ADVANCES IN ALZHEIMER'S
AND PARKINSON'S THERAPIES
AN AAT-AD/PD™ FOCUS MEETING

2 - 5 APRIL 2020 | VIENNA, AUSTRIA

VACCINEX

Science in the Service
of Medicine

REGULATION OF GLIAL CELL ACTIVATION AND NEURODEGENERATION BY ANTI-SEMAPHORIN 4D ANTIBODY PEPINEMAB, POTENTIAL TREATMENT FOR ALZHEIMER'S AND HUNTINGTON'S DISEASE

Elizabeth Evans, Senior VP Discovery and Translational Science

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Disclosures:

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership/ Equity Position	Employee	Other
Vaccinex				x	x		x	

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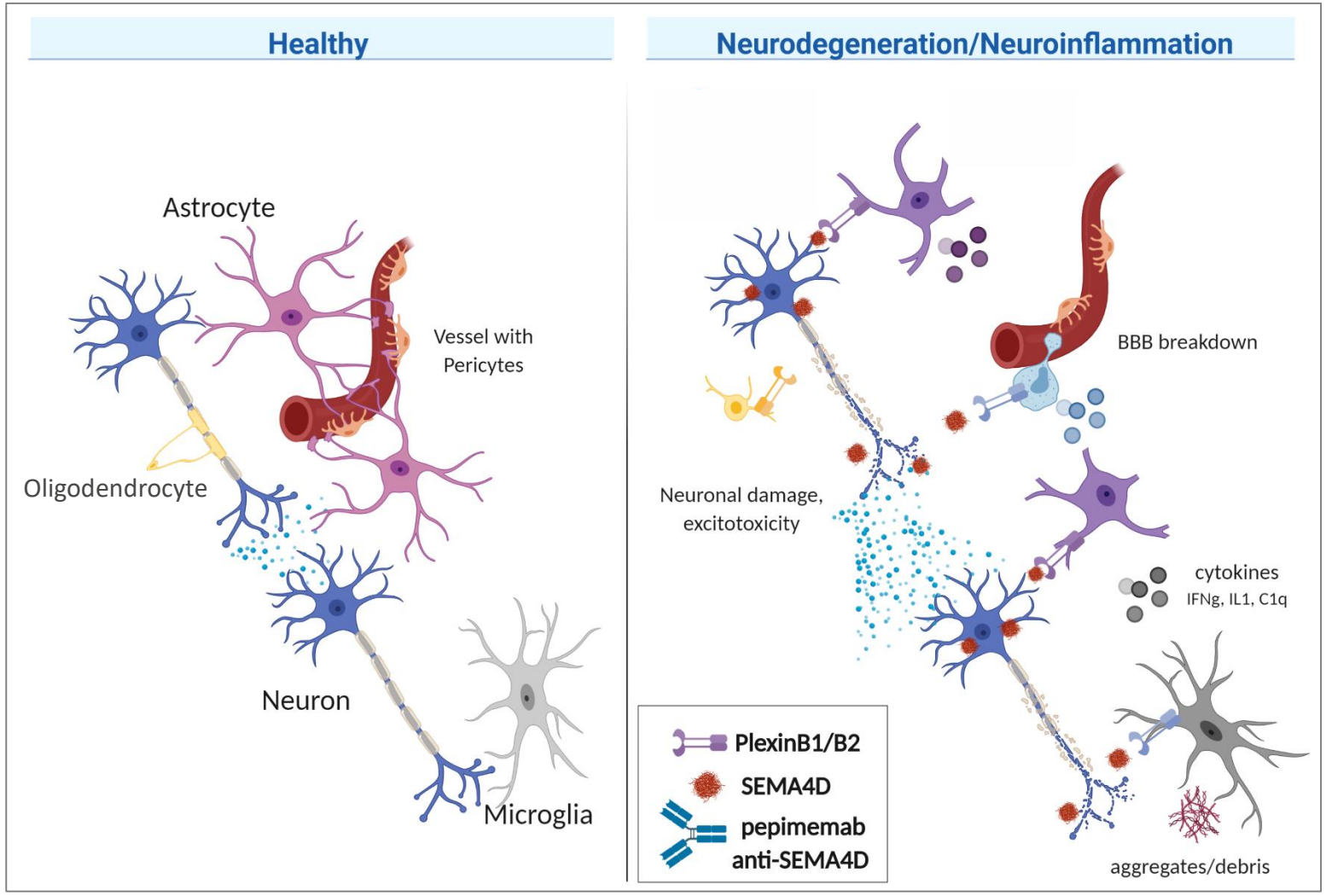
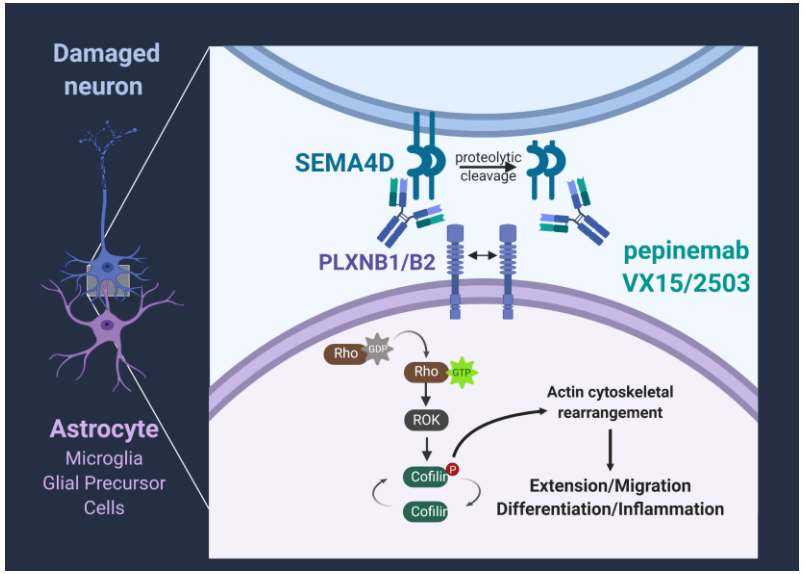
Glia undergo inflammatory transformation that aggravates brain damage

Semaphorin 4D is upregulated during Huntington's disease progression and signals through PlexinB receptors to regulate glial cell inflammatory transformation

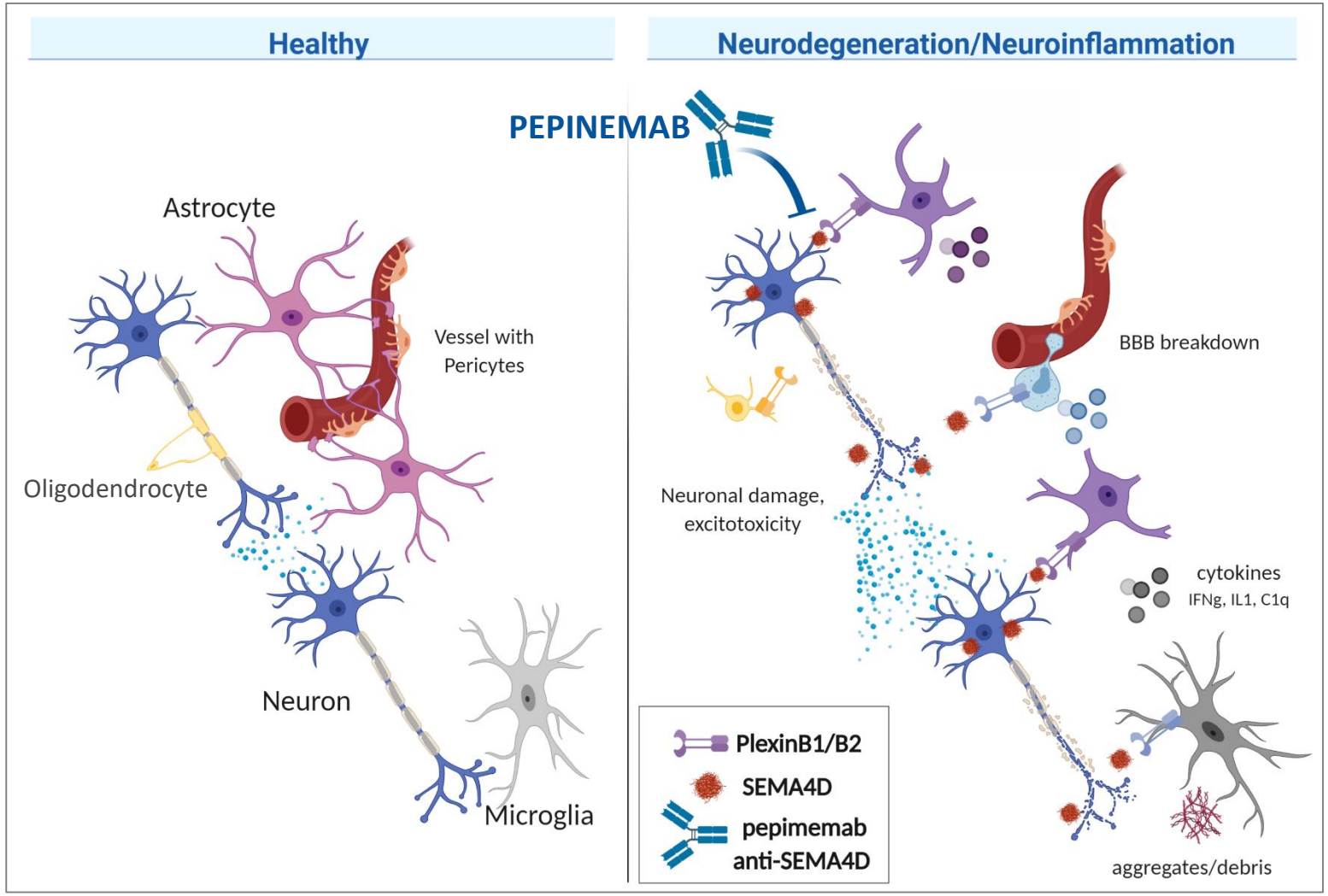


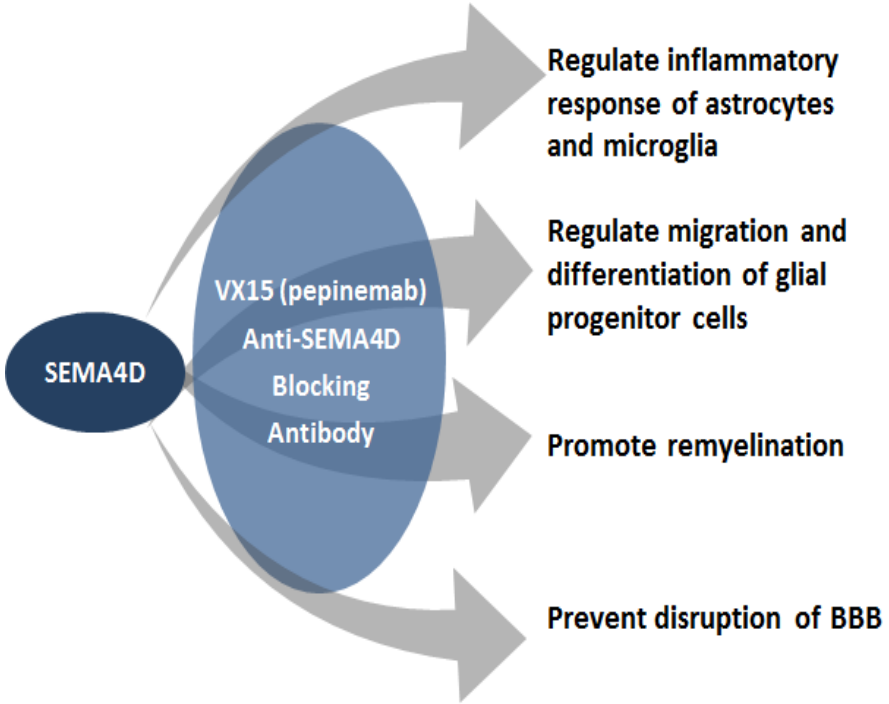


Smith et al. **SEMA4D compromises blood–brain barrier, activates microglia, and inhibits remyelination in neurodegenerative disease.** Neurobiology of Disease, 2015

Glia undergo inflammatory transformation that aggravates brain damage

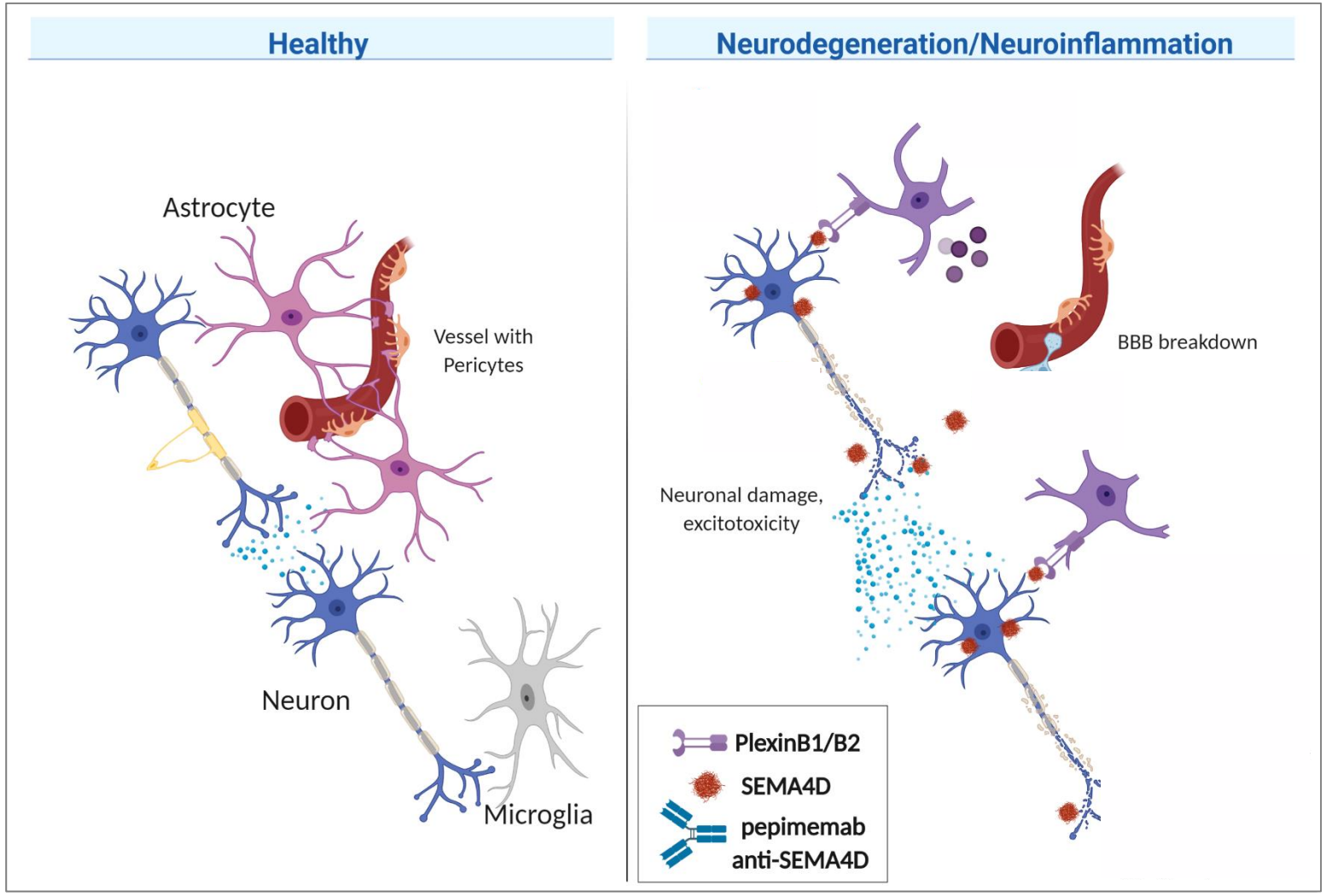
Pepinemab blocks SEMA4D signaling to restore normal glial function

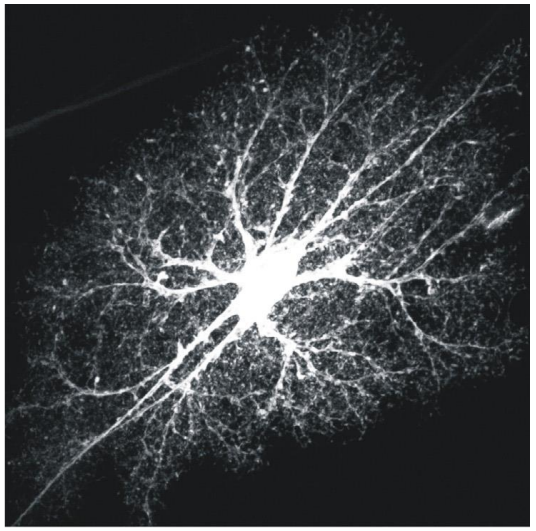




Smith et al. **SEMA4D compromises blood–brain barrier, activates microglia, and inhibits remyelination in neurodegenerative disease.** Neurobiology of Disease, 2015

Astrocytes provide functional support and respond to neuronal stress

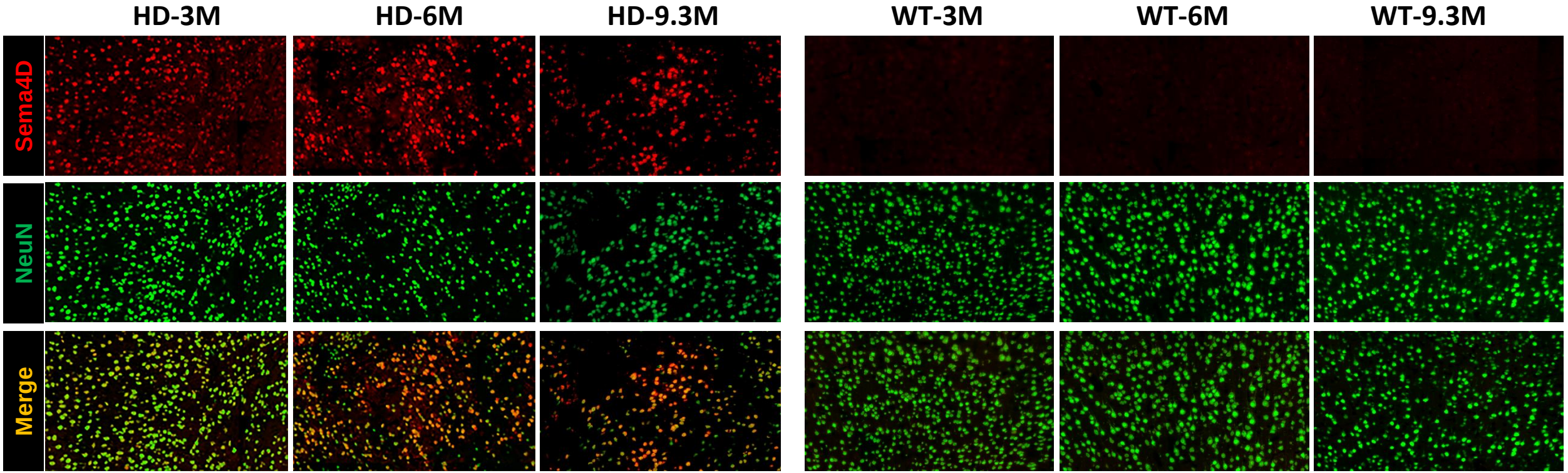




- Astrocyte “arms” provide essential functional support to couple energy metabolism with neuronal activity
  - Facilitate glucose uptake from circulation
  - Cradle synapses and recycle glutamate to prevent excitotoxicity

SEMA4D is progressively upregulated in neurons of HD mice

Q175 transgenic mouse model of HD

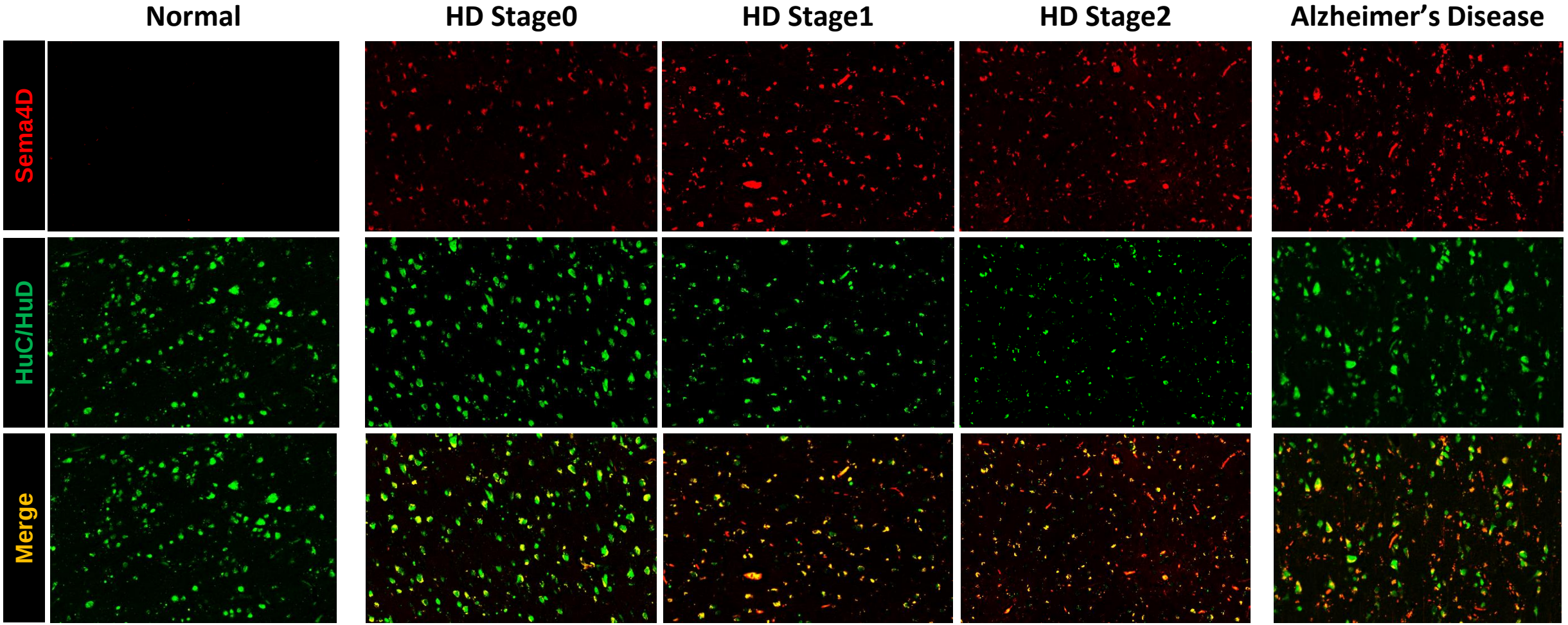


- **SEMA4D expression is upregulated in HD mice as disease progresses, compared to low expression in WT control.**
  - SEMA4D is upregulated early in disease, prior to onset of symptoms, which occurs ~ 5 months of age in Q175 HD transgenic mice.
- **SEMA4D co-localizes with NeuN+ neurons.**

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.

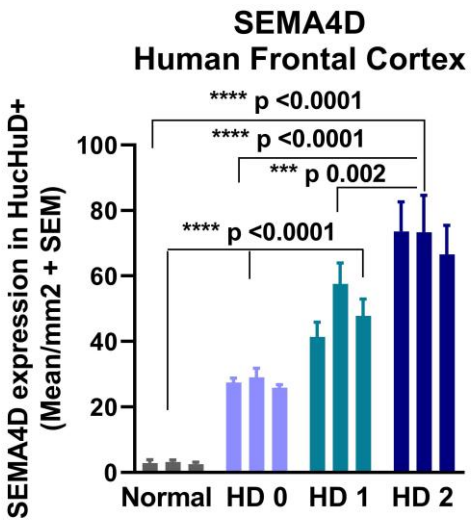
SEMA4D is upregulated in neurons in human AD and during progression of HD

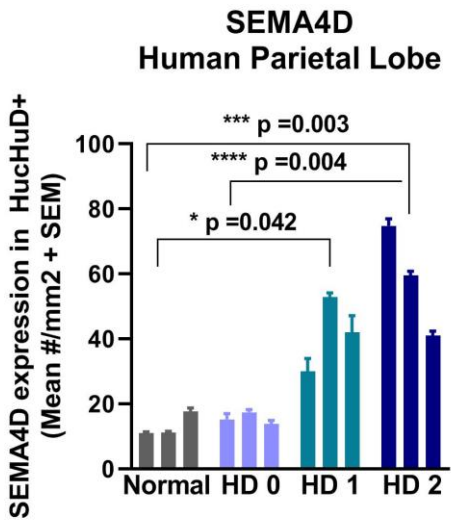
Frontal Lobe



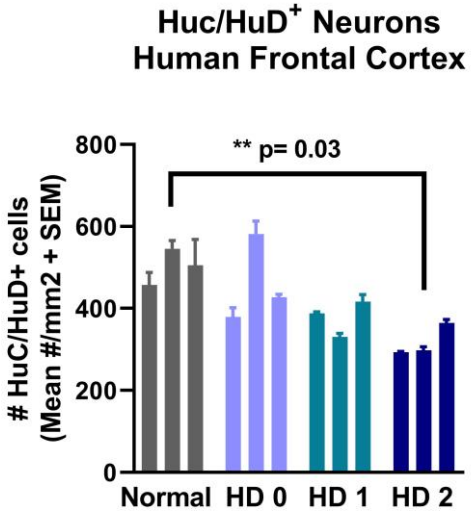
Changes in SEMA4D and Neuronal HuC/HuD Marker Expression with HD Progression

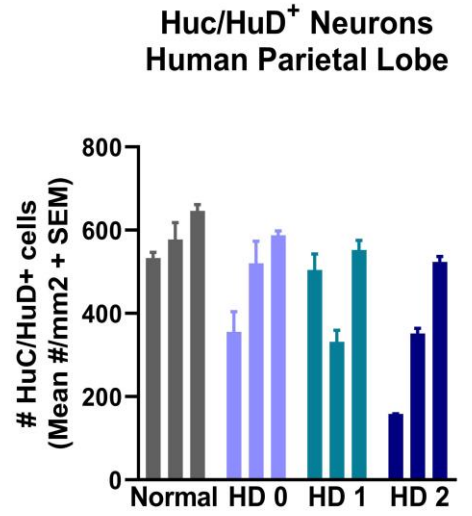
- **Progressive upregulation of SEMA4D expression is observed in Huc/HuD+ neurons with increasing pathologic stage of HD**





- **Evidence of neuronal loss is also observed as disease progresses**

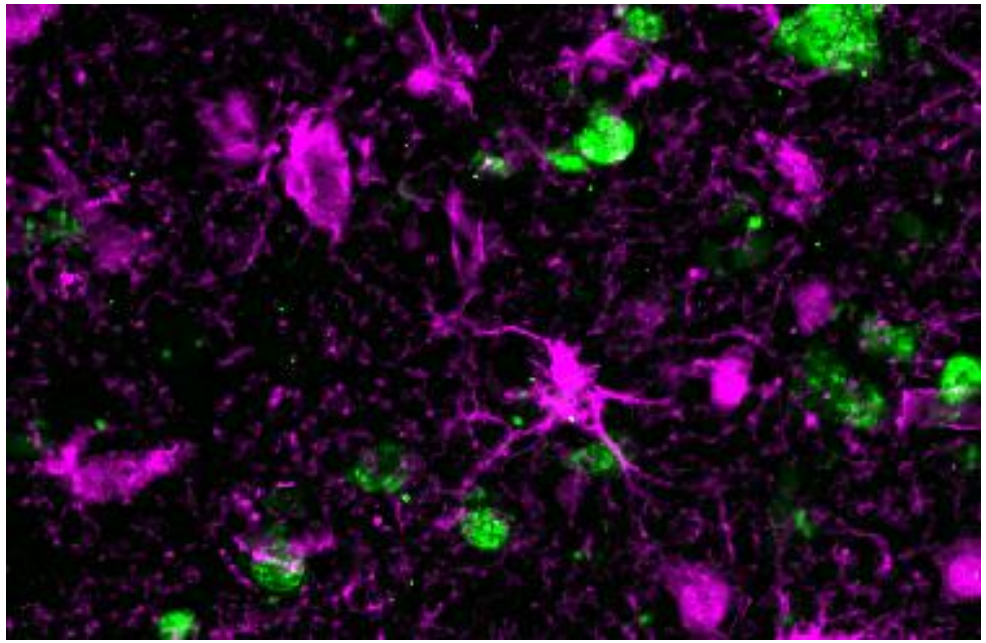




Astrocyte processes collapse upon activation

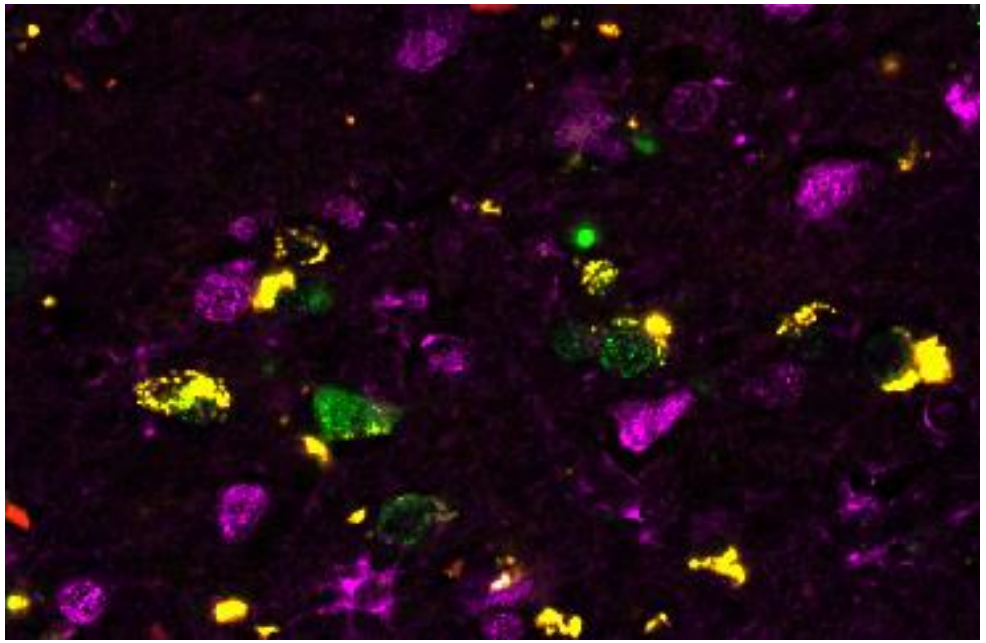
Astrocytes transform to activated inflammatory state along with cytoskeletal collapse and retraction of astrocytic end feet, concurrent neuronal upregulation of SEMA4D in HD.

Control Human



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

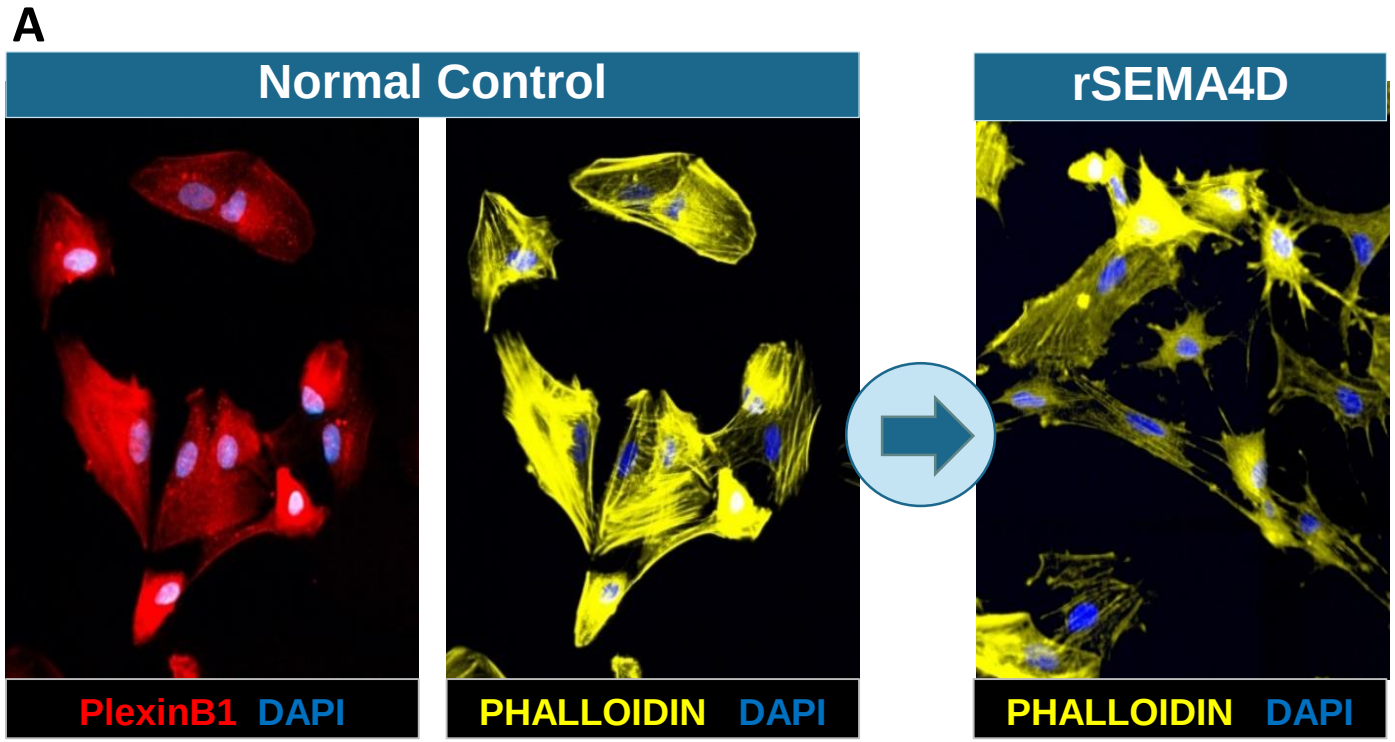
HD Stage 1

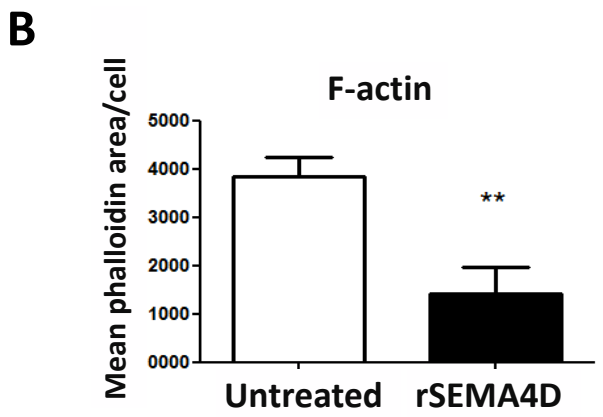


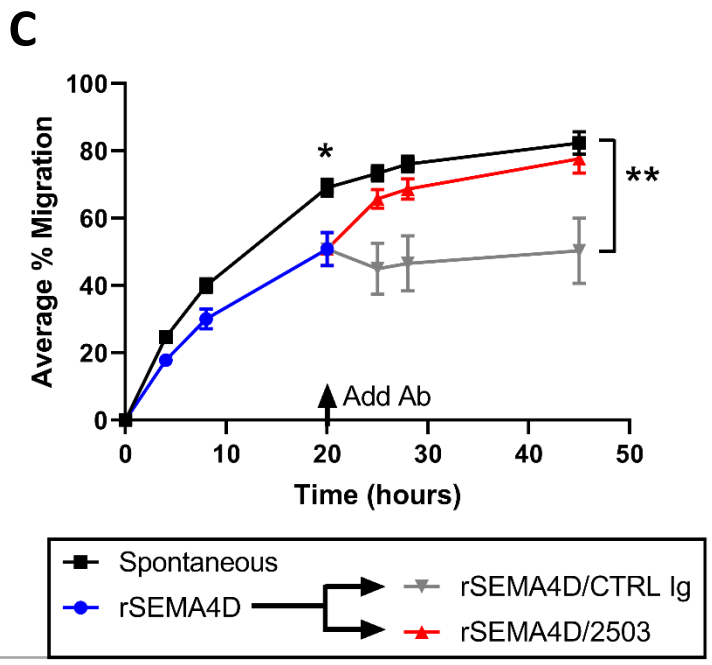
Glutamine Synthetase expressed in astrocyte cell body and end feet

SEMA4D HuC/HuD MERGE

SEMA4D Inhibits Cell Migration and Process Extension







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

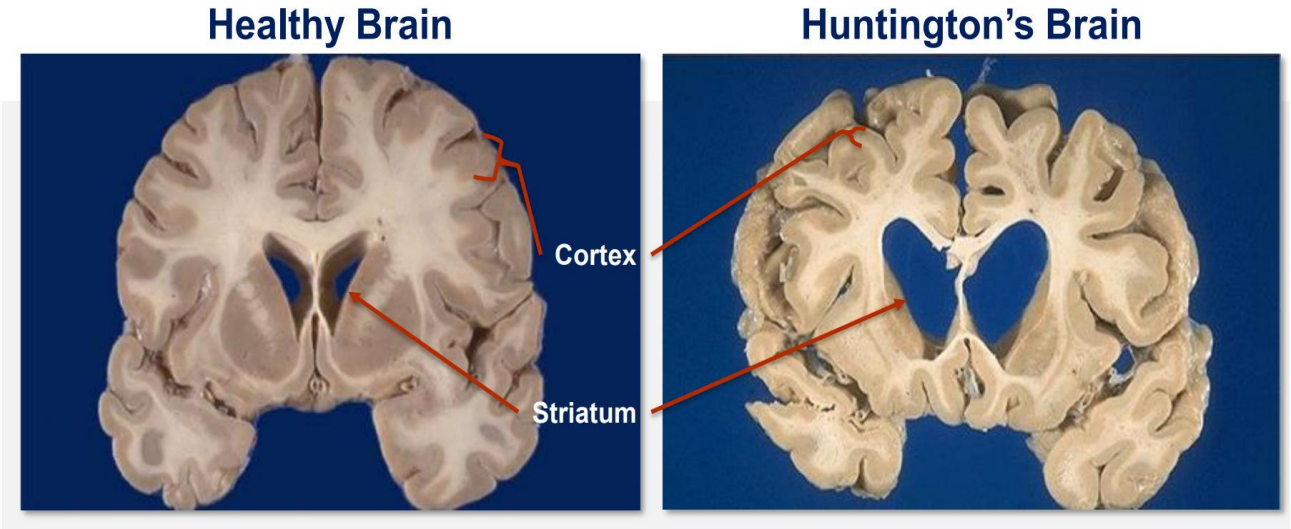
- SEMA4D is upregulated on neurons during underlying neurodegenerative disease progression
- Astrocytes express high levels of receptors for SEMA4D
  - SEMA4D triggers depolymerization of F-actin associated with transformation of astrocytes from normal to inflammatory state
- Blocking SEMA4D signaling 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



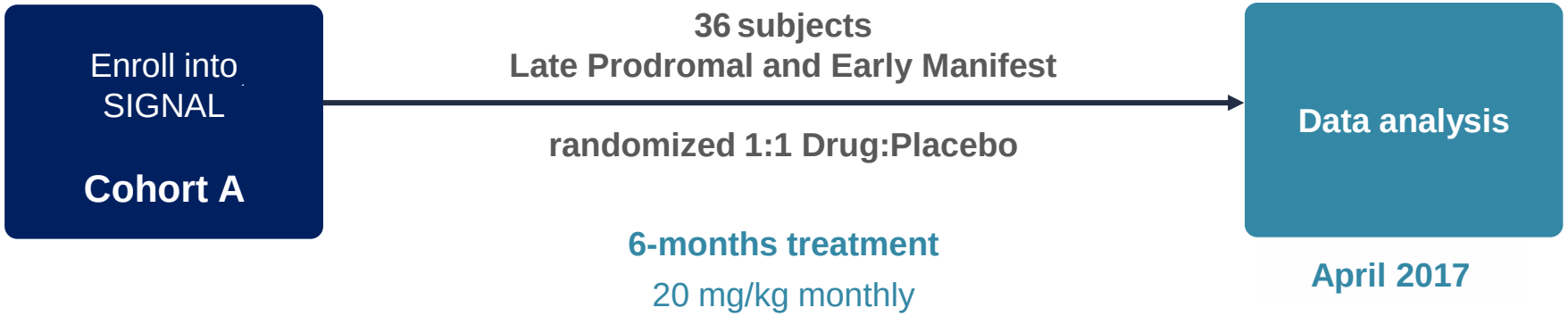
Estimated patient population ~30,000 manifest disease and 100,000 pre-manifest with inherited mutation (prodromal) in the U.S. Similar number in EU 5

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



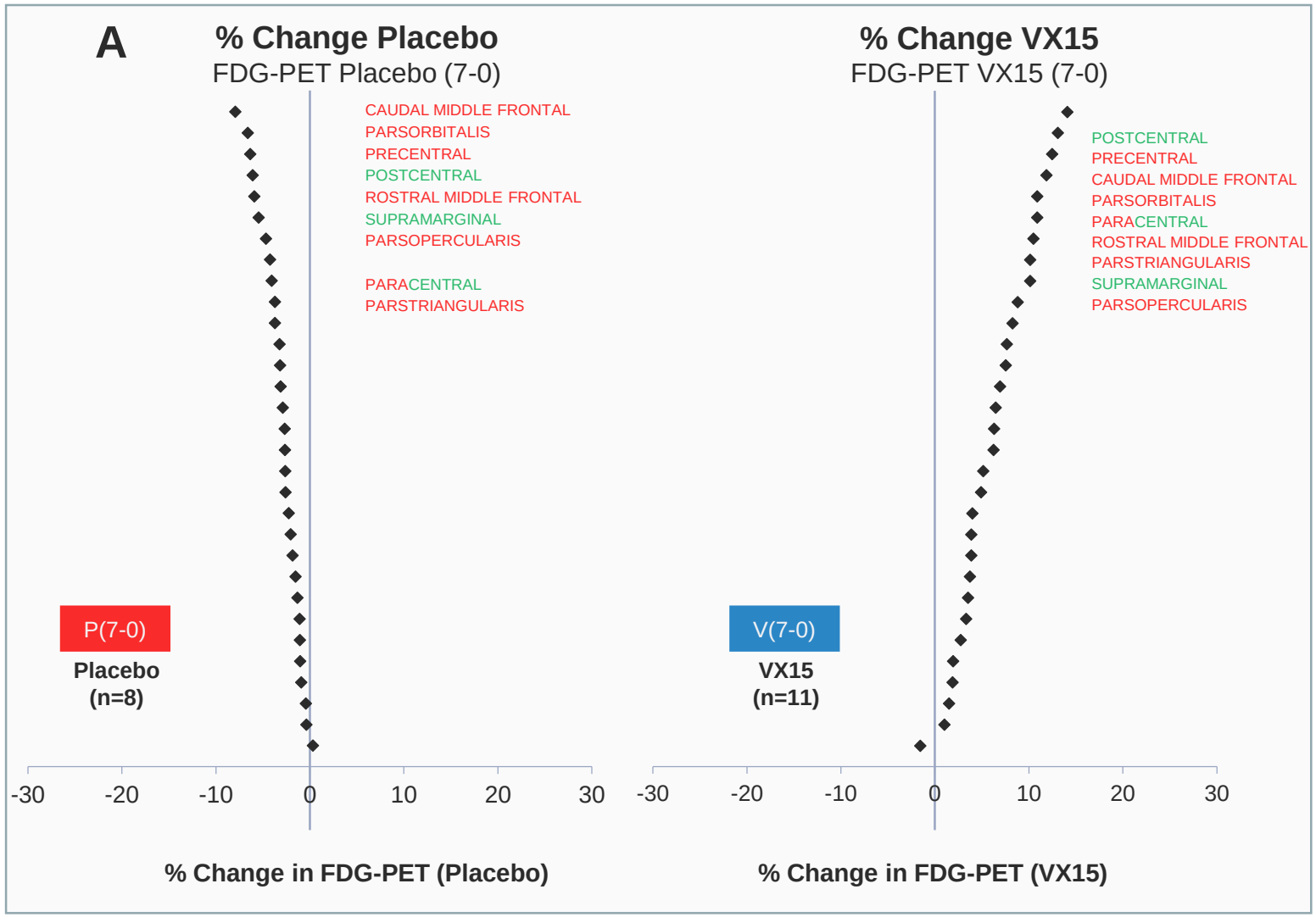
Pepinemab has been well-tolerated in SIGNAL-HD, and previously in a Phase 1 MS trial

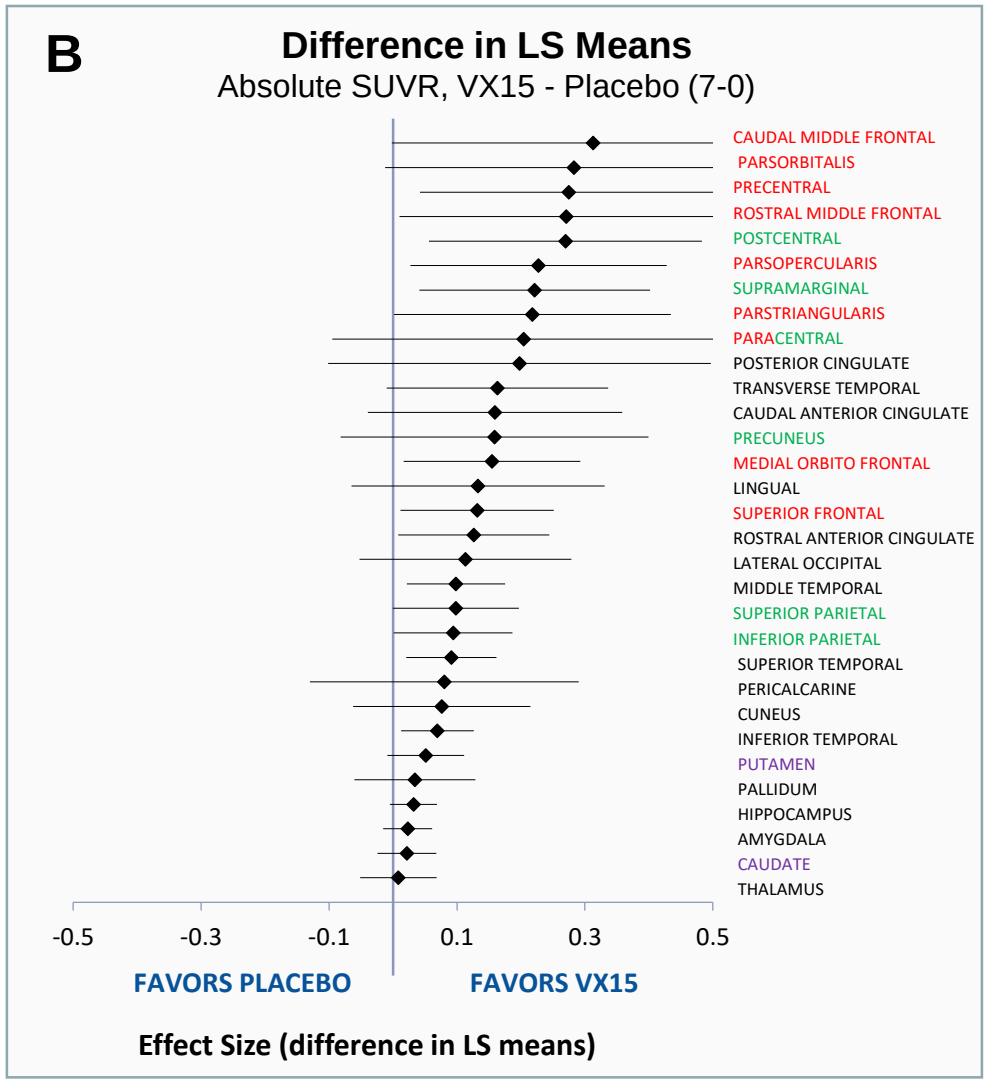
Cohort A provided important data to determine required sample size and treatment duration for potentially pivotal Cohort B study and also identified a biomarker of treatment effect

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.

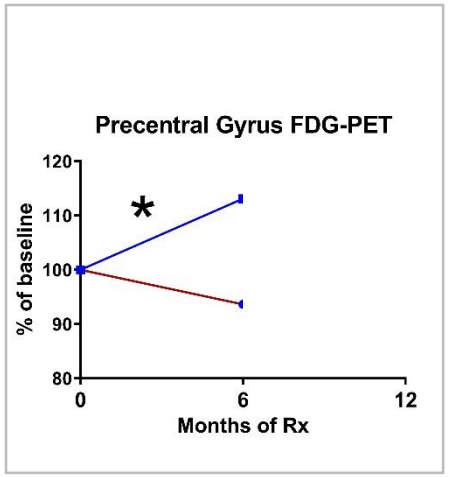
Clinical Treatment effect: FDG-PET biomarker

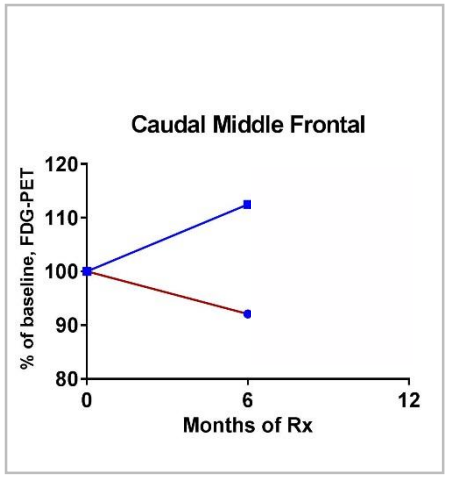


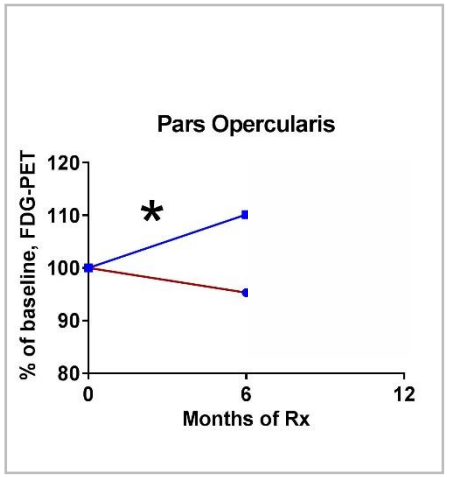


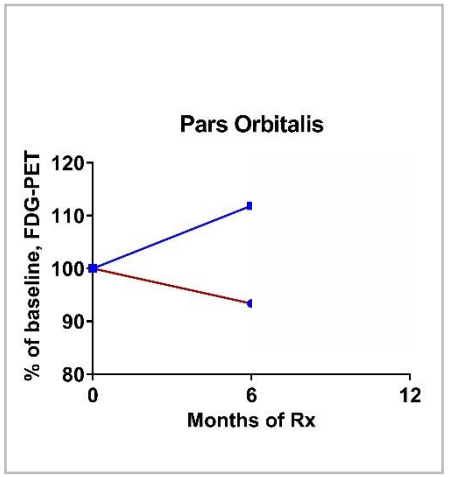
frontal lobe (red)
parietal lobe (green)

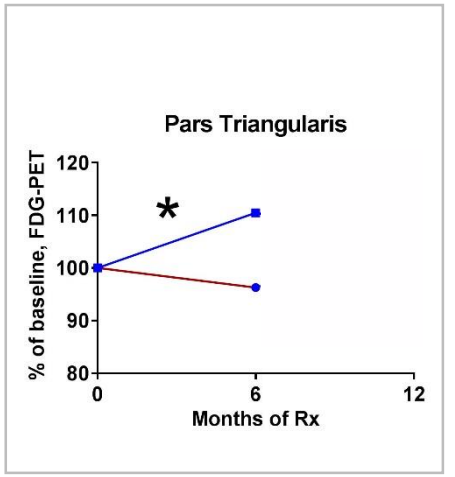
Clinical Evidence of Improved Brain Metabolic Activity in Frontal Lobe and Adjacent Parietal Regions: FDG-PET

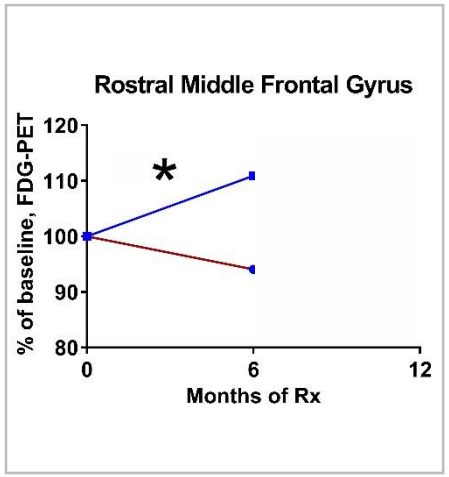


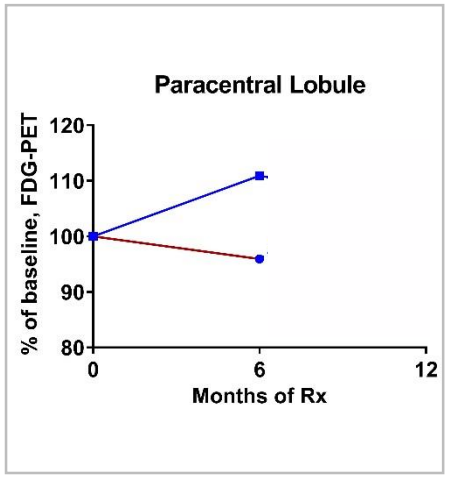


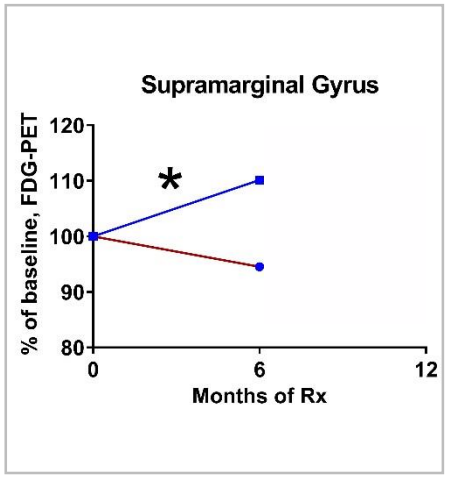


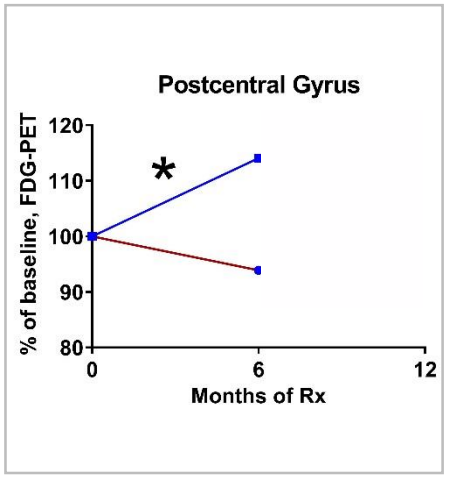


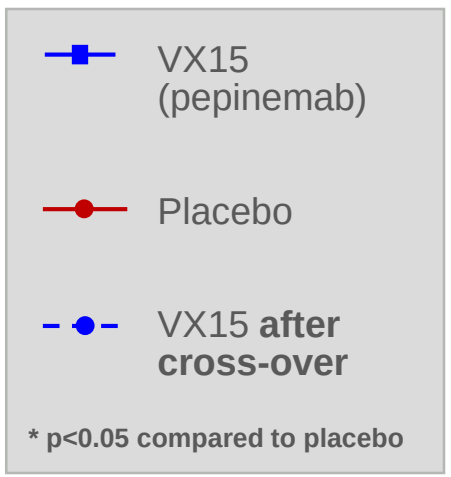




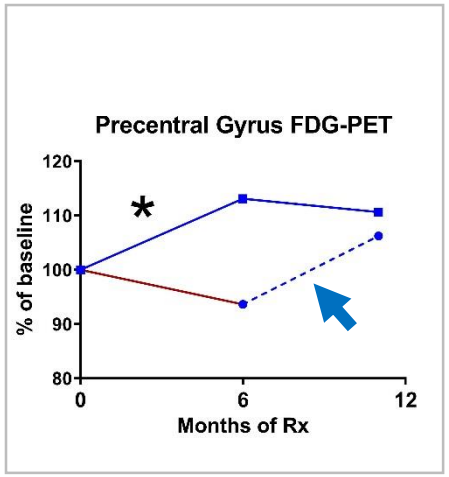


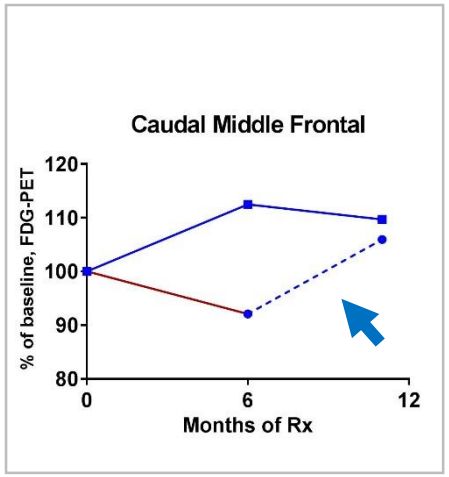


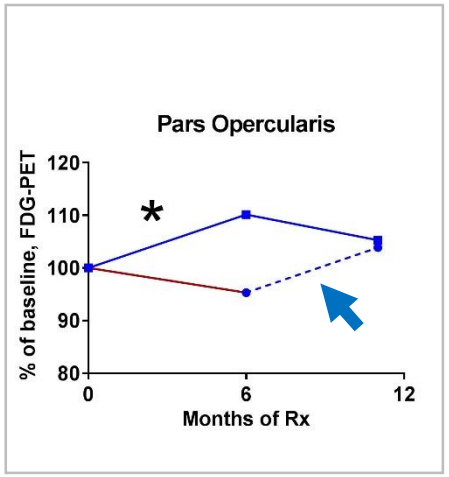


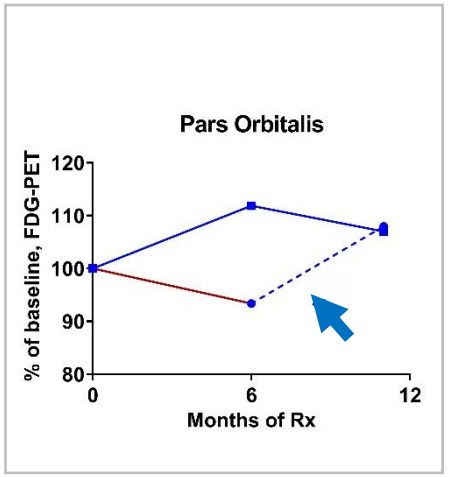


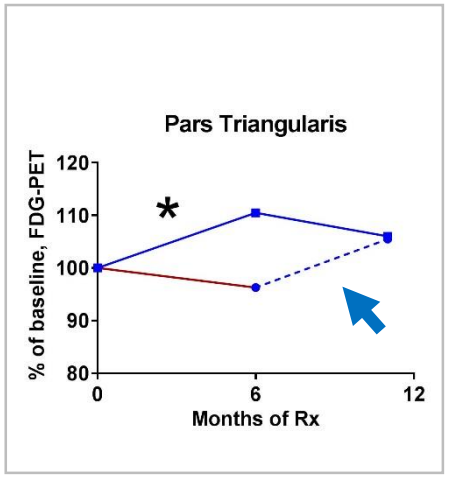
Clinical Evidence of Improved Brain Metabolic Activity in Frontal Lobe and Adjacent Parietal Regions: FDG-PET

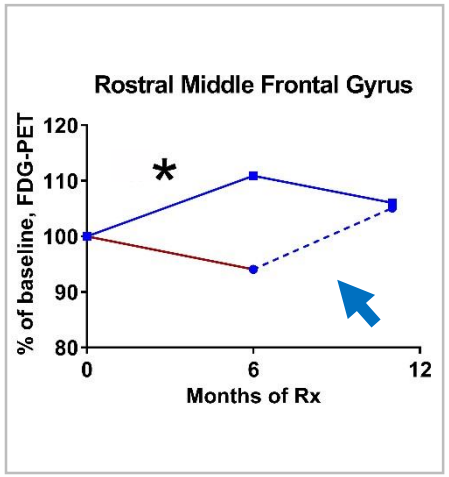


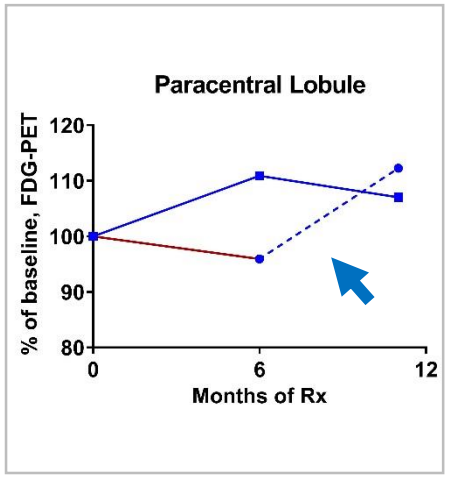


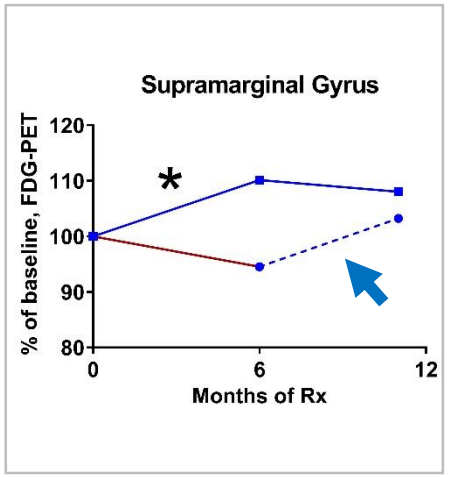


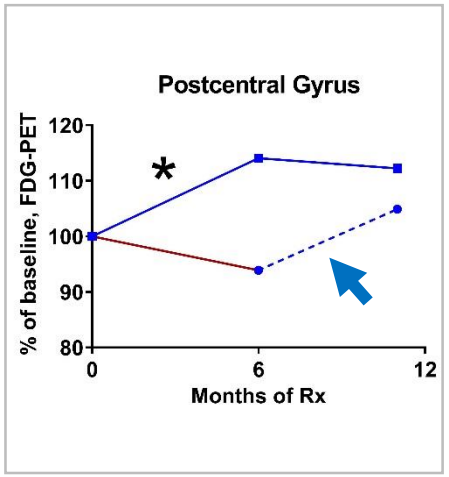


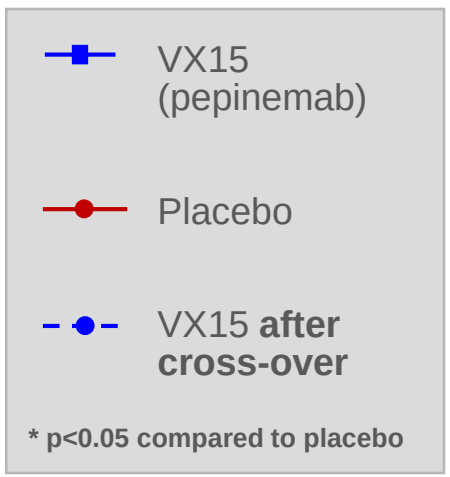




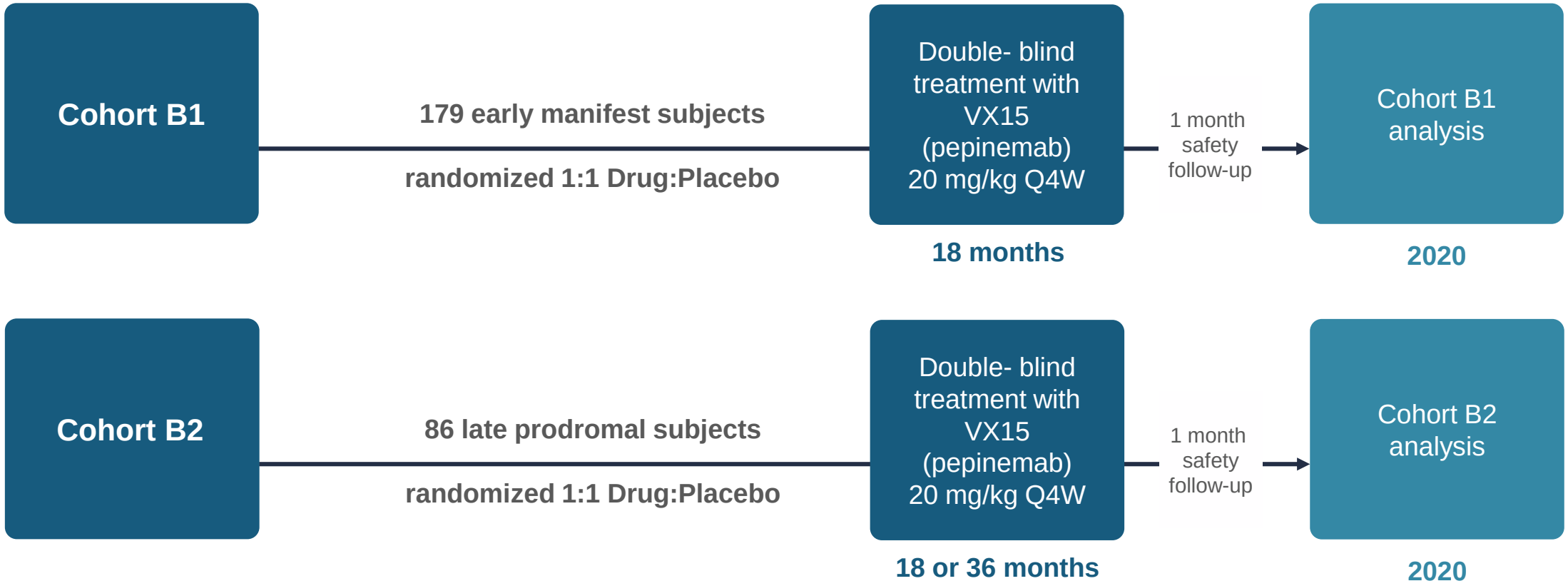








Huntington's Disease Clinical Trial Design: Cohort B



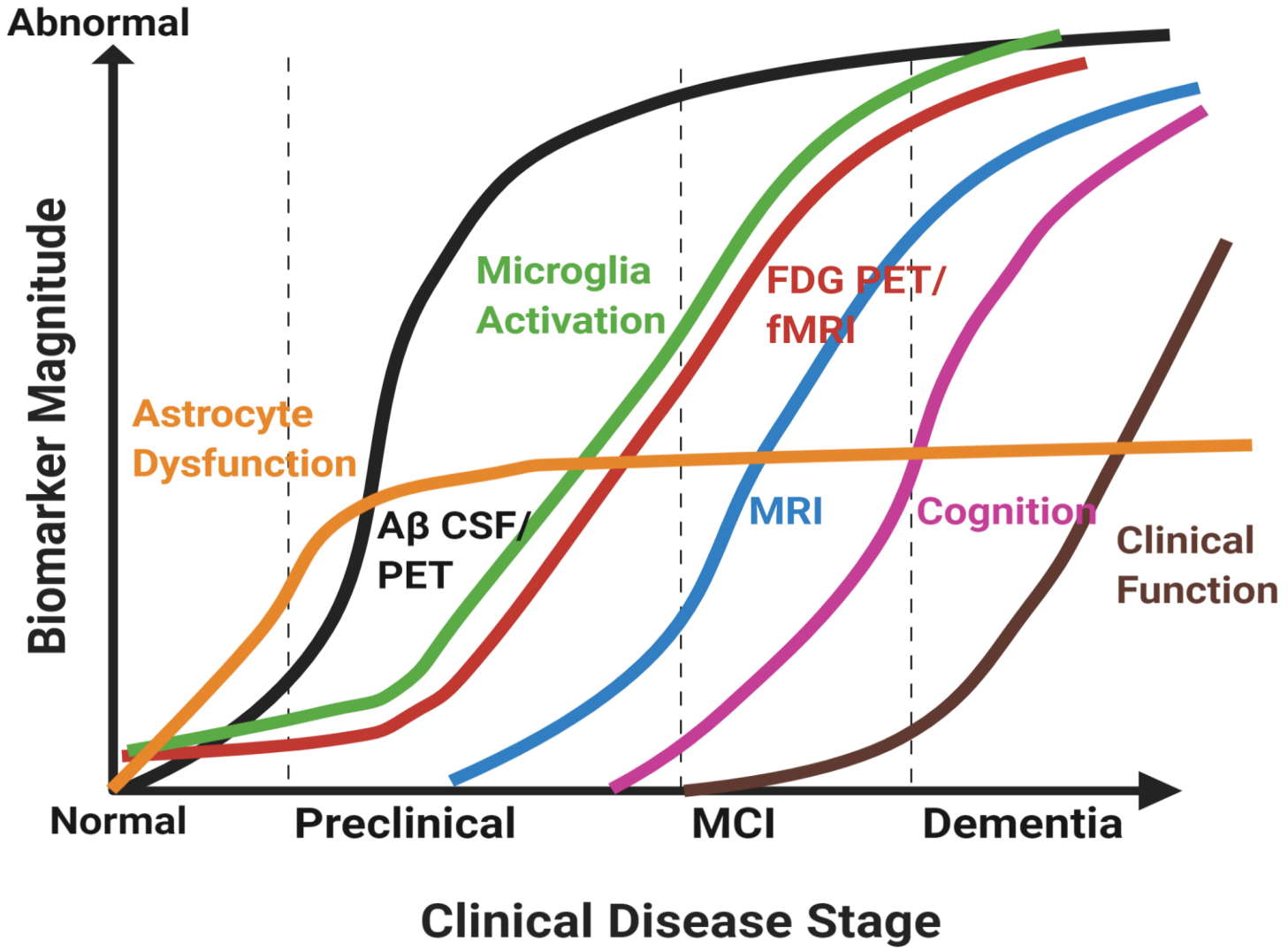
Encouraging treatment effects on FDG-PET, preservation of brain matter (reduced atrophy) and improvement in multiple motor and cognitive assessments seen in Cohort A provided important data to determine required sample size and treatment duration for potentially pivotal Cohort B study

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



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
    - Placebo (n=20)
    - Pepinemab: 20 mg/kg Q4W (n=20)
    - Pepinemab: 40 mg/kg Q4W (n=20)
  - **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)

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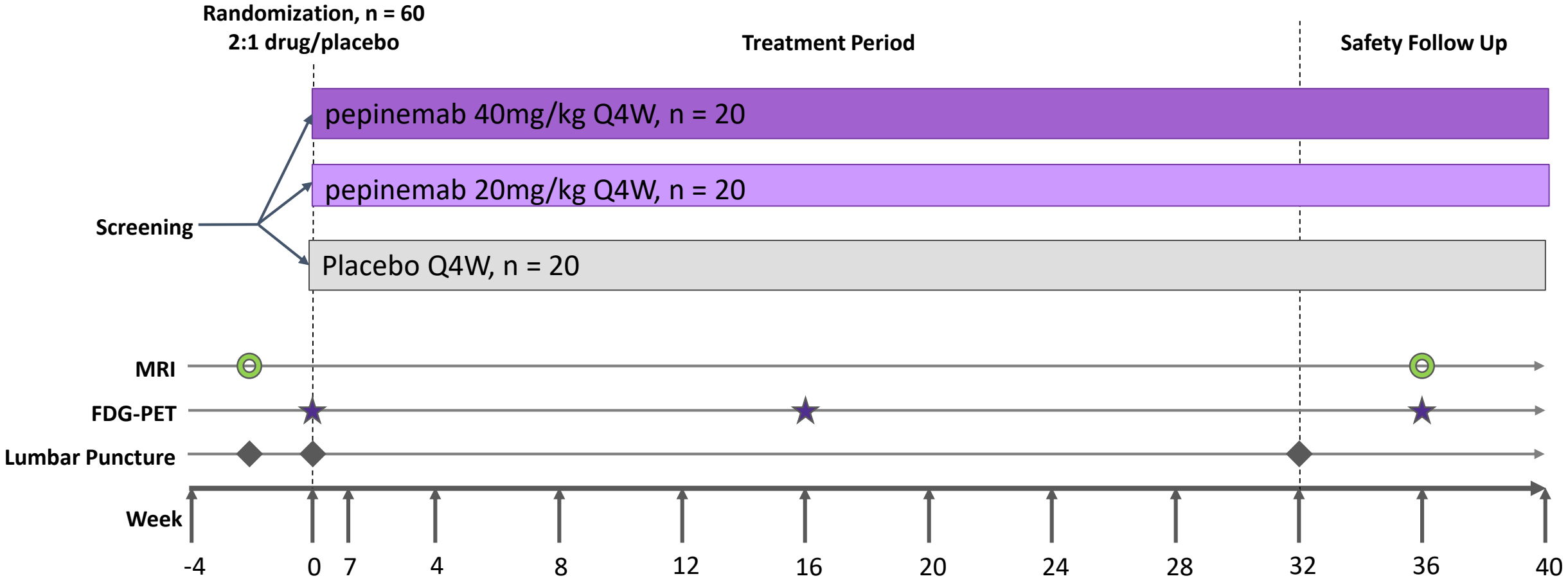
Alzheimer's Disease Trial

Proposed Trial Design



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Patients and their families

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