HEALEY ALS Platform Trial

Investigational Products Tested in the Trial

Zilucoplan
February 25, 2021

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The AMG Foundation
ALS ONE
MDA
ALS Association
ALSN
NEALS
Neuronal Clinical Research Institute
Barrow Neurological Institute
UCB
Ra Pharma
Biohaven Pharmaceuticals
Clene Nanomedicine
Prelenia
The Arthur M. Blank Family Foundation
Run2Revive
# 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 B

Regimen C

Regimen D

3:1 Randomization within each Regimen

Zilucoplan
Placebo

Verdiperstat
Placebo

CNM-Au8
Placebo

Pridopidine
Placebo

Shared Placebo

Open Label Extension

Screening

24 weeks on study drug (active:placebo = 3:1)
Regimen Leads

Sabrina Paganoni, MD, PhD
MGH, Boston, MA
Regimen Lead

Christina Fournier, MD
Emory University, Atlanta, GA
Regimen co-Lead
Complement Inhibition in Amyotrophic Lateral Sclerosis

Camil Sayegh, PhD
UCB, Inc.

Zilucoplan is an investigational drug product that has not been approved for any use by the U.S. Food and Drug Administration. This information is being provided pursuant to an unsolicited request for scientific information. This presentation is not intended to provide medical advice
Complement Inhibition

Complement is part of the innate immune system

- Complement can be activated by antibodies or foreign cells, including bacteria
- In some diseases, including IMNM, complement can be activated by auto-antibodies, which leads to tissue damage
- Zilucoplan is understood to inhibit the cleavage of complement component C5 into C5a and C5b, thereby inhibiting the terminal complement pathway including formation of the membrane attack complex and strong proinflammatory signals
  - C5a is a proinflammatory ‘anaphylatoxin’
  - C5b associates with C6, C7, C8 and C9 to form the membrane attack complex (MAC) which is a hydrophilic pore that inserts itself into membranes and can lead to cell lysis
Zilucoplan: Potential as a Self-Administered, Subcutaneous, Macrocylic Peptide Inhibitor of Complement C5

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**Multiple indications, pipeline-in-a-product potential**

### Alternative Pathway
Activated by non-self cells
- Factor D, Factor B
- C3
- C5a
  - Proinflammatory cytokine

### Classical Pathway
Activated by antibody-antigen complexes
- C1q – C1r – C1s
- C5
- C5b
- C6
- C5b6
- C7, C8, C9
- Membrane attack complex (MAC)

### Lectin Pathway
Activated by pathogen surfaces

### Multiple Indications
- gMG: Phase 2 positive
- IMNM: Phase 2 ongoing
- ALS: Platform trial ongoing
- PNH: Phase 2 positive
- Renal Disorders: Phase 1b positive

**Zilucoplan (SC)**
- Binds C5, blocks cleavage; Blocks MAC assembly
- 15 amino-acid cyclic peptide inhibitor of C5

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**Confidential**

gMG – generalized myasthenia gravis; IMNM – immune-mediated necrotizing myopathy; ALS – amyotrophic lateral sclerosis; PNH – paroxysmal nocturnal hemoglobinuria
The Neuropathological Hallmark of ALS Is the Loss of Upper and Lower Motor Neurons

Neurodegeneration involves upper (corticospinal) and lower (ventral horn and cranial nerve nuclei) motor neurons. Motor neurons are nerve cells that carry messages from the brain and spinal cord to muscles.

ALS, amyotrophic lateral sclerosis.

Preclinical Studies Suggest an Important Role for Terminal Complement Components in ALS Pathophysiology

**The expression of terminal complement components is upregulated compared to healthy controls**

- ↑ C5aR1 with disease progression in lumbar spinal cord\(^1\) and tibialis anterior muscle\(^2\)
- ↑ C5a in tibialis anterior muscle\(^2\)
- ↑ MAC deposition on motor endplates\(^3\)
- ↑ CD59a (inhibitory regulator of MAC formation) in the lumbar spinal cord\(^1\) and tibialis anterior muscle\(^2\)

**Inhibition of C5a-C5aR1 signaling reverses disease progression**

- Genetic deletion of C5aR1 reversed denervation of neuromuscular junctions and improved motor deficits\(^2\)
- Administration of C5aR1 antagonist significantly extended survival and slowed disease progression\(^4\)
- Genetic deletion of C5aR1 extended survival\(^5\)

**Expression Studies**

- SOD1\(^{G93A}\) ALS mouse model

**Ablation Studies**

These findings are limited to preclinical data in animals.

ALS, amyotrophic lateral sclerosis; C5aR1, complement component 5a receptor; CD59, cluster of differentiation 59; MAC, membrane attack complex; SOD1, superoxide dismutase type-1.

Complement MAC Proteins Are Associated With Neuroinflammation in Patients With ALS

Activation of the immune system, including a high expression of complement proteins, has been observed in the spinal cord and motor neurons of patients with ALS\(^1,2\)

- C5b-9 (MAC) detected in glial cells associated with the motor neurons of the spinal cord of patients with ALS, which is absent in healthy controls


\(P\) value calculated using a nonparametric Wilcoxon rank-sum test. sC5b-9, serum complement components C5b through C9, also known as membrane attack complex (MAC).

Motor end plates

MAC detected on the innervated motor end plates of intercostal muscle from patients with ALS, which is absent in healthy controls

Arrows indicate positive MAC staining on glial cells
Questions?
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/