Thank you for joining the weekly webinar!
We are admitting audience members from the waiting room.
Please allow a few moments for the webinar to begin.
HEALEY ALS Platform Trial

Weekly Q&A – July 6, 2023
Guest Speaker

Bill Cho, MD PhD
Head of Clinical Science
ABBV-CLS-7262 for ALS

HEALEY ALS Platform Trial
Regimen F
Calico Life Sciences in collaboration with AbbVie

**Calico**

*Founded* by Google (now Alphabet) and Art Levinson in 2013

**Mission:** To understand human aging and develop therapies for age-related disorders, including neurodegeneration

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**Partnership with AbbVie**, a global biopharmaceutical company with a proven track record of developing medicines and solutions for people living with neuropsychiatric disorders such as Parkinson’s Disease, schizophrenia, and depression
What is the Integrated Stress Response (ISR)?
The Integrated Stress Response (ISR)

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

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

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

**Legend**
- Normal proteins
- Stress proteins
- Stress granules
- TDP-43
- TDP-43 aggregates
TDP-43 aggregates are a hallmark of ALS pathology

Adapted from Ling et al., Neuron 2013
Can the ISR be inhibited?
The first ISR inhibitor, ISRIB

ISRIB binds to eIF2B in the central pocket

- Increases the enzymatic activity of eIF2B
- Makes eIF2B less sensitive to stress

Discovered at UCSF by Carmela Sidrauski Principal Investigator
Calico Life Sciences LLC

Adapted from Tsai et al., Science 2018
eIF2B activators dissolve TDP-43 stress granules in human motor neurons

Activating the ISR drives TDP-43 into stress granules

Without treatment

TDP-43 Staining of Stressed Human Motor Neurons in Cell Culture

Without treatment

With treatment

IN VITRO EXPERIMENT
eIF2B activators rescue mice from neurological deficits caused by a persistent ISR in the brain and spinal cord

2B Activator preserves the white matter in the spinal cord

Luxol Fast Blue

Normal  eIF2B5^{R191H} Mutant  Mutant + 2BAct

Wong et al., eLife 2019

2B Activator improves motor function and balance*

Better  Worse

Time to Cross (sec)

0  10  20  30  40

24  27  31  35

Baseline

Mutant + 2BAct

Mutant

Normal

*p ≤ 0.00001 vs. eIF2B5^{R191H} Mutant

as measured by time to cross a balance beam

Sadowski et al., 2019; SFN, Chicago, IL poster

IN VIVO (MOUSE) EXPERIMENT
How can eIF2B activators potentially treat ALS?
eIF2B activators may help motor neurons survive harmful stress conditions by:

1. Restoring normal protein production in stressed nerve cells
2. Reducing stress proteins that may lead to nerve cell death
3. Dissolving stress granules that may lead to TDP-43 aggregates

**Legend**
- Normal proteins
- Stress proteins
- Stress granules
- TDP-43
- TDP-43 aggregates

**Persistent ISR**
- Chronically increased stress
- eIF2 activation
- eIF2B activator reduces stress granules
- eIF2B activator dissolves stress granules
- eIF2B activator prevents further TDP-43 sequestration
- eIF2B activator improves protein synthesis

**Chronic stress**
- Reduced synthesis of essential proteins
- Increased stress proteins to toxic levels
- Increased build-up of TDP-43 aggregates
- Cell death

**Neurodegeneration**
- ALS

**ABBV-CLS-7262**
- Normal protein synthesis
- Normal stress proteins
- Normal stress granules
Has ABBV-CLS-7262 been given to people?
Results from the first study in healthy people

**ABBV-CLS-7262**, our eIF2B activator, has been given to over 100 healthy volunteers.

**ABBV-CLS-7262** can be administered by mouth once a day.

Adverse events were non-serious, and mild to moderate in severity.

**ABBV-CLS-7262** increased eIF2B activity and inhibited the ISR as expected by its mechanism of action.

The drug entered the cerebrospinal fluid (CSF) and was present at concentrations hypothesized to activate eIF2B.
ABBV-CLS-7262 increases eIF2B activity and inhibits the ISR in blood cells collected from trial participants.

**ABBV-CLS-7262 enhances the enzyme activity of eIF2B**

**ABBV-CLS-7262 suppresses the ISR stress gene TRIB3**

**Sampling Time after Dosing**

<table>
<thead>
<tr>
<th>TRIB3 (% Change from Baseline)</th>
<th>6 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABBV-CLS-7262</td>
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</tbody>
</table>

**Sampling Time after Dosing**

<table>
<thead>
<tr>
<th>Reaction Rate (% Change from Baseline)</th>
<th>6 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
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<td>ABBV-CLS-7262</td>
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</table>

**p ≤ 0.001 vs. Placebo**

**p ≤ 0.05 vs. Placebo**
Has ABBV-CLS-7262 been given to people with ALS?
# Preliminary blinded safety information from an ongoing study in people with ALS

The most frequent adverse events possibly related to ABBV-CLS-7262 or placebo were*:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>10%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7%</td>
</tr>
<tr>
<td>Itchiness</td>
<td>7%</td>
</tr>
<tr>
<td>Constipation</td>
<td>7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7%</td>
</tr>
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</table>

ABBV-CLS-7262 has been given to 31 people with ALS. Some participants have been treated for more than a year.

*As of 08 Jan 2023; Study data remains blinded and includes adverse events for participants who may have received placebo for four weeks.
We are excited that ABBV-CLS-7262 is part of the Healey ALS Platform Trial as Regimen F

ABBV-CLS-7262 will be taken by mouth once daily

Participants will be randomly assigned to receive ABBV-CLS-7262 or placebo in a 3:1 ratio

Participants will be randomized to 1 of 2 dose levels, both of which are hypothesized to activate eIF2B

Participants may receive ABBV-CLS-7262 for approximately 1 year

MGH is the Sponsor of the study
Calico is the Regimen Industry Partner
AbbVie is the manufacturer of ABBV-CLS-7262
In summary...
<table>
<thead>
<tr>
<th>Problem</th>
<th>ABBV-CLS-7262 is ready to be evaluated as a new potential treatment for ALS</th>
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</thead>
<tbody>
<tr>
<td>ISR is activated in ALS</td>
<td>ABBV-CLS-7262 is a potent inhibitor of the ISR by binding to, and activating, eIF2B</td>
</tr>
<tr>
<td>Aggregates of the protein TDP-43 are observed in most ALS cases</td>
<td>ABBV-CLS-7262 dissolves stress granules containing TDP-43 which may reduce formation of new TDP-43 aggregates</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>The right dose needs to be administered in clinical trials</td>
<td>ABBV-CLS-7262 was measured in the CSF at levels hypothesized to activate eIF2B</td>
</tr>
<tr>
<td>The 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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</tbody>
</table>
Questions
Learn more about Calico and our clinical trials:

calicolabs.com/patients

Watch this video explaining the ISR and its connection to ALS …