The HEALEY ALS Platform Trial

Working together to develop new treatments for ALS
SOMETHING NEW IS HERE
The platform trial continues to grow to test more drugs

1 Protocol (Phase 2/3)
1 single IRB
Central Governance

7 Regimens
70+ Enrolling Sites
~1300 Participants

Regimen: Active Study Drug + Matching Placebo

Regimen G
Regimen F
Regimen E
Regimen D
Regimen C
Regimen B
Regimen A
The HEALEY ALS Platform Trial is a perpetual trial to provide decisive answers and direction with efficient execution.

### Regimen A
- **Zilucoplan**
  - by UCB

### Regimen B
- **Verdiperstat**
  - by Biohaven

### Regimen C
- **CNM-Au8**
  - by Clene

### Regimen D
- **Pridopidine**
  - by Prilenia

### Regimen E
- **Trehalose**
  - by Seelos

### Regimen F
- **ABBY-CLS-7262**
  - by Calico & AbbVie

### Regimen G
- **DNL343**
  - by Denali

### Considering Phase 3 Trial
- **DNL343**
  - by Denali

- **Regimen G**

- **Regimen B**

- **Regimen E**

### Summer 2020 | 2021 | 2022 | 2023
2023 Regimens – F and G

**Placebo Controlled Period followed by Active Period Extension**

**Screen for eligibility** → **Randomization 3:1** → **Placebo** → **Active** → **Active Treatment Extension**

**Screening Period** → **Placebo-Controlled Period** (24 weeks) → **Active Treatment Extension**

**Primary Endpoint (Placebo-Controlled Period)**
Change in disease severity

**Safety, Secondary, and Exploratory Endpoints**
Including respiratory function, muscle strength, biomarkers
Regimen F – Enrolling now

The Integrated Stress Response (ISR)

**No ISR**
- eIF2
- eIF2B
- Normal protein synthesis

**Transient ISR**
- Stress
- eIF2
- eIF2B
- Reduced protein synthesis
- Production of stress proteins
- Formation of TDP-43 stress granules

**Persistent ISR**
- Chronic stress
- eIF2
- eIF2B
- Lack of essential proteins
- Toxic levels of stress proteins
- Build-up of TDP-43 aggregates
- Cell death

**Legend**
- Normal proteins
- Stress proteins
- Stress granule
- TDP-43
Regimen F Drug Science Q&A Webinar

**Topic:** Regimen F Drug Science and Mechanism of Action

**Recording Available:** [https://bit.ly/3mQy5qQ](https://bit.ly/3mQy5qQ)

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<thead>
<tr>
<th>Problem</th>
<th>Calico</th>
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<tr>
<td>IDR is activated in ALS</td>
<td>ABBV-CLS-7262 is a potent inhibitor of the ISR by binding to, and activating, eIF2B</td>
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<td>Aggregates of the protein TDP-43 are observed in most ALS cases</td>
<td>ABBV-CLS-7262 dissociates stress granules containing TDP-43 which may reduce formation of new TDP-43 aggregates</td>
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<td>Drugs tested in ALS clinical trials must have their intended biological effect in people</td>
<td>Blood cells from people given ABBV-CLS-7262 show increased eIF2B activity and reduced ISR</td>
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<td>The right dose needs to be administered in clinical trials</td>
<td>ABBV-CLS-7262 was measured in the CSF at levels predicted to be pharmacologically active at tolerated doses</td>
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<td>Our understanding of ALS is incomplete</td>
<td>CSF and blood samples will improve our understanding of the ISR in ALS and may identify people most likely to respond to ABBV-CLS-7262</td>
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“DNL343 is a novel investigational ALS therapy that targets eIF2B, a central regulator of the integrated stress response (ISR). The ISR appears to be overactive in ALS, leading to the formation of stress granules containing TDP-43. Buildup of TDP-43 is harmful and leads to neuronal degeneration. In the lab, inhibition of the ISR by DNL343 dissolves TDP-43 containing stress granules and decreases ISR biomarkers.

The safety, pharmacokinetics, and pharmacodynamics of DNL343 have been characterized in both healthy participants and people with ALS, in a Phase 1 (N=47) and a Phase 1b (N=29) study, respectively, with dosing for up to 28 days. Results from both studies demonstrated that once-daily oral dosing with DNL343 was generally well tolerated and exhibited extensive Cerebrospinal Fluid (CSF) penetration. In addition, robust inhibition of biomarkers associated with the ISR pathway was observed in blood samples from study participants.”
The Patient Navigator Team is a central resource for information

Patient Navigator Team
Building Community & Partnership in ALS Research

Patient Navigator: Central Resource

Weekly Webinars: News & Updates

ALS Link

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We are immensely grateful to the trial participants and to everyone in the ALS community who is supporting research in many different ways.

Progress in ALS would not be possible without your partnership.

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