# HEALEY ALS Platform Trial

## Investigational Products Tested in the Trial

## Verdiperstat
## February 18, 2021

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# Accelerating ALS Therapy Development

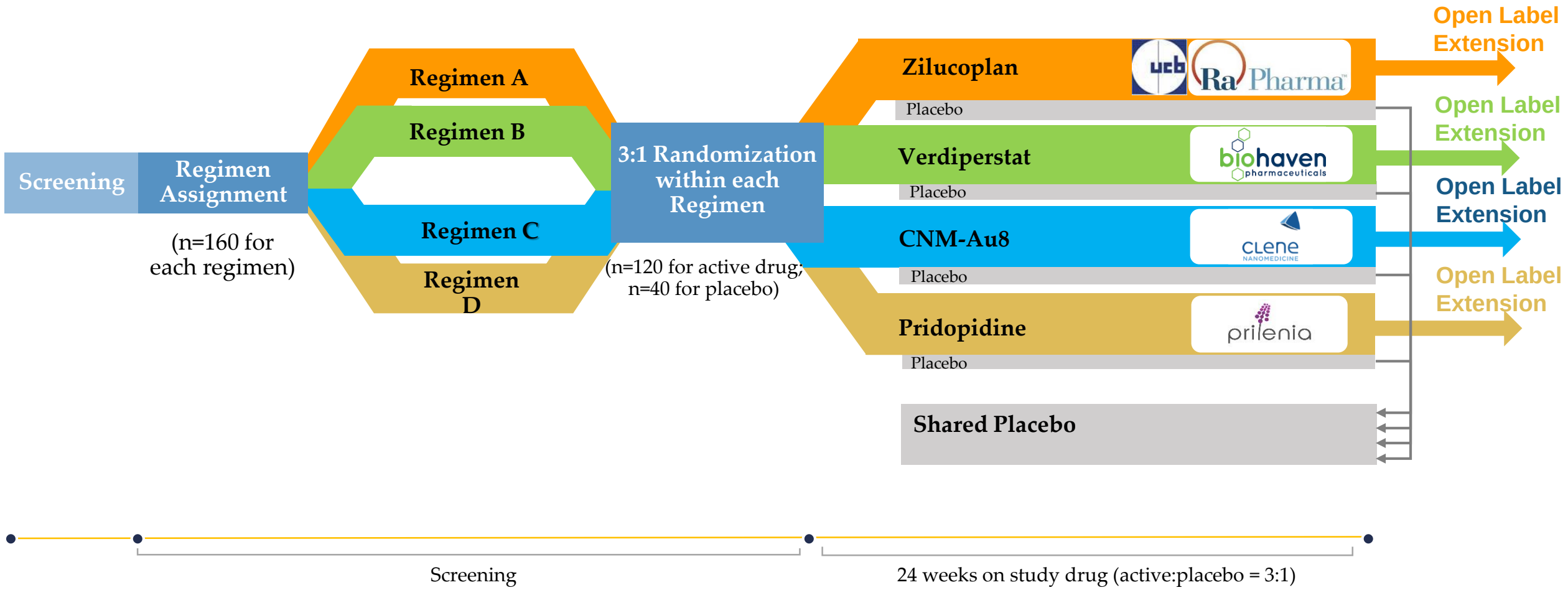
## Traditional

| | Intervention |
|---|---|
| **Disease** | Treatment A |

## Platform

| | Intervention | | | |
|---|---|---|---|---|
| **Disease** | Treatment A | Treatment B | Treatment C | Treatment D |

# Perpetual Adaptive Trial
# Randomization Ratio 3:1; Shared Placebo
# Open Label Extension offered



# Regimen Leads

**Jinsy Andrews, MD, MSc**
**Columbia University, NY, NY**
**Regimen Lead**

**Suma Babu, MBBS, MPH**
**MGH, Boston, MA**
**Regimen co-Lead**

# For More Updates

- **Weekly webinars**

  The idea of came from our Patient Advisory Committee: we are excited to be talking with you on a weekly basis and take any questions you might have

- **Find the schedule and registration links on our website**

**https://www.massgeneral.org/neurology/als/research/platform-trial-news/**

# Regimen B: Verdiperstat

HEALEY ALS Platform Trial

**NYSE: BHVN**

# What Is Myeloperoxidase (MPO)?

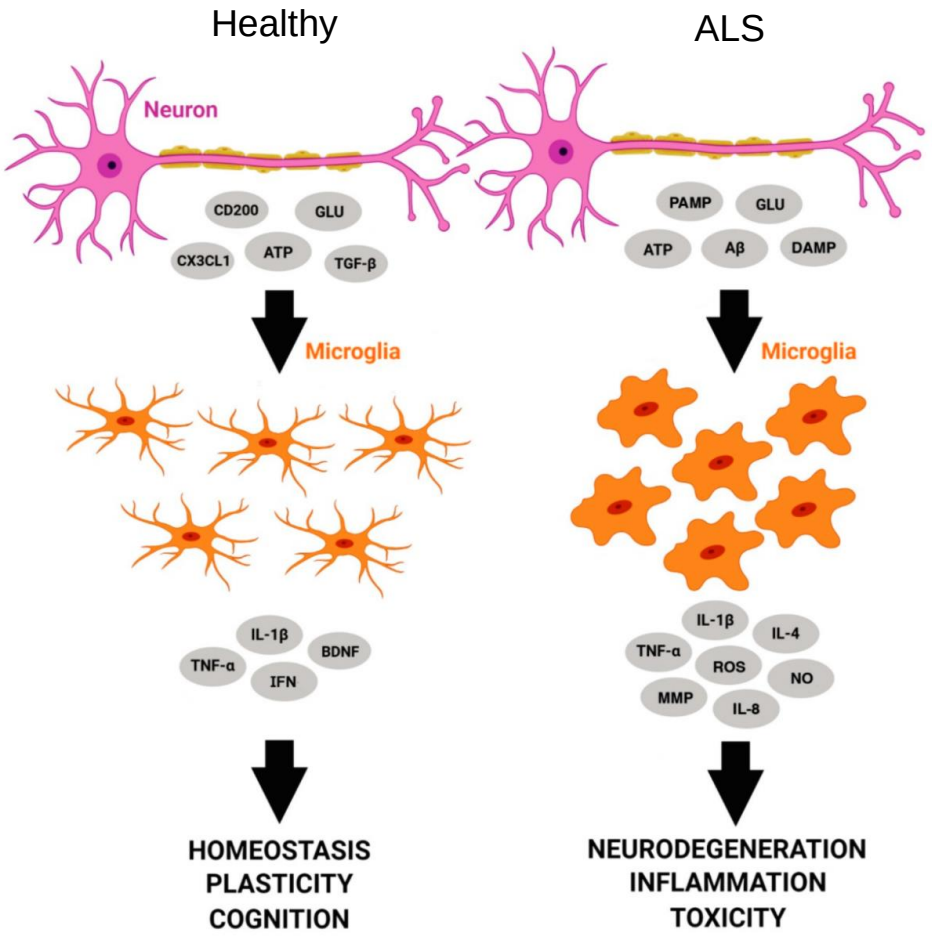
- Enzyme that plays essential roles in the immune system
- One of the most abundant enzymes in microglia, which are housekeeping cells in the brain
- Catalyzes the generation of toxic compounds
- In ALS, activation of microglia contributes to pathological oxidative stress, neuroinflammation and cellular injury
- Increasing evidence suggests that MPO is involved in pathophysiology of several neurodegenerative diseases

**MPO is implicated in neurodegenerative diseases like ALS**

# How Does Verdiperstat Work?

- Activated microglia express MPO
- MPO produces toxic compounds
- Verdiperstat inhibits MPO, rendering it inactive
- We hypothesize that verdiperstat will reduce oxidative stress, neuroinflammation and cell death

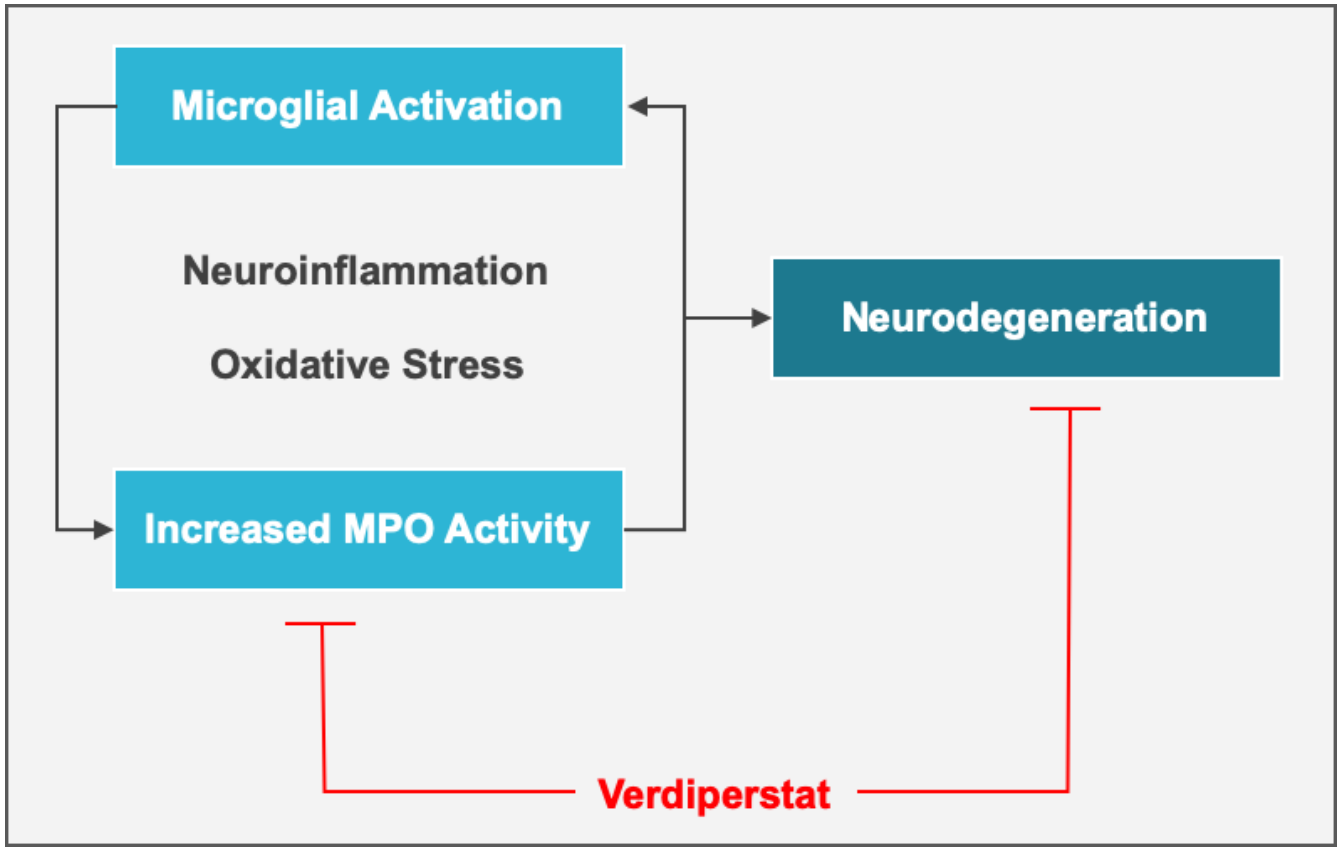
**Verdiperstat targets damaging microglial activation**




Augusto-Oliveira et al. 2019

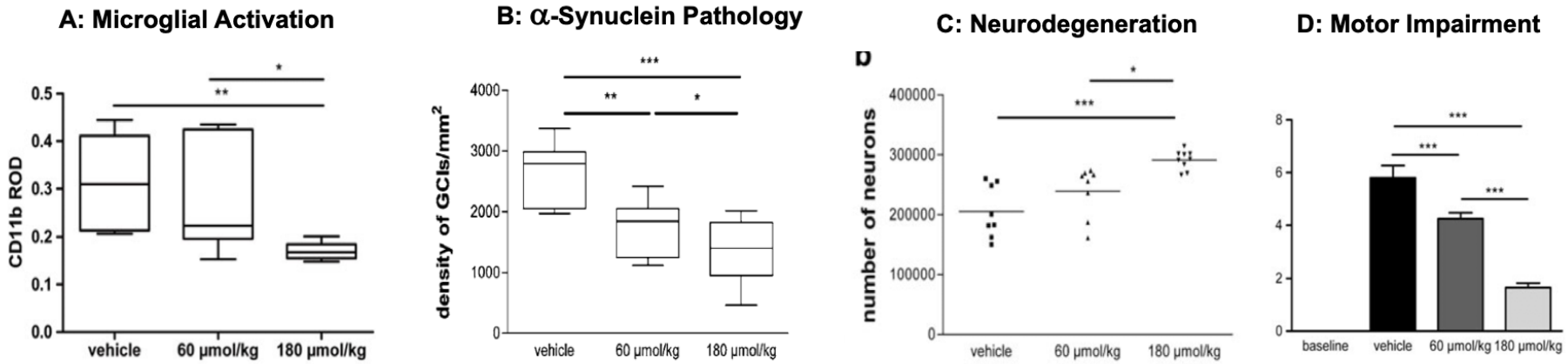
# How Does Verdiperstat Work?

First-in-class, potent, selective, brain-permeable, oral myeloperoxidase enzyme inhibitor



# What Is The Evidence That Verdiperstat Reduces Microglial Activation?

Verdiperstat reduced microglial activation, α-synuclein pathology, neurodegeneration and motor impairment in an animal model of multiple system atrophy



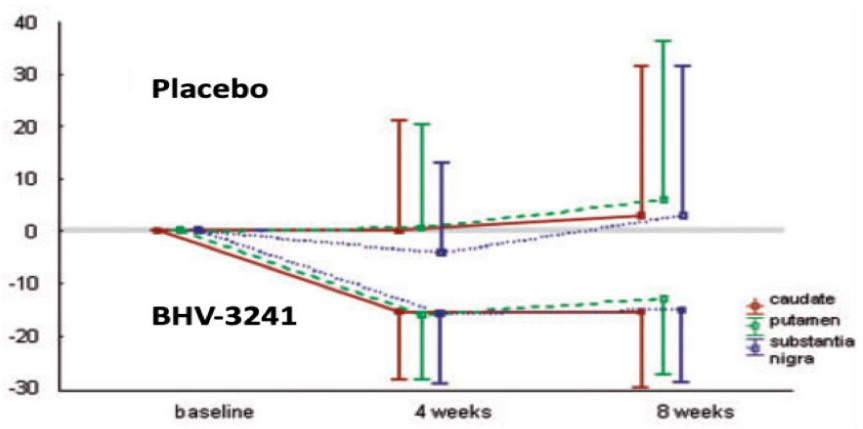

(A) Microglial activation, measured by relative optical density (ROD) of CD11b immunoreactivity, was reduced in striatum in mice treated with BHV-3241 at 180 µmol/kg, compared with vehicle. (B) α-synuclein pathology, measured by density of glial cytoplasmic inclusions (GCIs), was reduced in striatum in mice treated with BHV-3241 at 60 and 180 µmol/kg. (C) Neuronal loss in the striatum, measured by DARPP-32-immunoreactive neurons, was reduced in mice treated with BHV-3241 at 60 and 180 µmol/kg. (D) Motor impairment, measured by daily motor score, was reduced (low score = healthy) in mice treated with BHV-3241 at 60 and 180 µmol/kg. (*p < 0.05; **p < 0.01; ***p < 0.001).

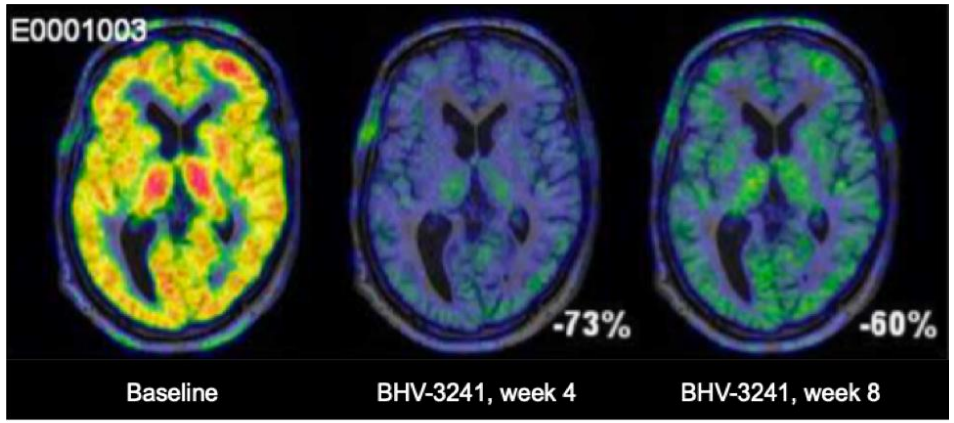
Stefanova et al. Neurotox Res. 2012

**Verdiperstat showed beneficial effects on microglial activation in animal models of neurodegenerative diseases including multiple system atrophy and Parkinson's disease**

# What Is The Evidence That Verdiperstat Reduces Microglial Activation?

[11C]-PBR28 PET imaging in subjects with Parkinson's disease treated with verdiperstat (BHV-3241)




(Left) Mean change from baseline in VT in striatal regions, bars denote SD
(Right) Sample images from a single subject

Jucaite et al., 2015.

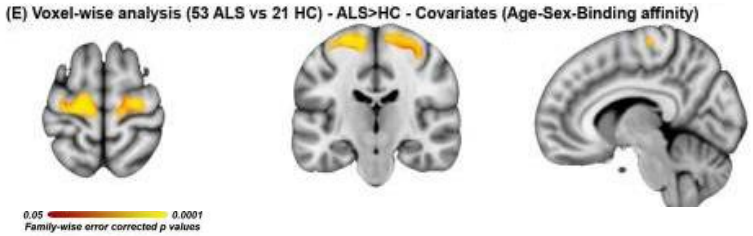
**Verdiperstat reduced microglial activation and neuroinflammation measured in people with Parkinson's disease by PET imaging**

# Why Use Verdiperstat in ALS?

- Verdiperstat targets well accepted ALS disease mechanisms (i.e., oxidative stress and microglial activation / neuroinflammation)
- Human ALS patients exhibit microglial activation / neuroinflammation as measured by [11C]-PBR28 TSPO PET imaging
- Verdiperstat is the only compound that has demonstrated the ability to decrease [11C]-PBR28 uptake in any human neurodegenerative disease

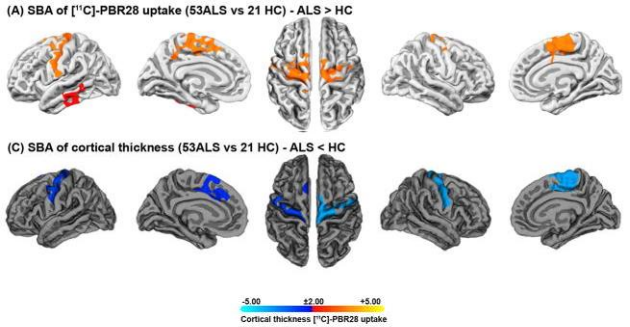
**Verdiperstat is uniquely positioned to potentially treat ALS**

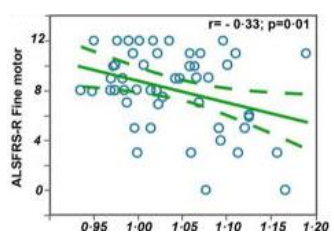
# What Is the Evidence for Microglial Activation Playing a Role in ALS?

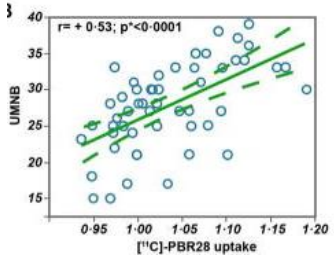



**Increased in ALS vs. controls**

**Co-Localizes with Cortical Thinning**



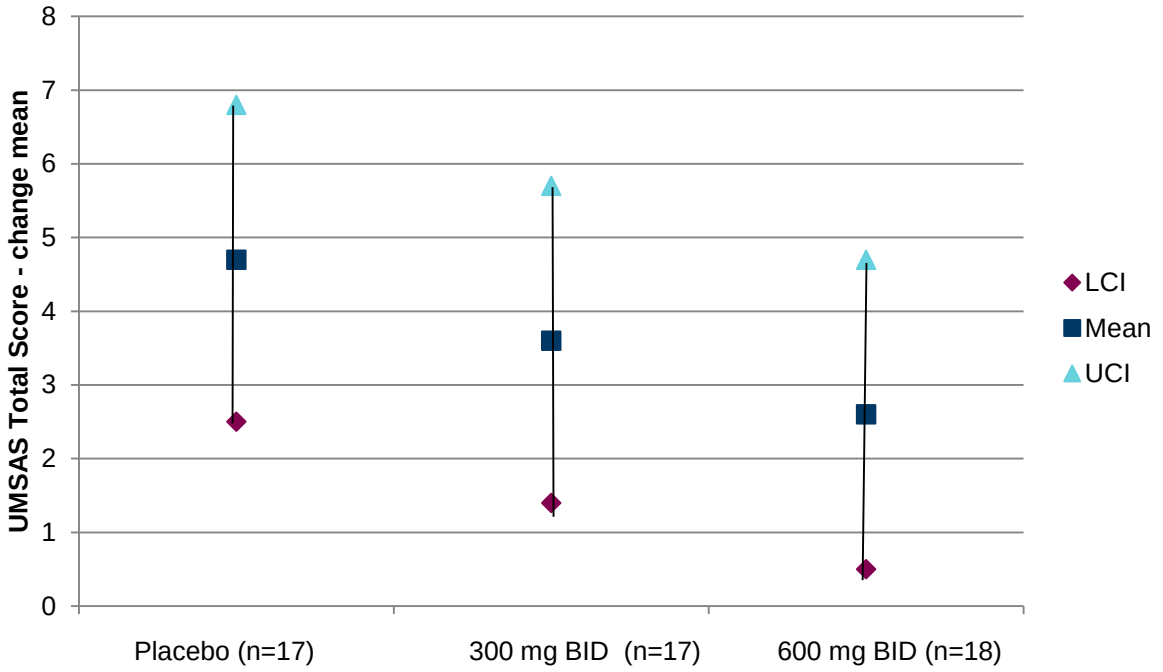

Alshikho MJ, et al., 2018

**Correlates with Disease Severity**

People with ALS exhibit microglial activation as measured by PET imaging

# Is There Evidence Verdiperstat Has a Beneficial Effect in People?

- Multiple System Atrophy (MSA) is a neurodegenerative disease, like ALS
- Verdiperstat was studied in phase 2 trial for people with MSA and showed a non-statistically significant dose-related trend towards slowing the progression of MSA
- Phase 3 trial in MSA is currently ongoing




Verdiperstat showed the potential to slow progression of MSA in a phase 2 trial

# Conclusion

**Strong scientific foundation showing that microglial activation plays a role in ALS (including studies done at Mass General)**

- Turner et al. 2018
- Johansson et al. 2007
- Corcia et al. 2012
- Zürcher et al. 2015
- Alshikho et al. 2018
- Paganoni et al. 2017
- Albrecth et al. 2017
- Alshikho et al. 2016
- Ratai et al. 2018

**Verdiperstat reduced microglial activation in people with a neurodegenerative condition (Parkinson's disease)**

**Verdiperstat showed a trend towards slowing the clinical progression of a neurodegenerative condition (Multiple System Atrophy) in a phase 2 trial**

**These data support the study of verdiperstat as a potential to help people with ALS**

biohaven pharmaceuticals