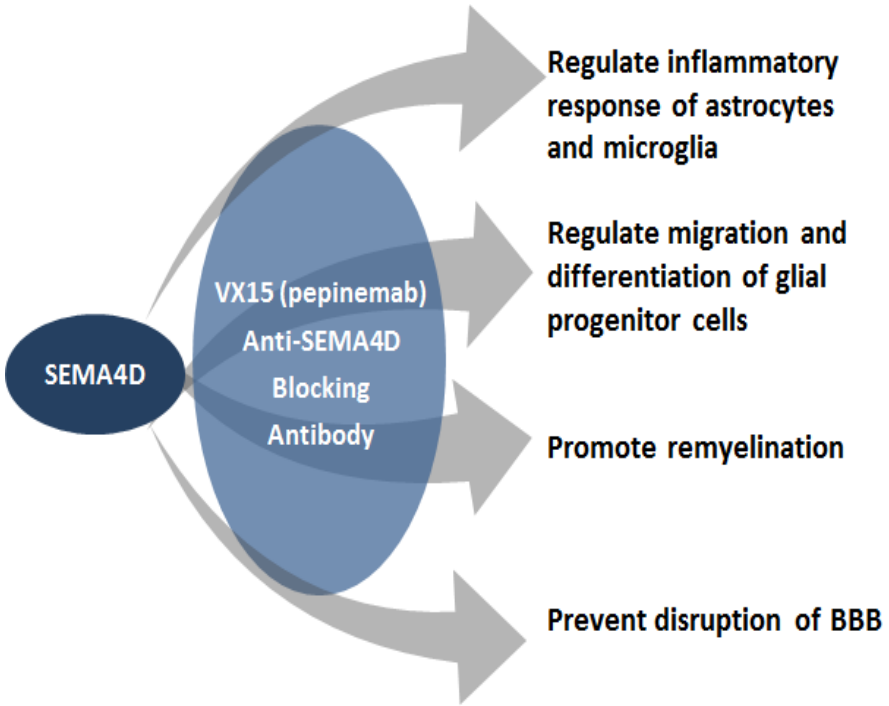
DISCLAIMER: *This document is provided for informational purposes only and does not constitute an offer to sell, or an invitation to subscribe for, purchase or exchange any securities of Vaccinex, Inc. or the solicitation of any vote or approval in any jurisdiction.*

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 our plans, expectations and objectives with respect to the CLASSICAL-Lung clinical trial, the combination of pepinemab and avelumab, and other statements identified by words such as "may," "will," "expect," "anticipate," "estimate," "intend," "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 our 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, risks related to our dependence on our lead product candidate pepinemab (VX15/2503), and other matters that could affect our development plans or the commercial potential of our product candidates. Except as required by law, we assume 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 our periodic reports filed with the Securities and Exchange Commission ("SEC") and the other risks and uncertainties described in our Form 10-K dated March 13, 2019 and subsequent filings with the SEC.*

Glia undergo inflammatory transformation that aggravates brain damage

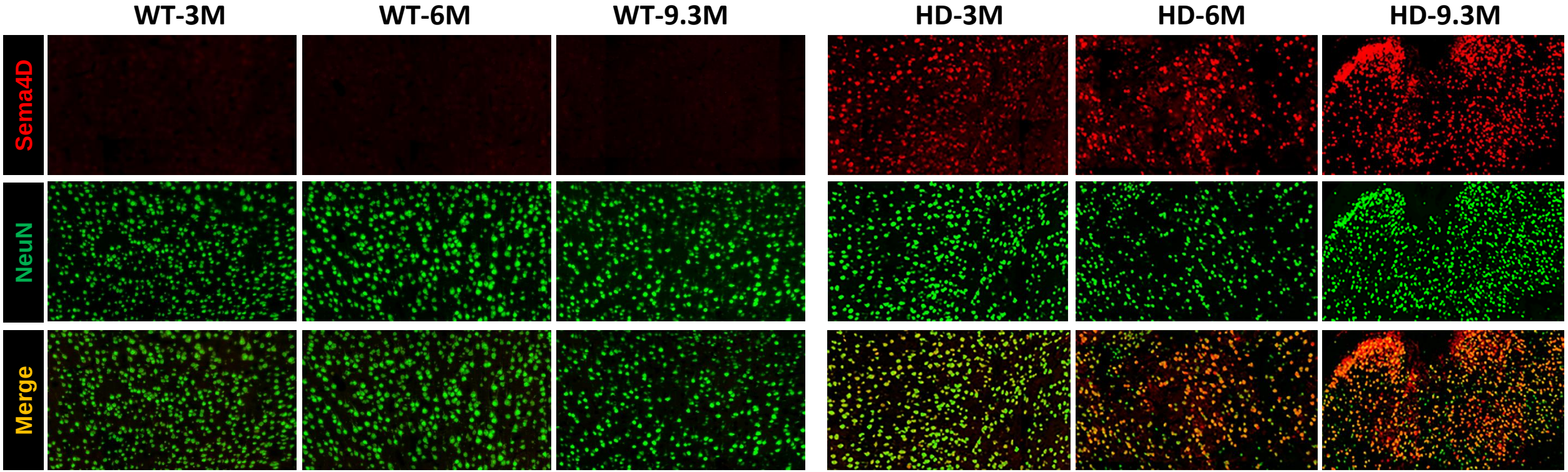
Semaphorin 4D is upregulated during injury and signals through PlexinB receptors to regulate glial cell cytoskeleton and inflammatory transformation





SEMA4D is progressively upregulated in neurons of HD mice

Q175 transgenic mouse model of HD

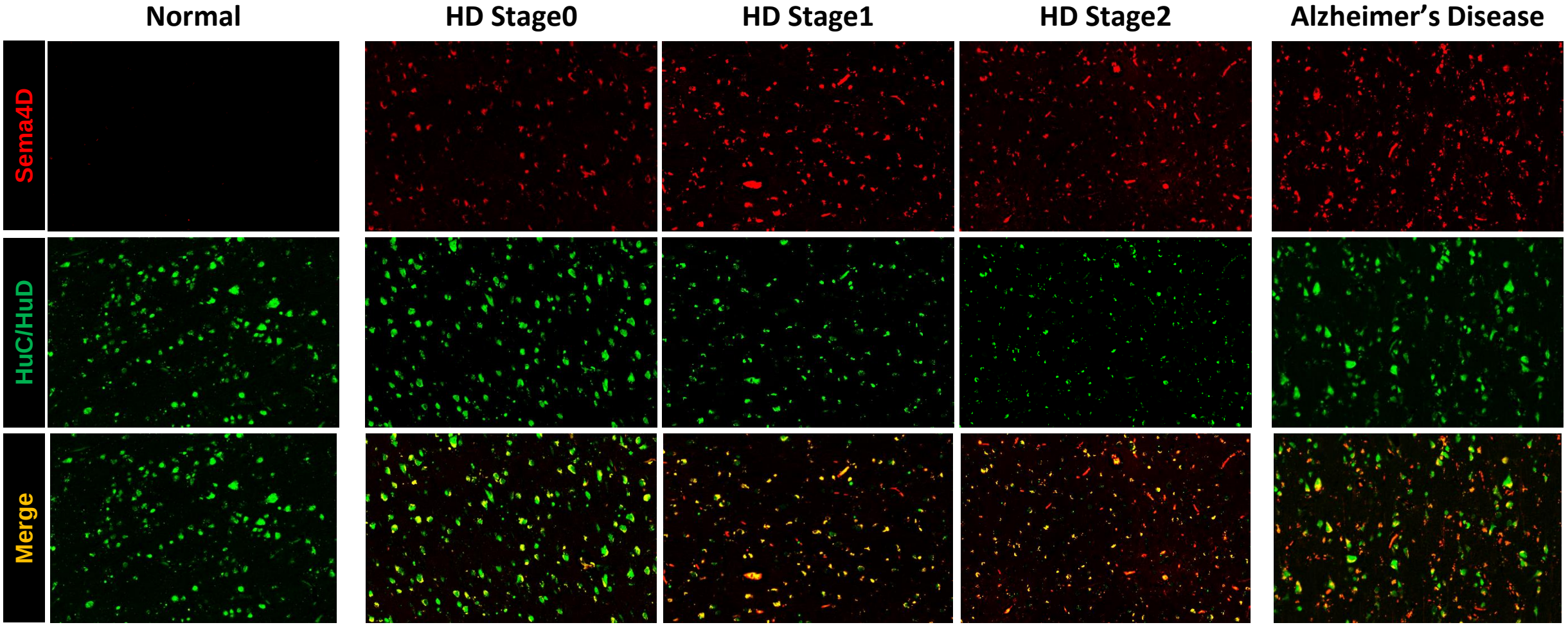


- **SEMA4D expression is upregulated in HD mice as disease progresses, compared to low expression in WT control.**
  - SEMA4D is upregulated early in disease, prior to onset of symptoms, which occurs ~ 5 months of age in Q175 HD transgenic mice.
- **SEMA4D co-localizes with NeuN+ neurons.**

NeuN/Sema staining of retrosplenial cortex region of Q175 knock-in mouse model of HD and age-matched wild type (WT) littermate controls. Representative images are shown from analysis of 3 mice/time-point. M = months of age.

SEMA4D is upregulated in neurons in human AD and during progression of HD

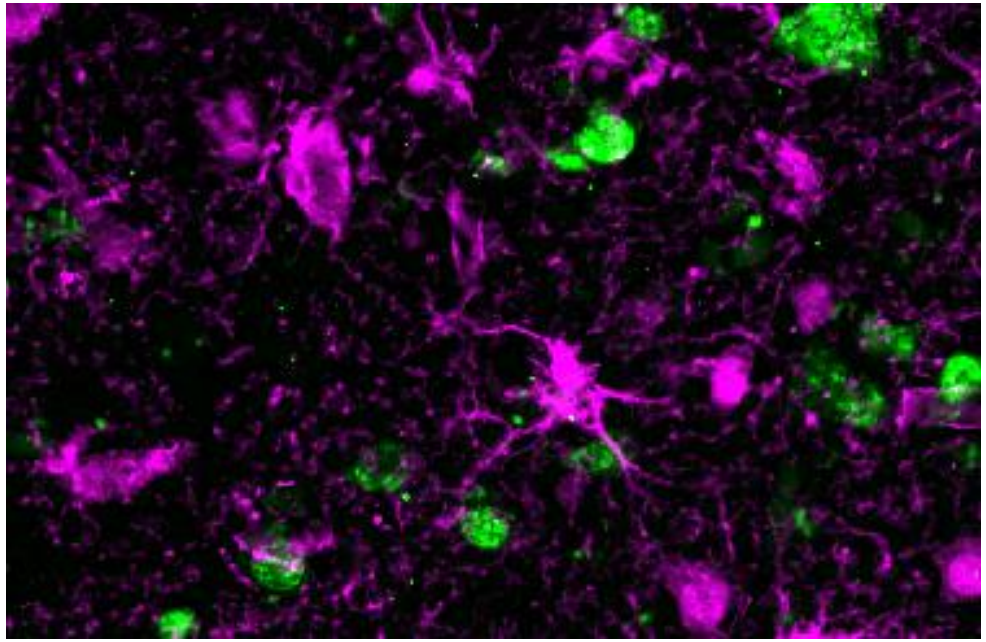
Frontal Lobe



Astrocyte processes collapse upon activation

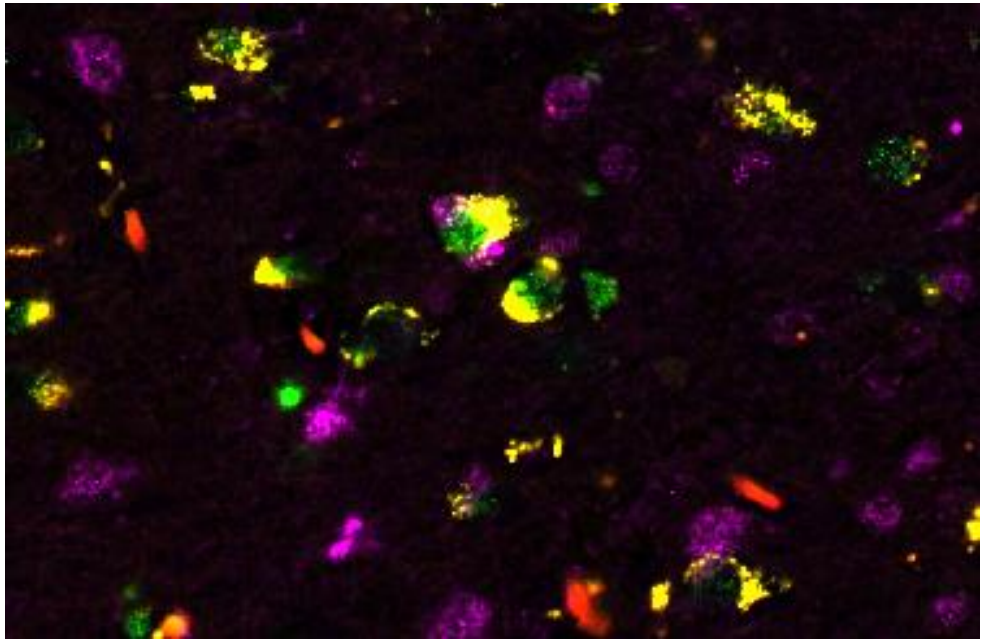
- Astrocytes transform to activated inflammatory state with disease progression
- Astrocytes express PlexinB receptors for SEMA4D

Control Human



Glutamine Synthetase expressed in astrocyte end feet
HuC/HuD expressed in neuronal body
SEMA4D

HD Stage 1

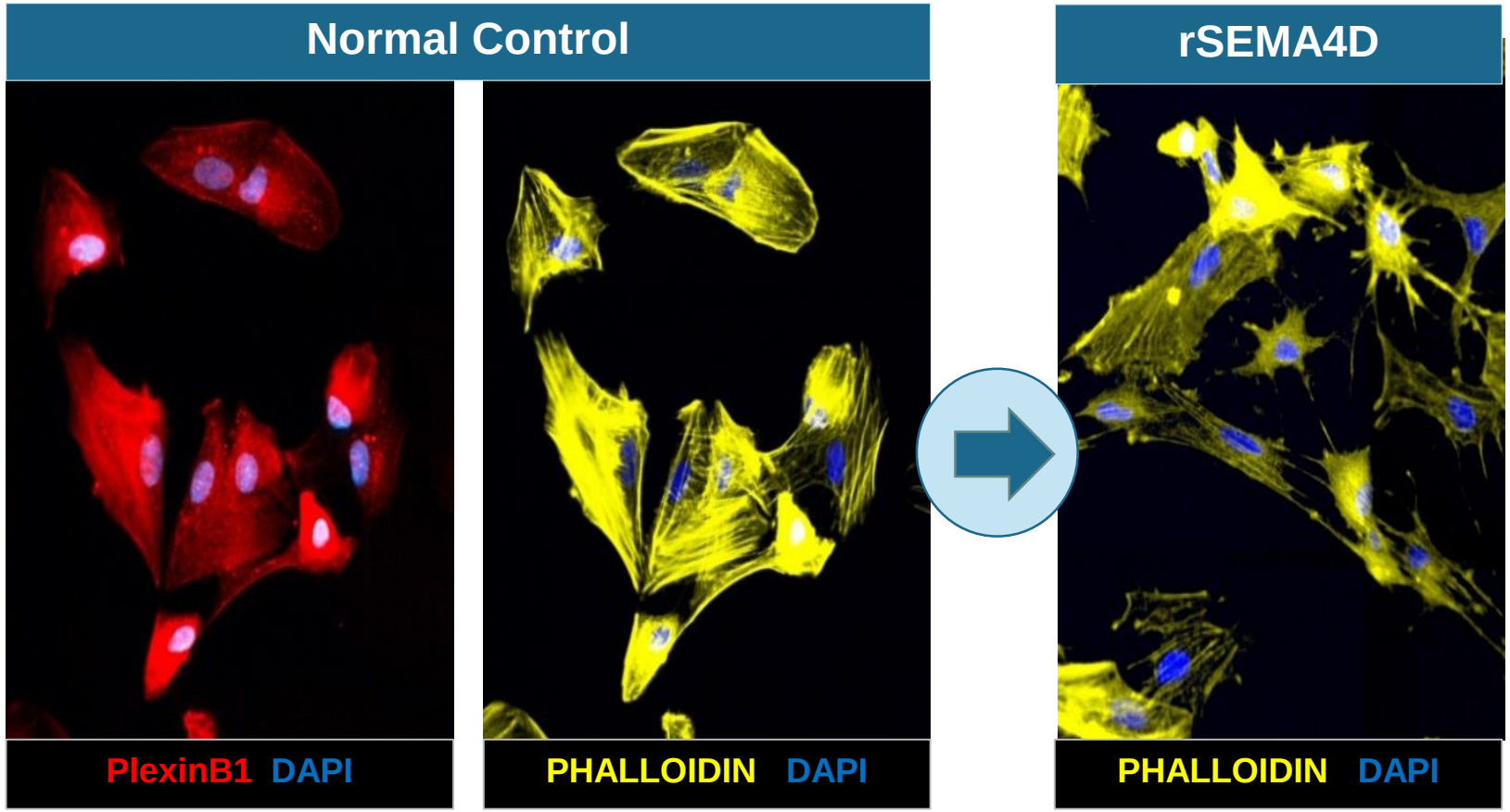


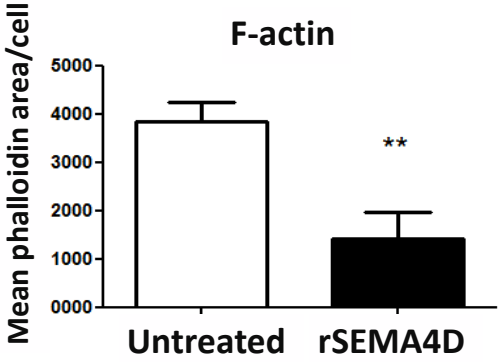
Glutamine Synthetase expressed in astrocyte end feet

SEMA4D HuC/HuD MERGE

PLXNB1+ Astrocytes collapse in presence of SEMA4D

SEMA4D-PLXNB1 binding triggers depolymerization of actin cytoskeleton





Treatment Rationale: Anti-SEMA4D Antibody can prevent inflammatory transformation of astrocytes that aggravates brain damage

- Astrocyte “arms” provide essential functional support to couple energy metabolism with neuronal activity
  - Facilitate glucose uptake from circulation
  - Cradle synapses and recycle glutamate to prevent excitotoxicity

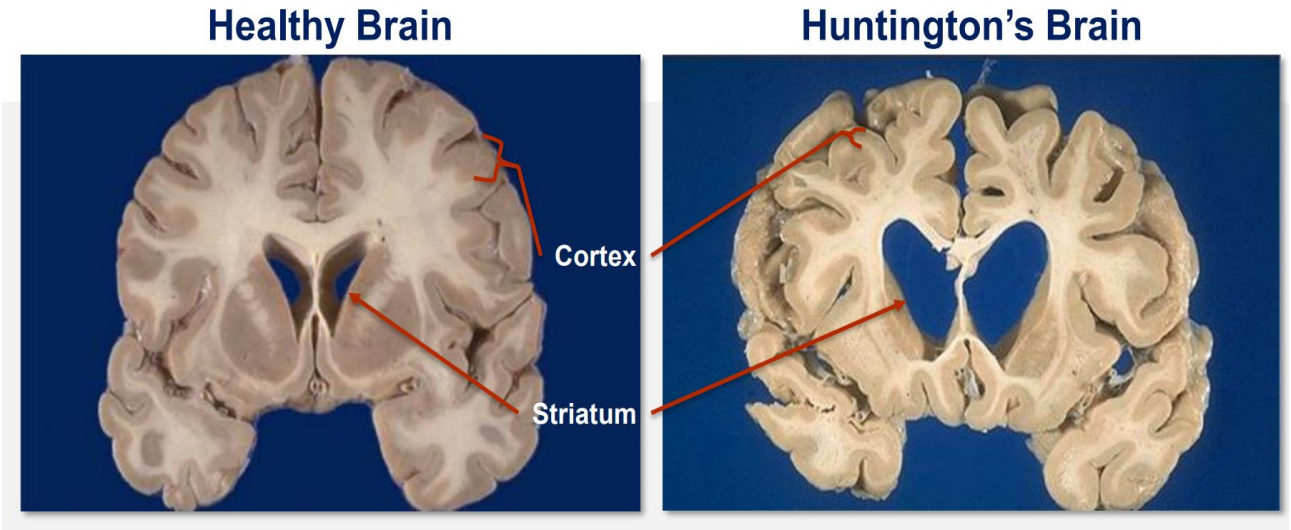
- SEMA4D is upregulated on neurons during underlying neurodegenerative disease progression
- Astrocytes express high levels of receptors for SEMA4D
  - SEMA4D triggers depolymerization of F-actin associated with transformation of astrocytes from normal to inflammatory state
- Blocking SEMA4D signaling prevents collapse of the cell cytoskeleton
  - This preserves normal astrocyte functions and prevents transition to inflammatory activity

- **HYPOTHESIS: treatment with anti-SEMA4D MAb pepinemab will prevent loss of glucose transport in brain**
  - **BIOMARKER: Glucose transport in brain is one of several important normal astrocyte functions that are known to be compromised in HD and AD and can be measured with FDG-PET**

Huntington's Disease (HD)

HD is an autosomal dominant neurodegenerative disease caused by mutation in a single gene

- Neuronal degeneration and severe atrophy is observed in multiple brain regions
- Symptoms usually appear between the ages of 30 to 50



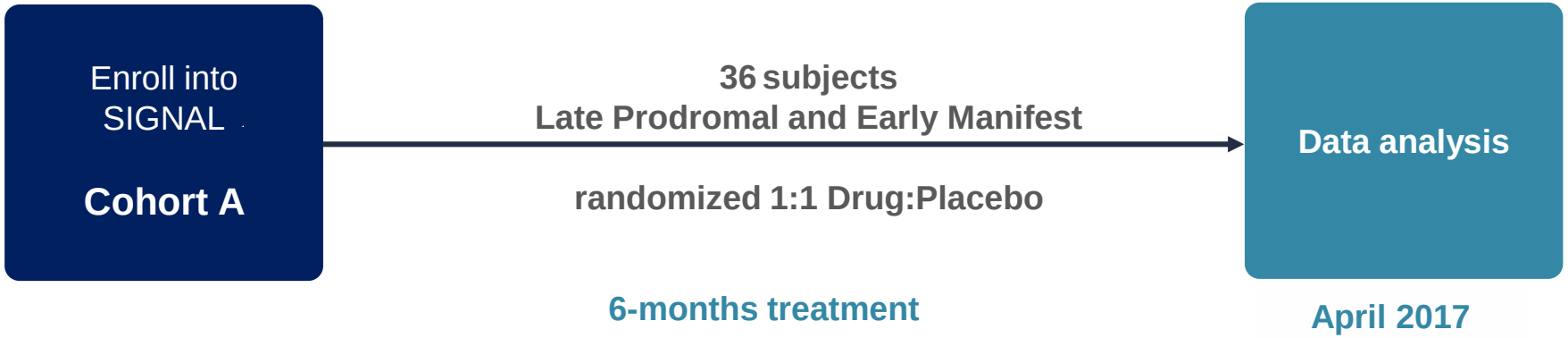
Estimated patient population ~30,000 manifest disease and 100,000 pre-manifest with inherited mutation (prodromal) in the U.S. Similar number in EU 5

There are currently no approved treatments to alter the course of HD

Preclinical proof of concept: **Southwell, et.al. Anti-semaphorin 4D immunotherapy ameliorates neuropathology and some cognitive impairment in the YAC128 mouse model of Huntington disease.** Neurobiology of Disease, 76:46–56, 2015.

Huntington's Disease Clinical Trial Design: Cohort A

Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Pharmacokinetics, and Efficacy of Pepinemab (VX15/2503) in HD



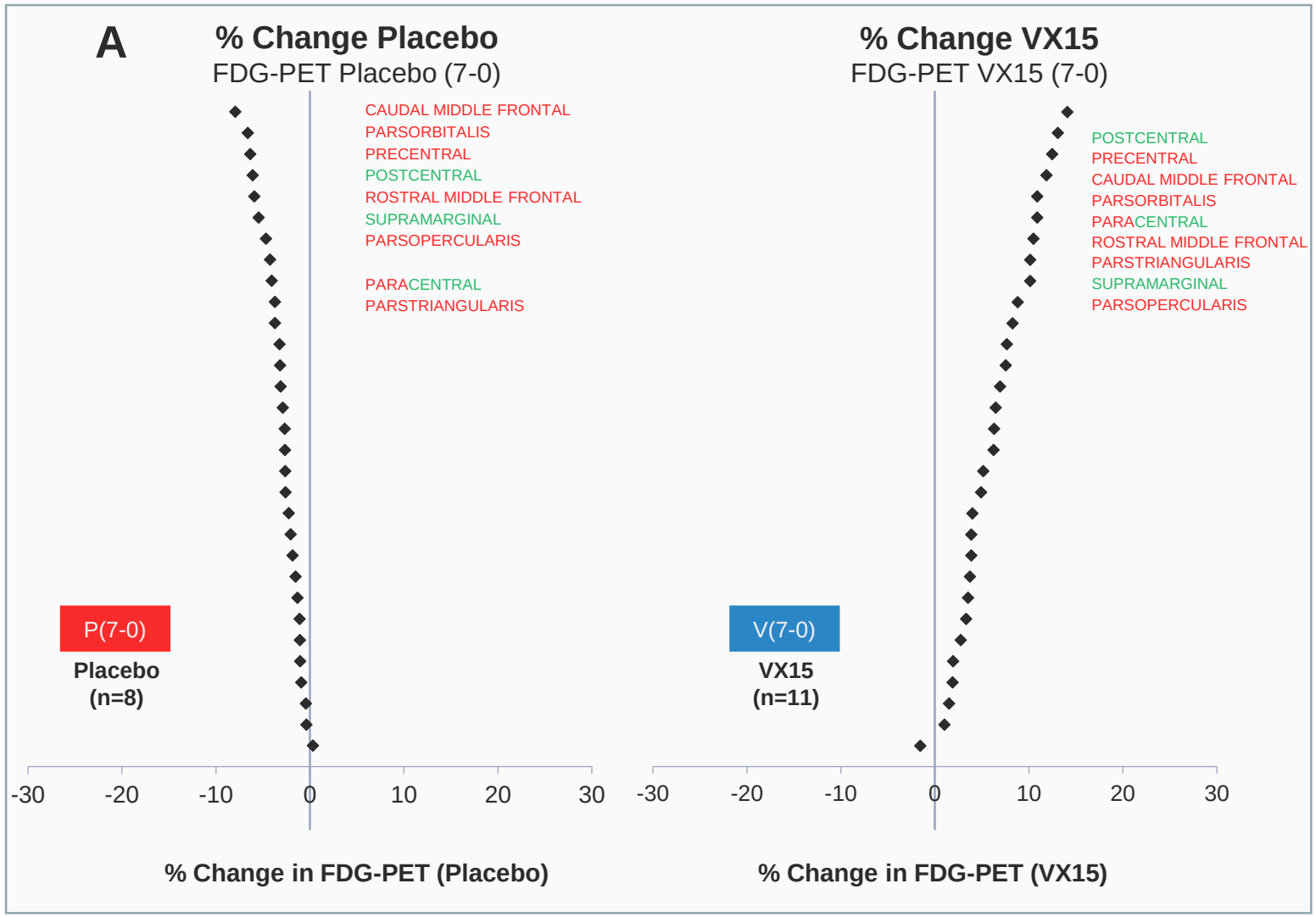
Pepinemab has been well-tolerated in SIGNAL-HD, and previously in a Phase 1 MS trial

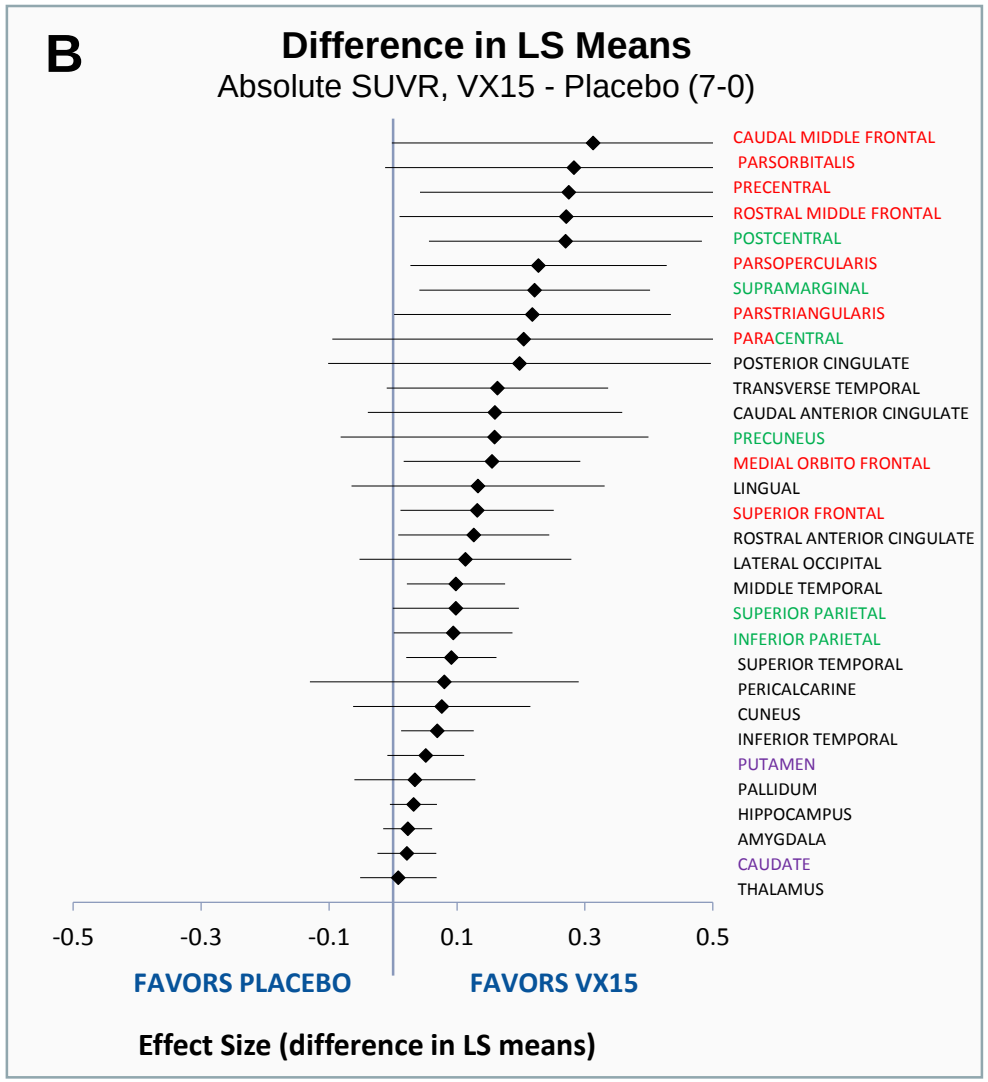
Cohort A provided important data to determine required sample size and treatment duration for potentially pivotal Cohort B study and also identified a biomarker of treatment effect

Program granted **Orphan Drug** and **Fast Track** Designation by the FDA Division of Neurology Products

Disclaimer: VX15 (pepinemab) is under clinical investigation for the treatment of Huntington's disease and has not been demonstrated to be safe and effective for this indication. There is no guarantee that VX15 (pepinemab) will be approved for the treatment of Huntington's disease by the U.S. Food and Drug Administration or by any other health authority worldwide.

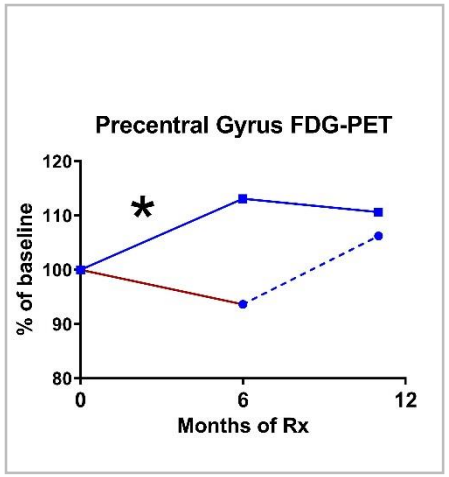
Clinical Treatment effect: FDG-PET biomarker

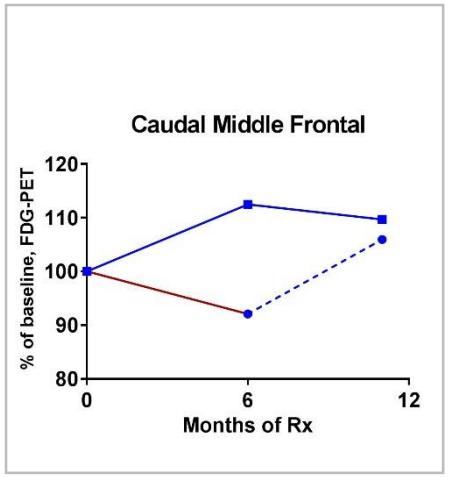


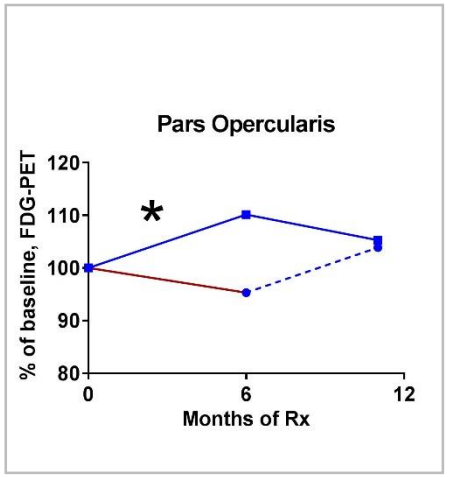


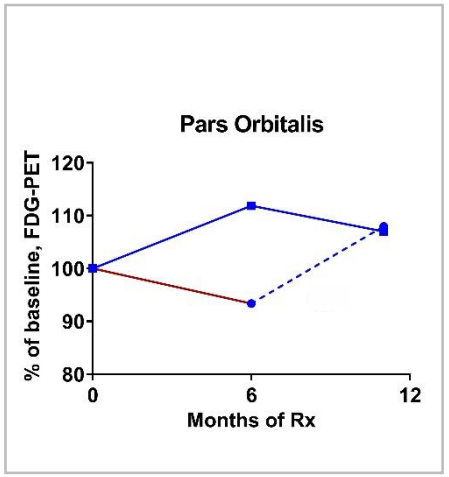
frontal lobe (red)
parietal lobe (green)

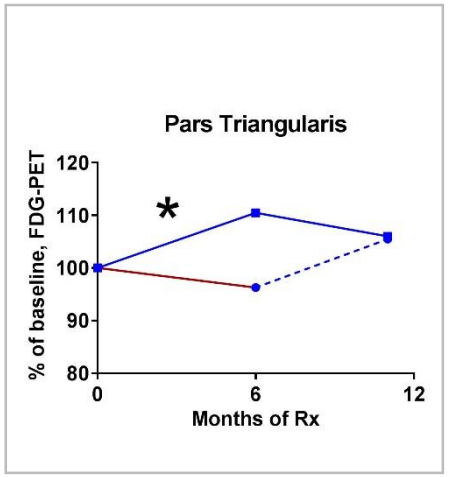
Clinical Evidence of Improved Brain Metabolic Activity in Frontal Lobe and Adjacent Parietal Regions: FDG-PET

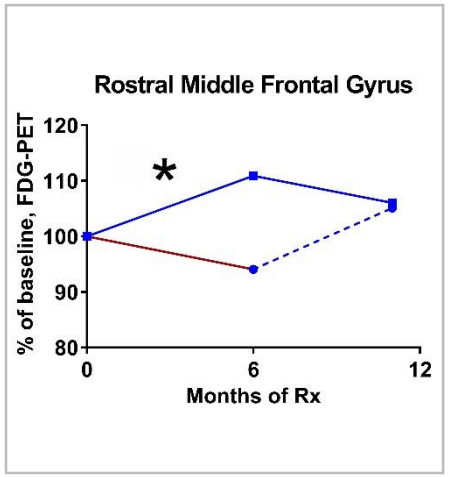


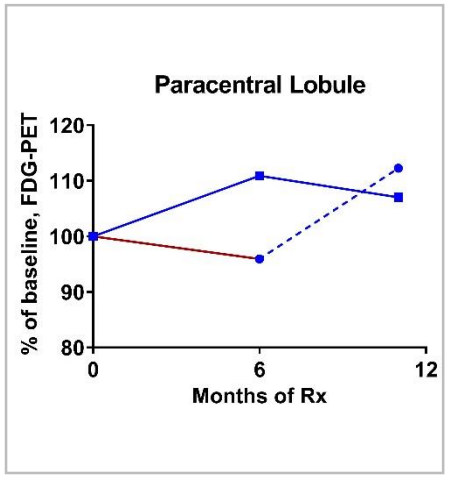


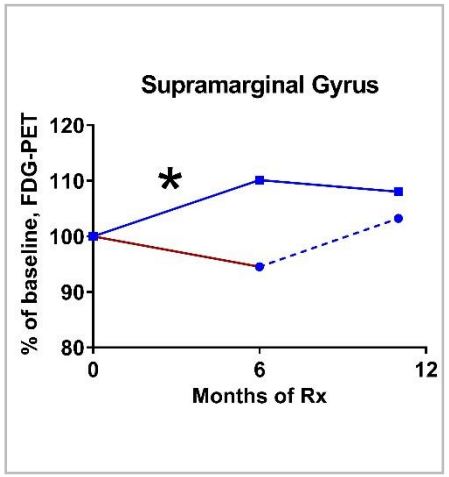


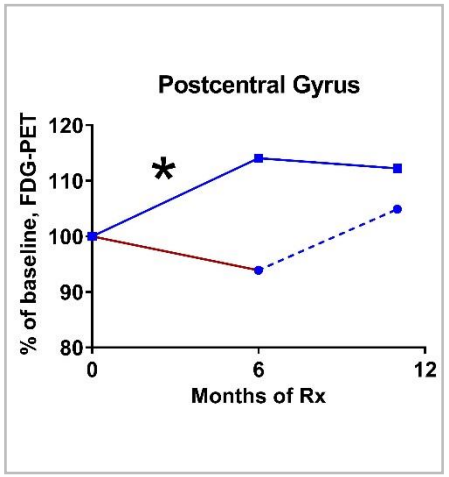


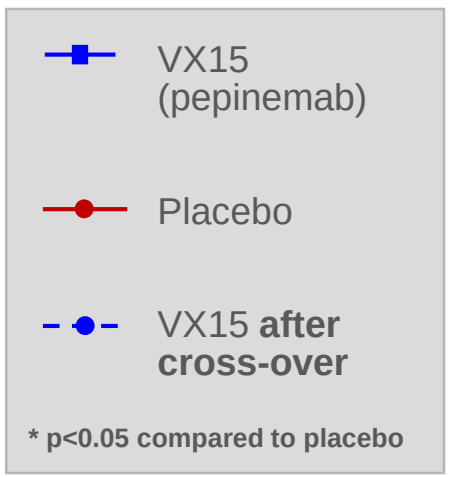




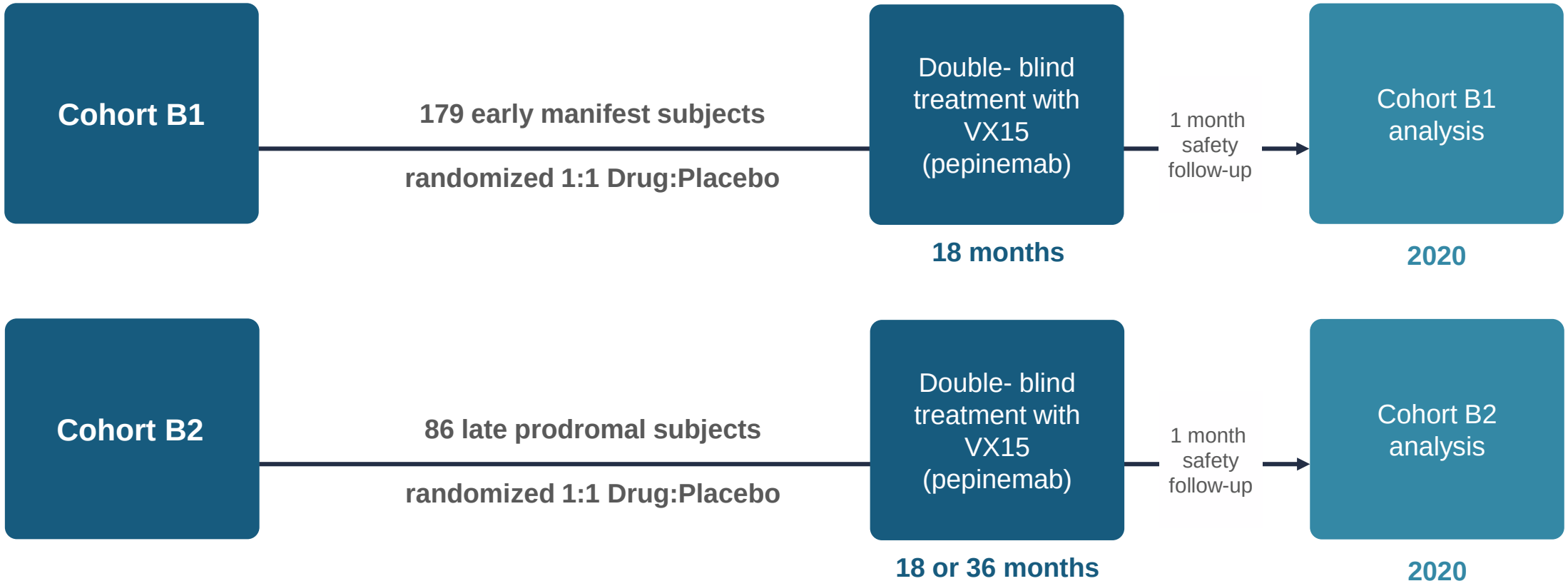








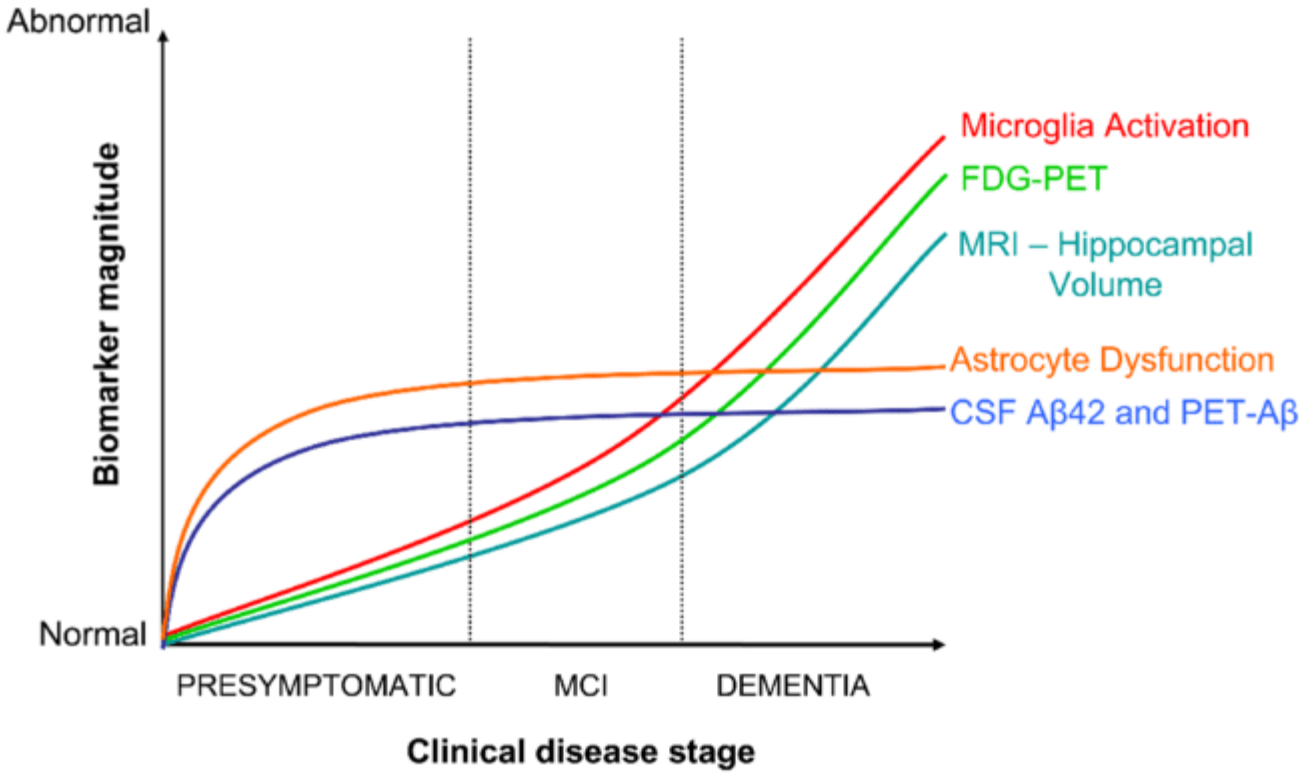
Huntington's Disease Clinical Trial Design: Cohort B



Encouraging treatment effects on FDG-PET, preservation of brain matter (reduced atrophy) and improvement in multiple motor and cognitive assessments seen in Cohort A provided important data to determine required sample size and treatment duration for potentially pivotal Cohort B study

FDG-PET is a clinically relevant biomarker in Alzheimer's Disease

- Previous studies in Alzheimer's Disease concluded that "glucose metabolism is a sensitive measure of change in cognition and functional ability and has value in predicting future cognitive decline" or "as an outcome measurement for monitoring clinically-relevant change over time"*
  - *Landau et. al., *Neurobiol Aging*. 2011; 32(7): 1207–1218
  - Hanseeuw et al, *Ann. Neurol*. 2017;81(4): 583-596



Lichtenstein, Mathieu & Carriba, Paulina & Masgrau, Roser & Pujol, Aurora & Galea, Elena. (2010). Staging Anti-Inflammatory Therapy in Alzheimer's Disease. Frontiers in aging neuroscience. 2. 142. 10.3389/fnagi.2010.00142.

Alzheimer's Disease

Phase 1b, Randomized, Double-Blind, Placebo-Controlled Safety and Biomarker Study of pepinemab Anti-SEMA4D Antibody in early Alzheimer's Disease (AD)

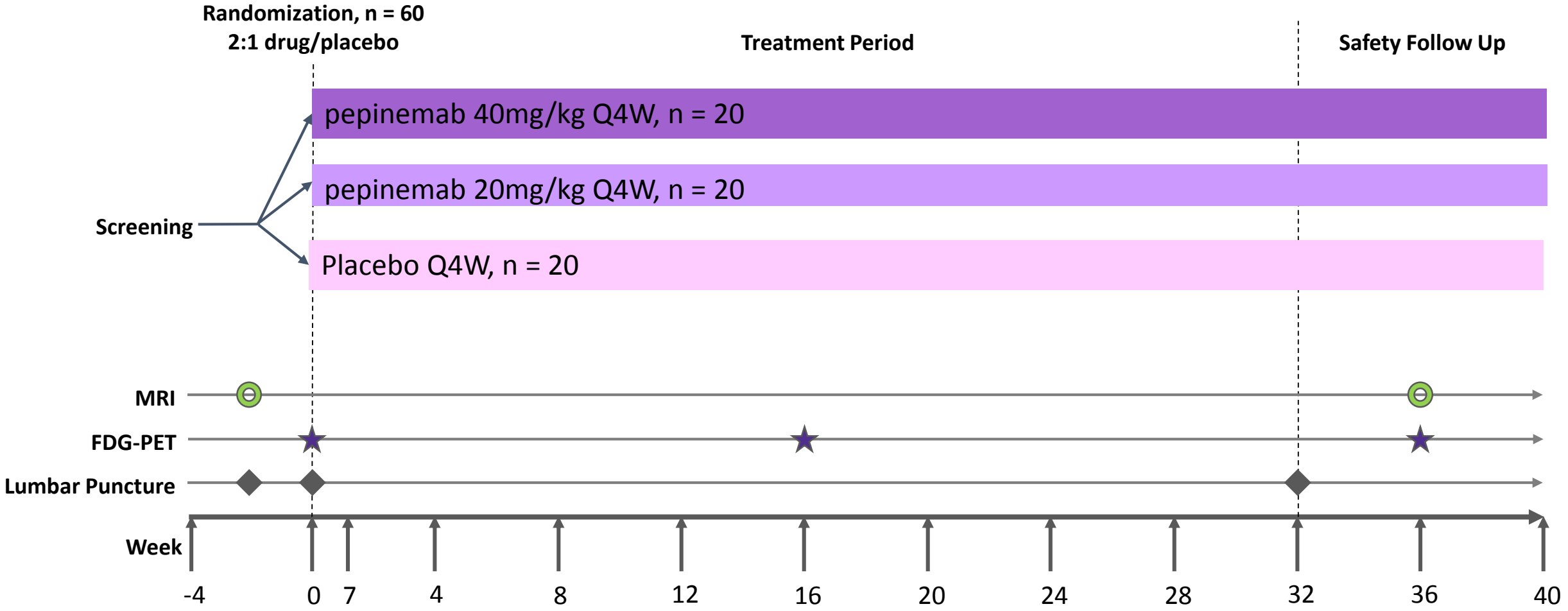
- FDG-PET may be a clinically relevant biomarker of a potential treatment effect of pepinemab and warrants clinical investigation in AD
  - Population: Early AD, defined as mild cognitive impairment (MCI) or mild Alzheimer's dementia

  - **Primary objective**: safety and tolerability
  - Key secondary objective: FDG-PET imaging at baseline, 16 weeks, and 36 weeks
  - Secondary and exploratory endpoints: cognitive and memory tests, PK/PD in blood and CSF, serum and CSF biomarkers (cytokines, NFL, $A\beta_{1-42}/A\beta_{1-40}$, p-tau, etc)

Program funding supported by Alzheimer's Association and Alzheimer's Drug Discovery Foundation

Alzheimer's Disease Trial

Proposed Trial Design



Program funding supported by Alzheimer's Association and Alzheimer's Drug Discovery Foundation

Acknowledgements

Vaccinex, Research:

- **Vikas Mishra, PhD**
- Crystal Mallow
- Leslie Balch
- Alan Howell

Vaccinex, Clinical Development:

- **Terrence Fisher, PhD**
- **Alisha Reader**
- Metodija Andonov
- Robert Parker
- Jason Condon
- Desa Rae Pastore

Vaccinex Leadership:

- Maurice Zauderer, CEO
- Ernest Smith, CSO
- John Leonard, SVP
- Raymond Watkins, COO
- Scott Royer, CFO

Eric Siemers, MD

Huntington Study Group, Andrew Feigin, Elise Kayson and Jody Goldstein and their staff at the University of Rochester Clinical Trials Coordination Center for their excellent operational support
Dr. David Oakes and his colleagues at the University of Rochester for Biostatistical and Computational analysis.
Finally, we wish to particularly thank the clinical investigators and staff at the thirty sites that are participating in the SIGNAL trial.

Patients and their families

eevans@vaccinex.com