HEALEY ALS Platform Trial

Investigational Products Tested in the Trial

Verdiperstat
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### Accelerating ALS Therapy Development

#### Traditional

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Disease</th>
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<td>Treatment A</td>
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#### Platform

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

Regimen A
(n=160 for each regimen)

Regimen C
(n=120 for active drug; n=40 for placebo)

Regimen B

Regimen D

3:1 Randomization within each Regimen

Zilucoplan
Placebo

Verdiperstat
Placebo

CNM-Au8
Placebo

Pridopidine
Placebo

Shared Placebo

Screening

24 weeks on study drug (active:placebo = 3:1)
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
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
Verdiperstat reduced microglial activation, α-synuclein pathology, neurodegeneration and motor impairment in an animal model of multiple system atrophy

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

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

Jucaite et al., 2015.
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
What Is the Evidence for Microglial Activation Playing a Role in ALS?

People with ALS exhibit microglial activation as measured by PET imaging.

- Increased in ALS vs. controls
- Co-localizes with cortical thinning
- Correlates with disease severity

Alshikho MJ, et al., 2018
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
- Albrech 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