Calico abbvie

ABBV-CLS-7262 for ALS

HEALEY ALS Platform Trial

Regimen F

Calico Life Sciences in collaboration with AbbVie

Calico

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

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

abbvie

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)?

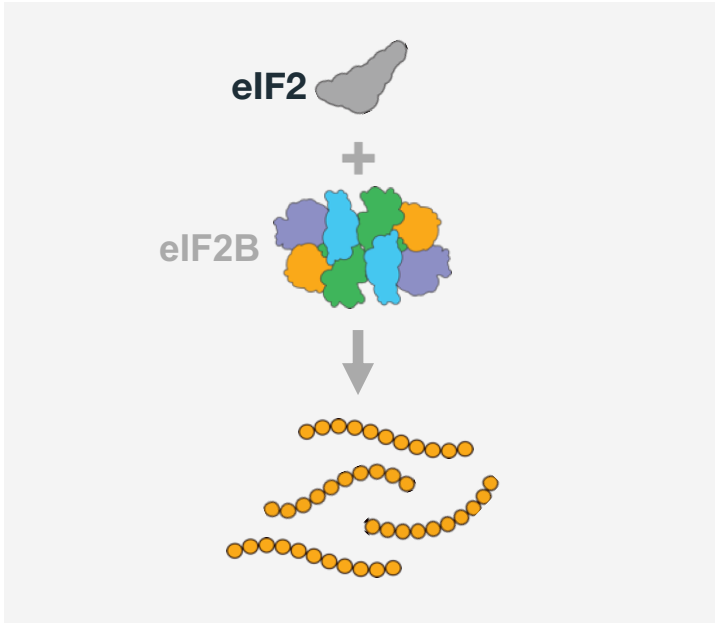
The Integrated Stress Response (ISR)

2 key players:

eIF2 

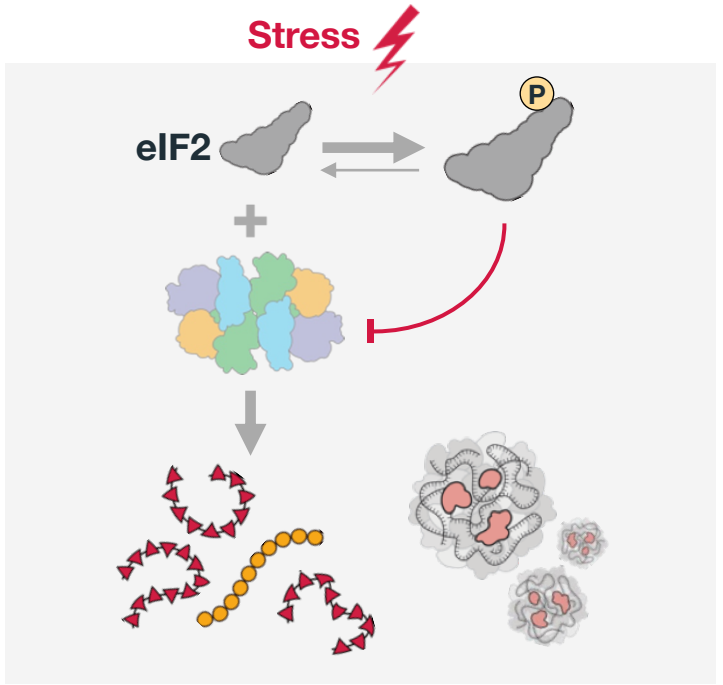
eIF2B 

No ISR



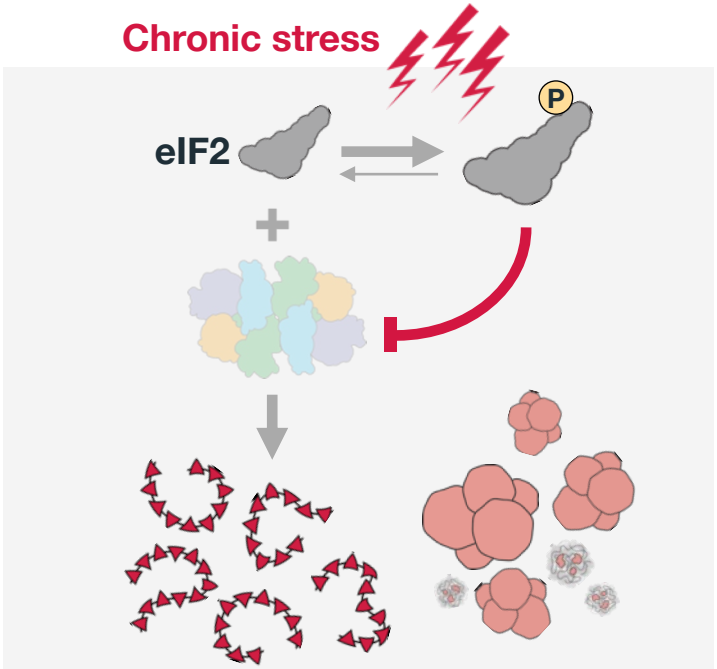
Normal protein synthesis

Transient ISR



Reduced protein synthesis
Production of stress proteins
Formation of TDP-43 stress granules

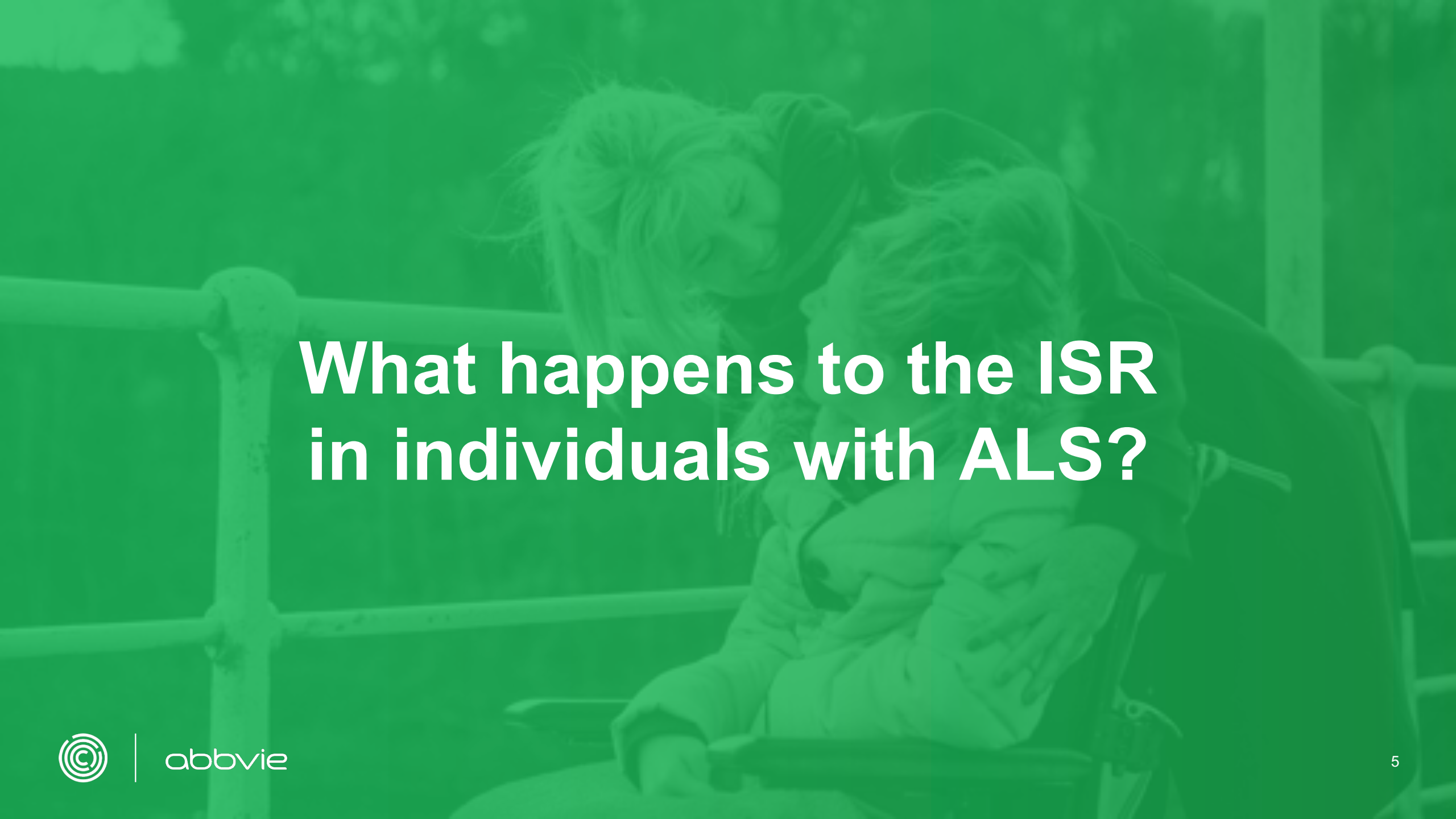
Persistent ISR



Lack of essential proteins
Toxic levels of stress proteins
Build-up of TDP-43 aggregates

Cell death

LEGEND

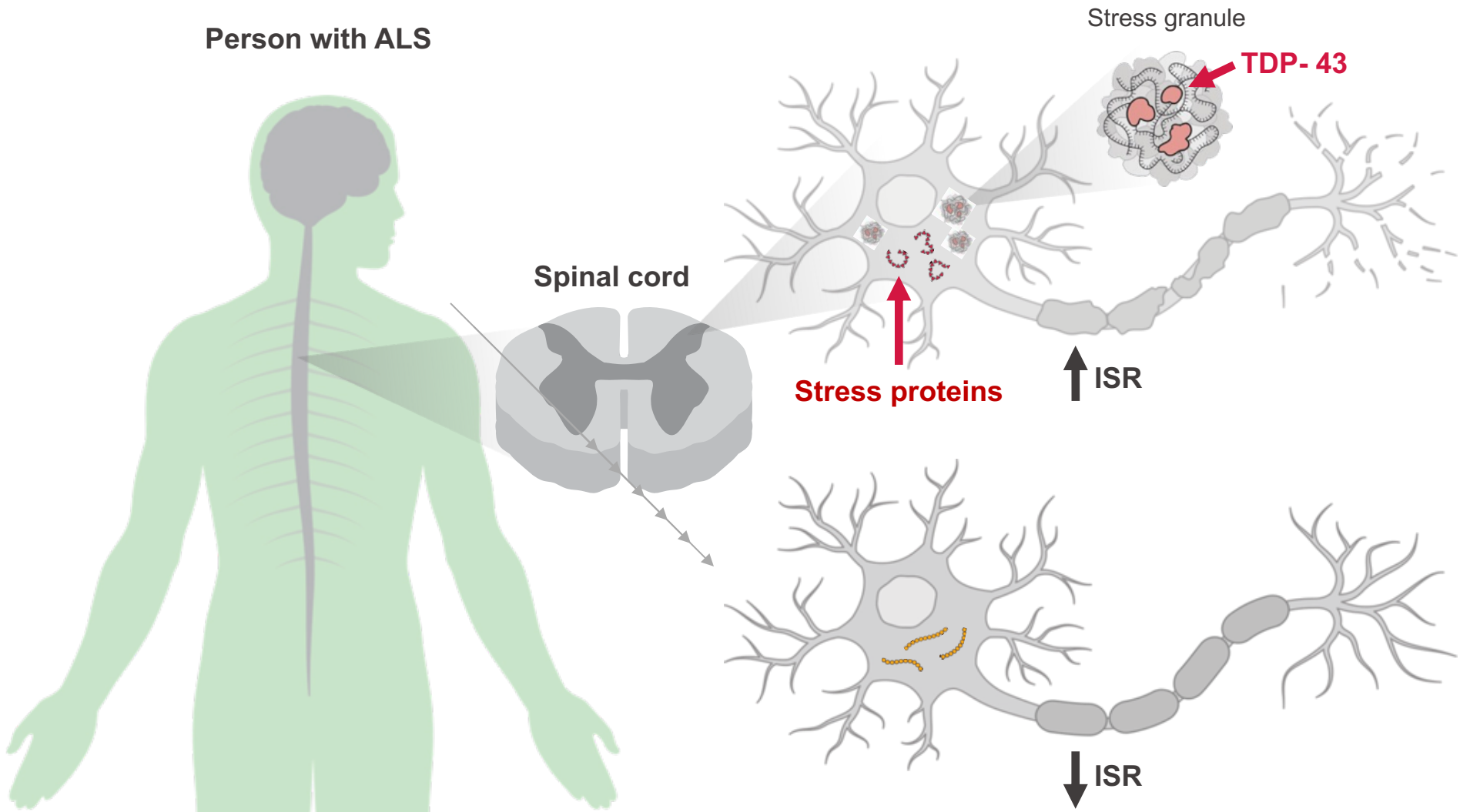


What happens to the ISR in individuals with ALS?

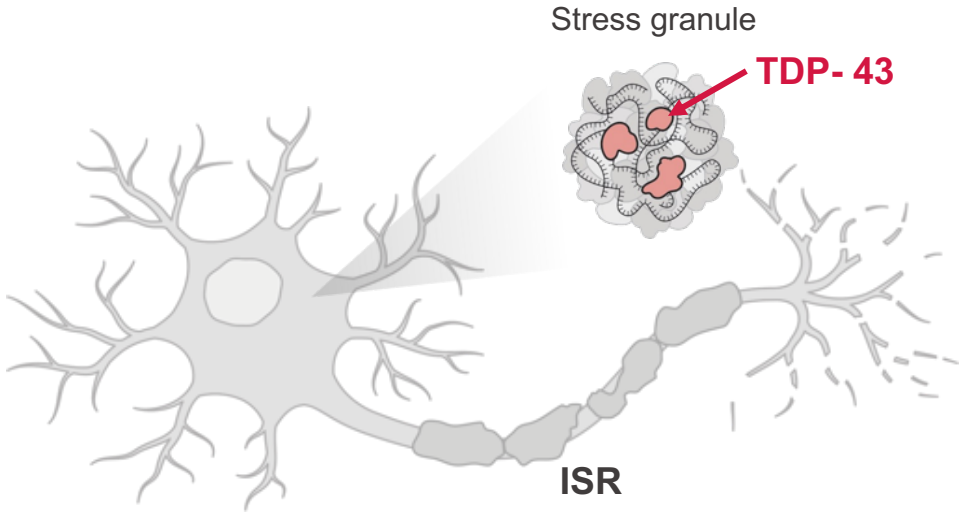
The ISR in ALS

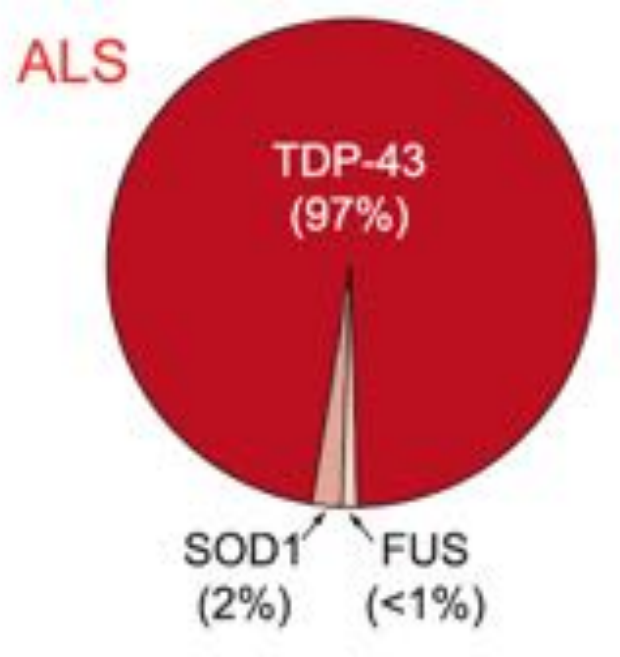
The ISR is activated in people with ALS causing:

- Reduction in normal protein synthesis
- Increase in production of stress proteins
- Formation of stress granules containing TDP-43



TDP-43 aggregates are a hallmark of ALS pathology

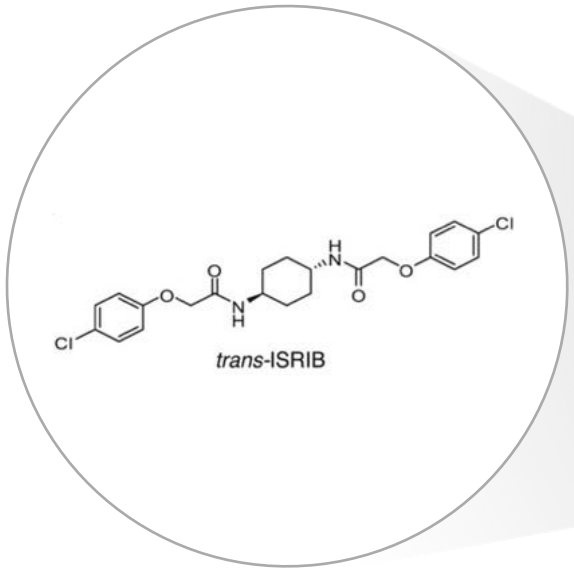




Ling et al., *Neuron* 2013

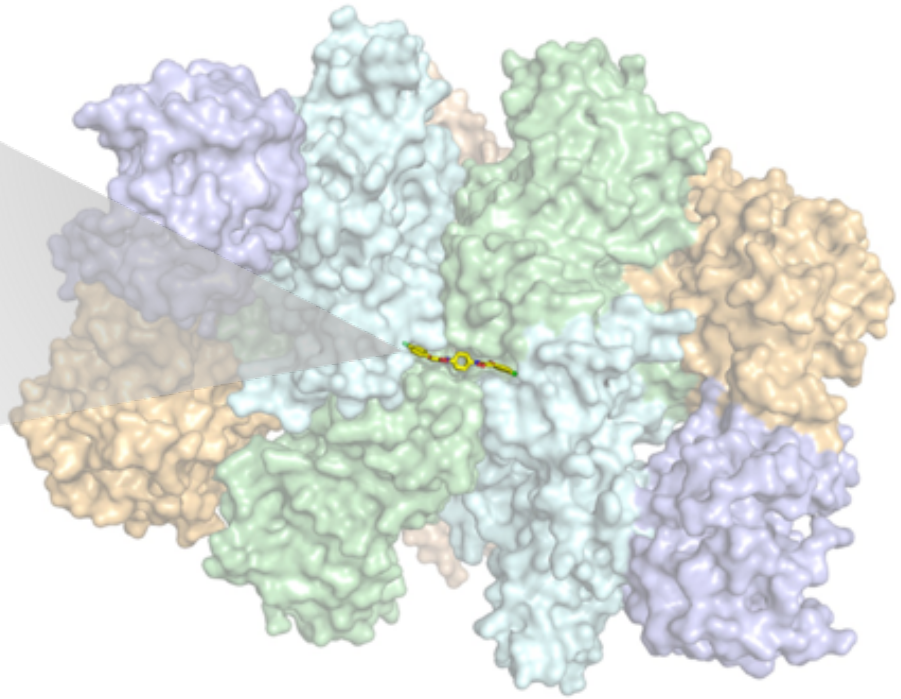
How does the ISR inhibitor work?

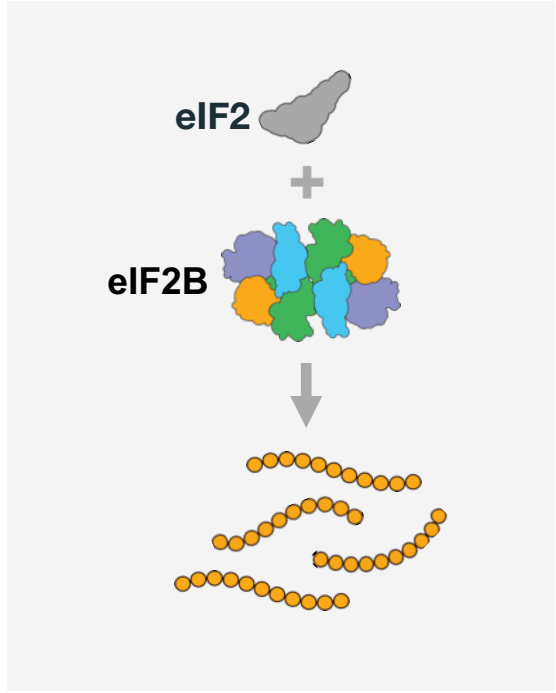
The first ISR inhibitor, ISRIB



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

ISRIB bound to Human eIF2B



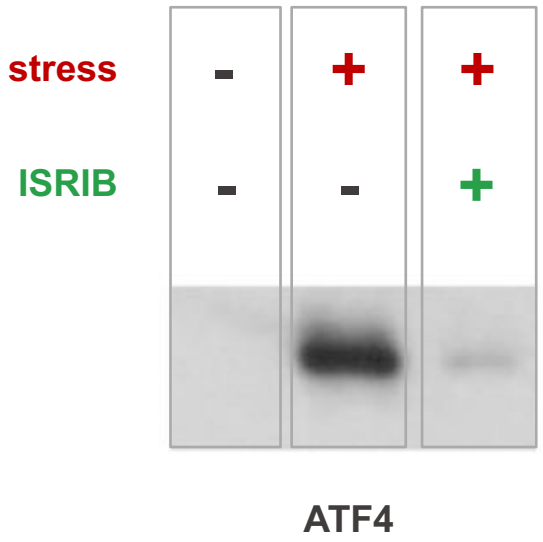


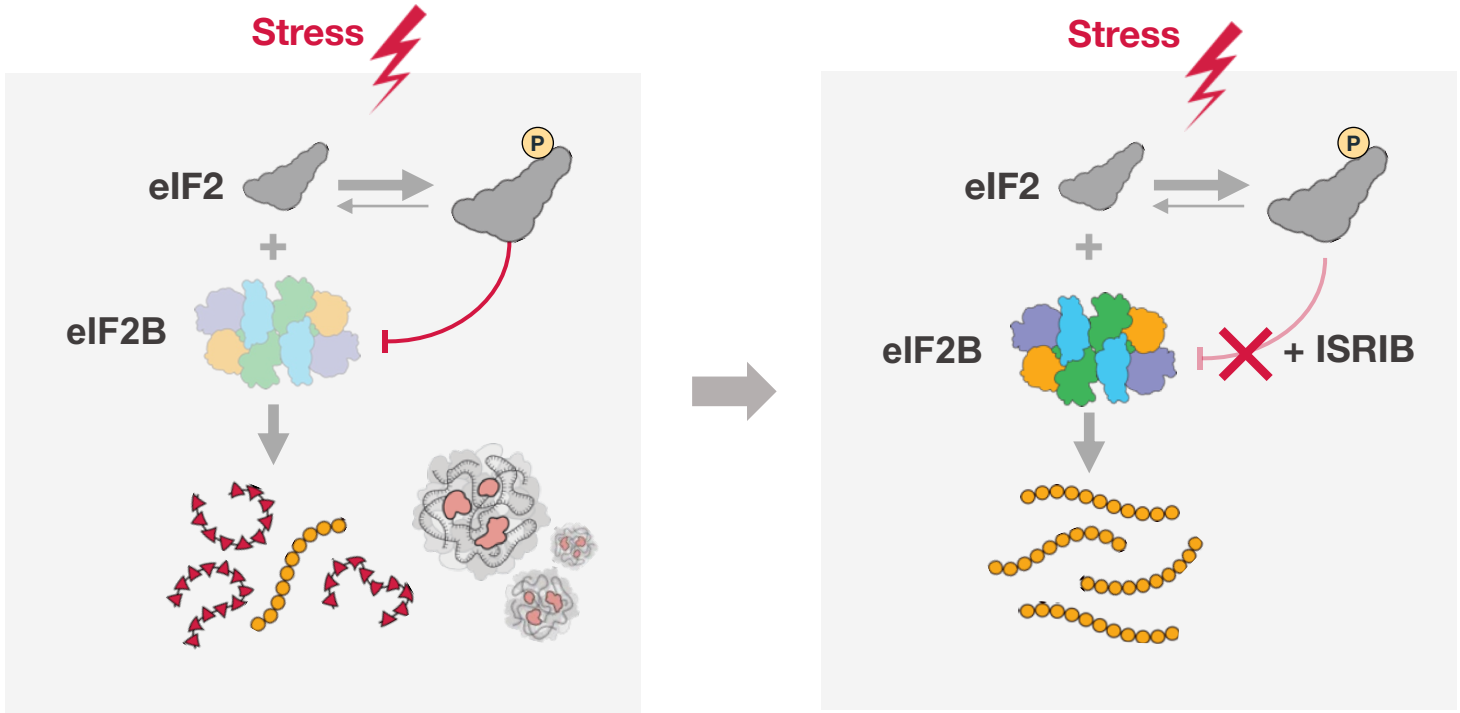
ISRIB binds to eIF2B in the central pocket

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

ISRIB makes cells less sensitive to stress

ISRIB attenuates induction of stress protein ATF4

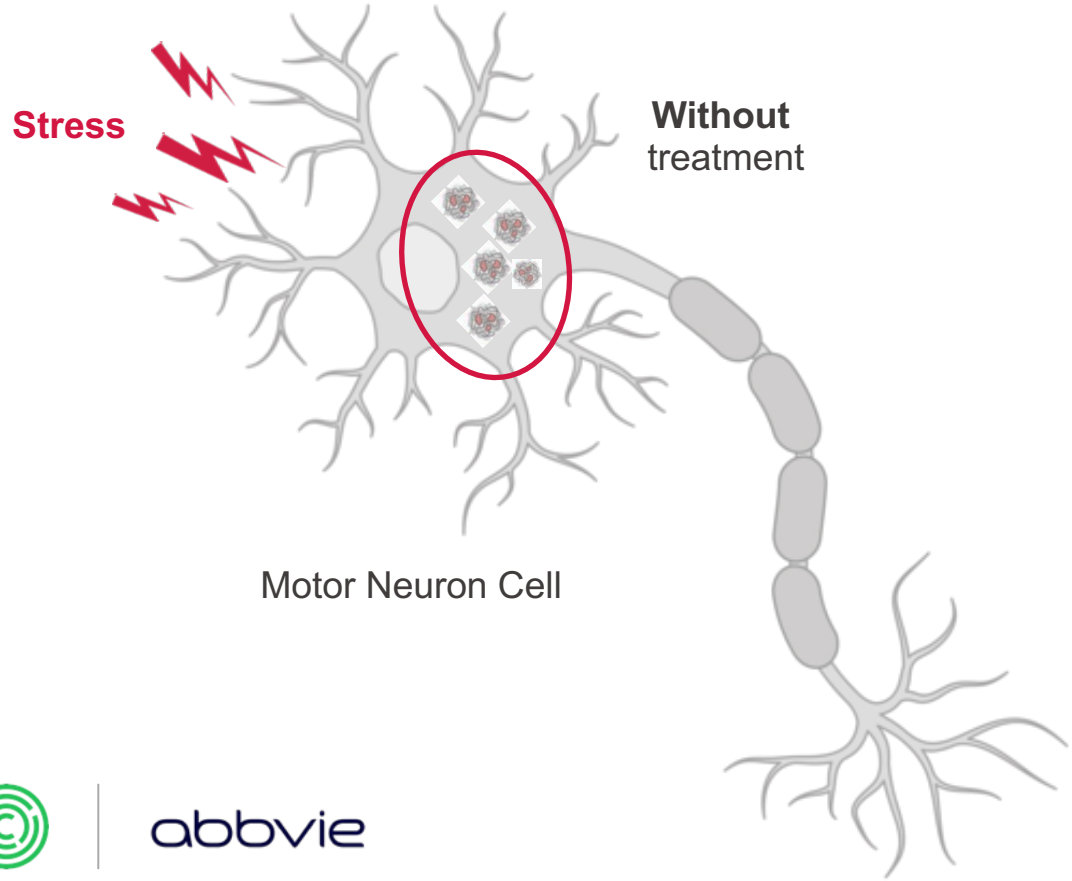




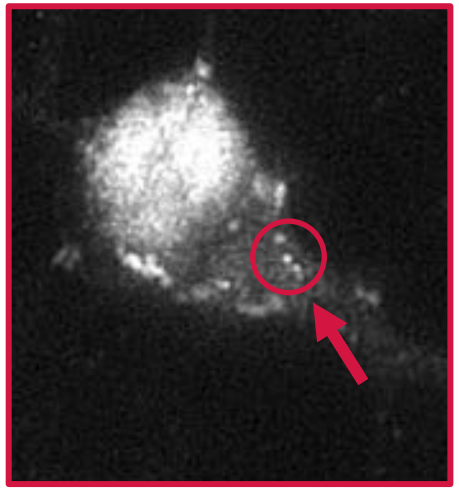
What eIF2B testing has been done so far?

eIF2B activators dissolve TDP-43 stress granules in human motor neurons

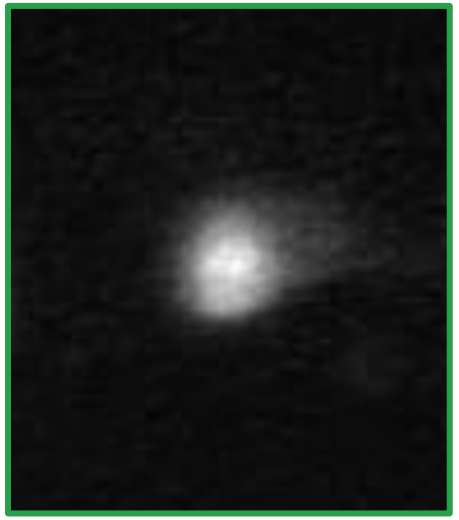
Activating the ISR drives TDP-43 into stress granules



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



Without treatment

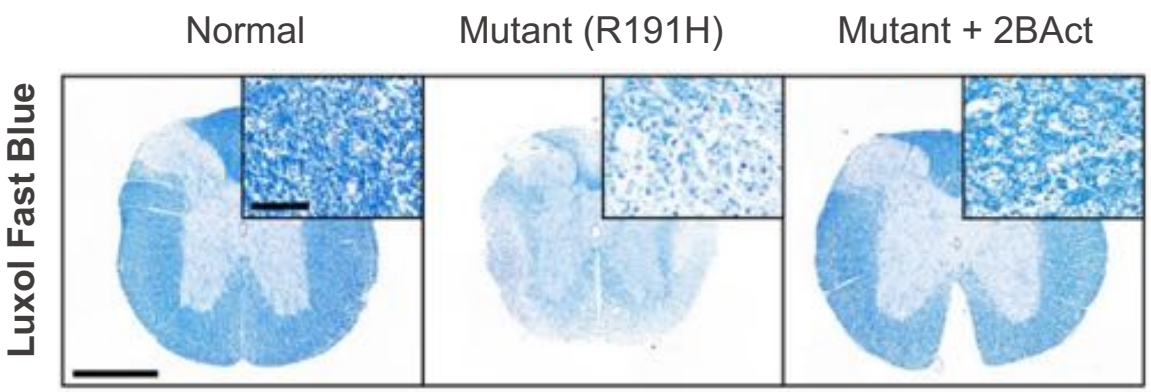


With treatment

in vitro Experiment

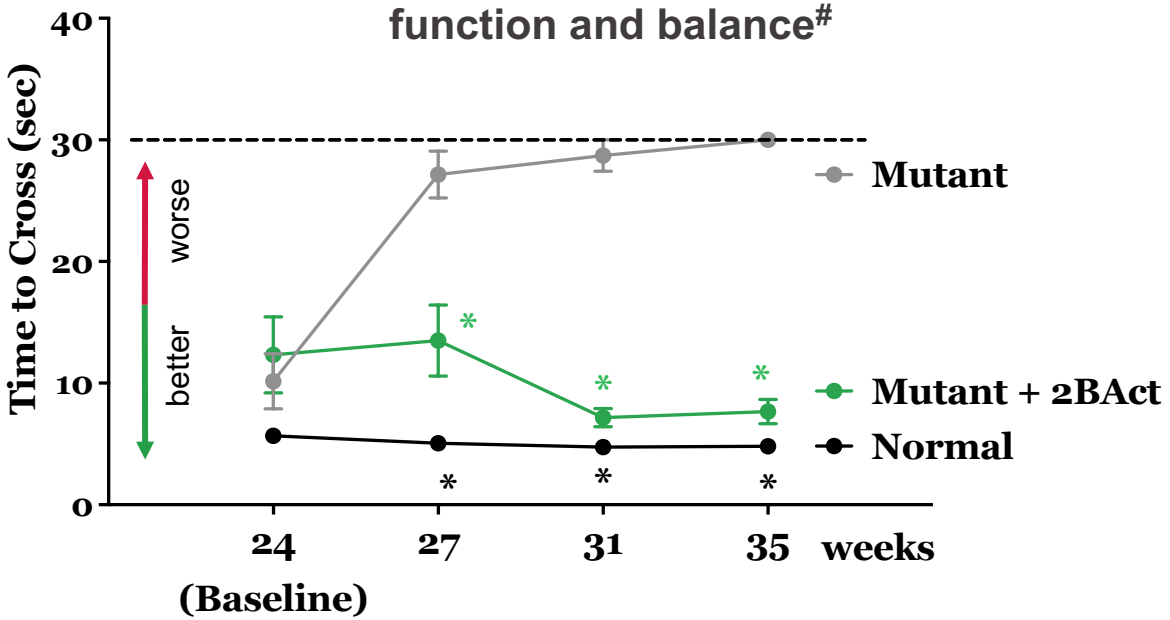
eIF2B activators rescue mice from neurological deficits caused by a persistent ISR in the brain and spinal cord

2BActivator preserves the white matter in the spinal cord



Wong et al., eLife 2019

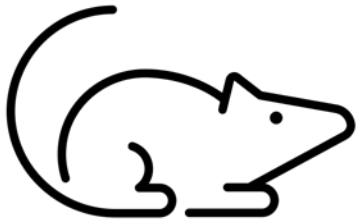
2B Activator improves motor function and balance#



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

* p ≤ 0.00001 vs. Mutant

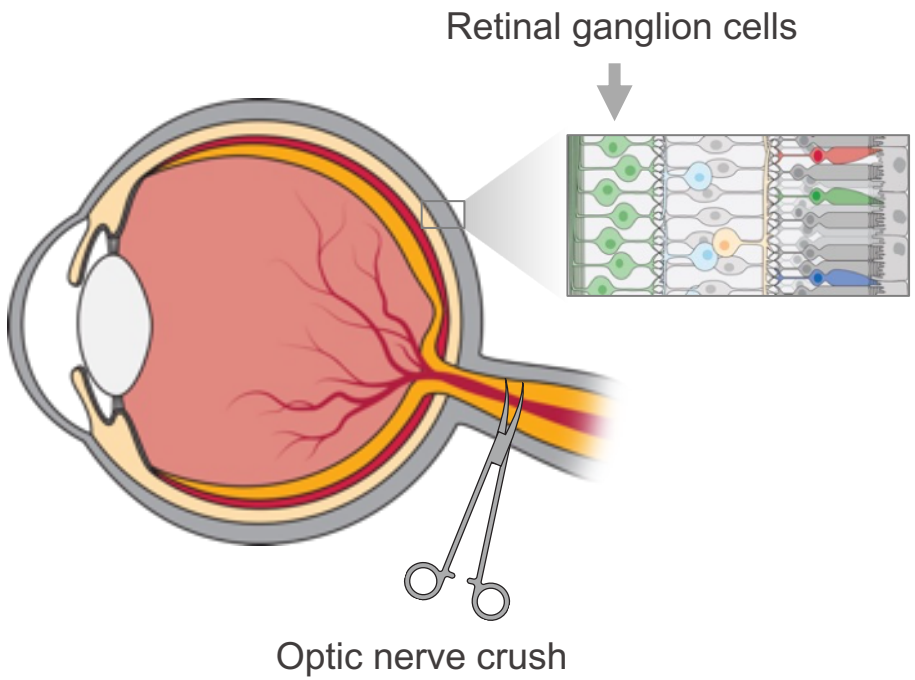
as measured by time to cross a balance beam



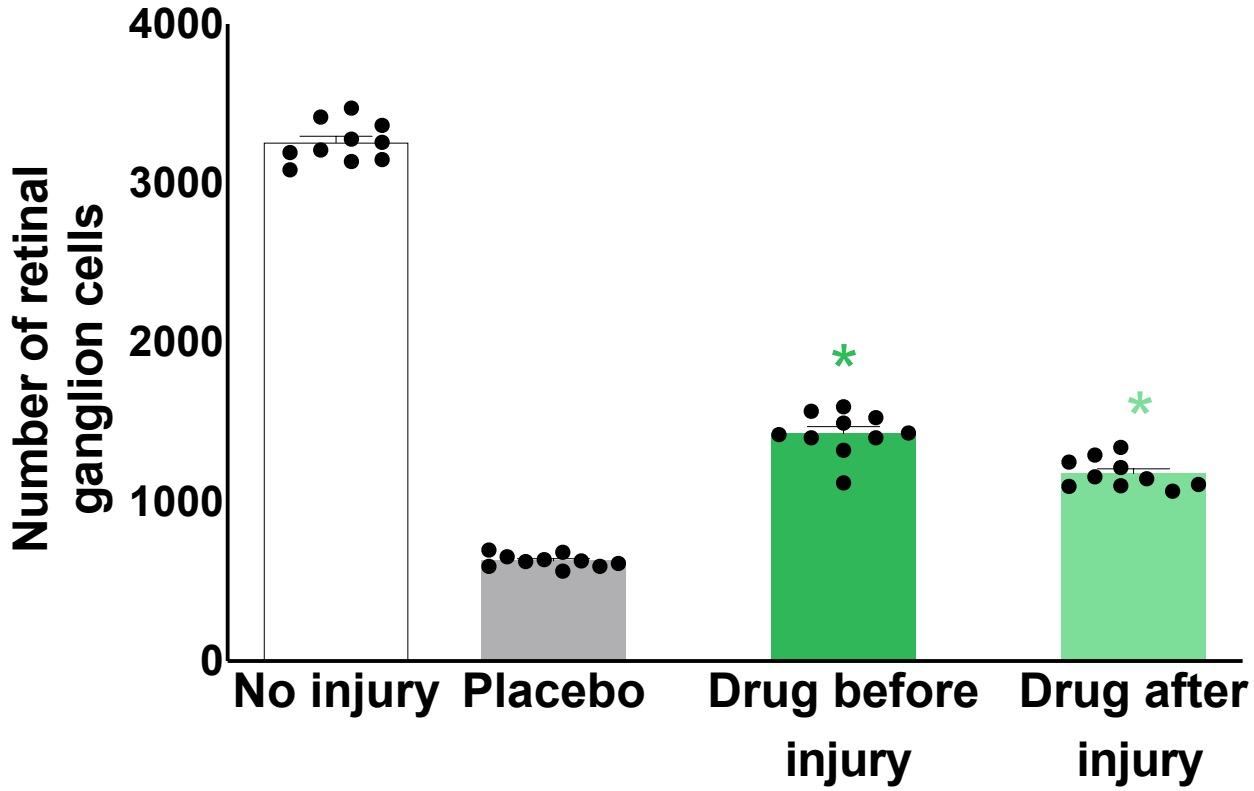
in vivo (mouse) Experiment

eIF2B activators protect neurons from dying after injury

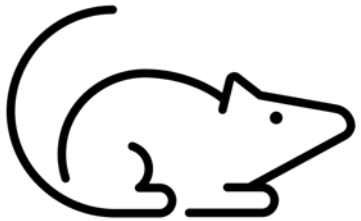
Trauma to the optic nerve induces the ISR in retinal neurons and leads to death



eIF2B activators protect retinal neurons



* p≤0.001 vs. Placebo

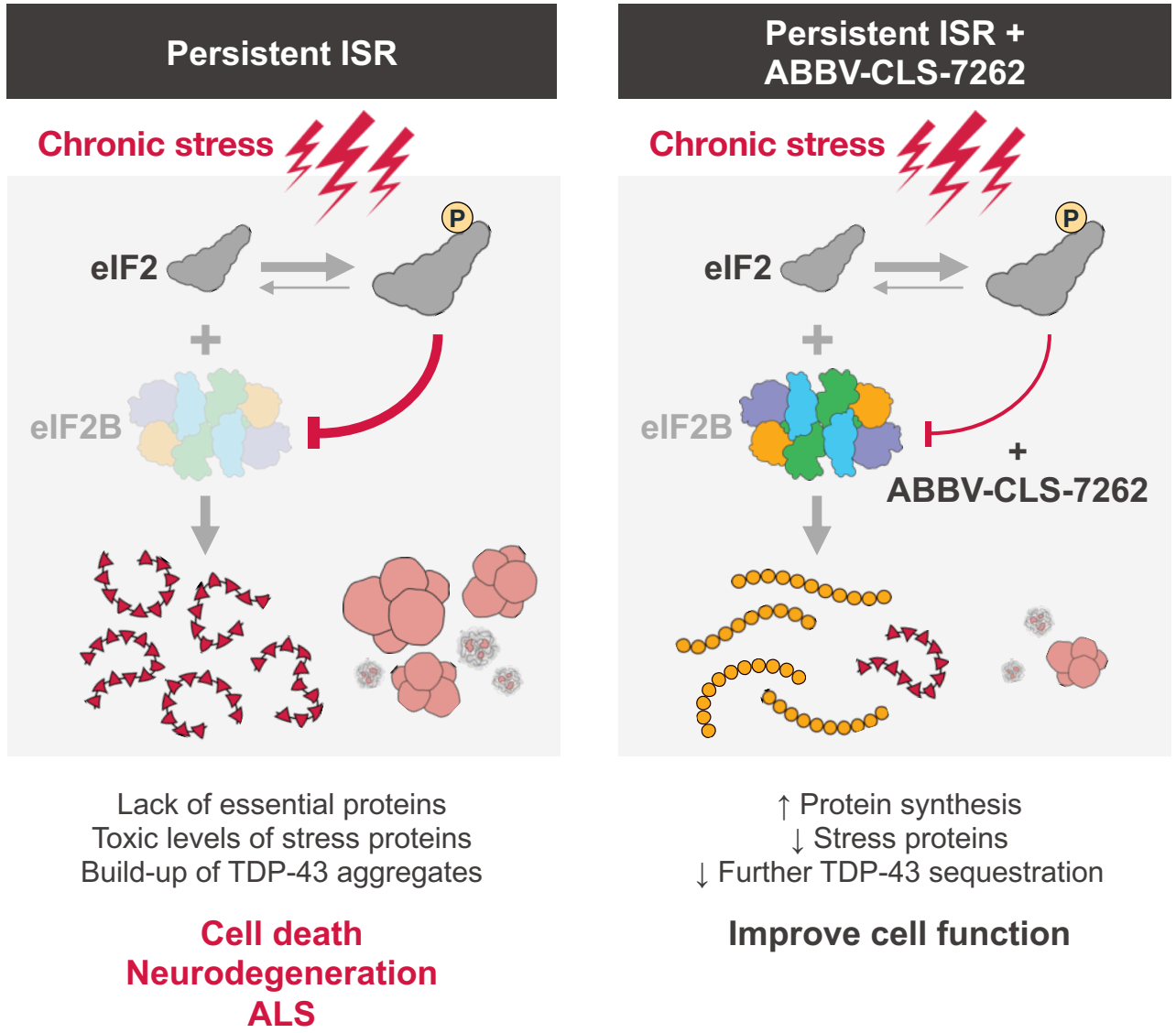


in vivo (mouse) Experiment

How can eIF2B activators potentially treat ALS?

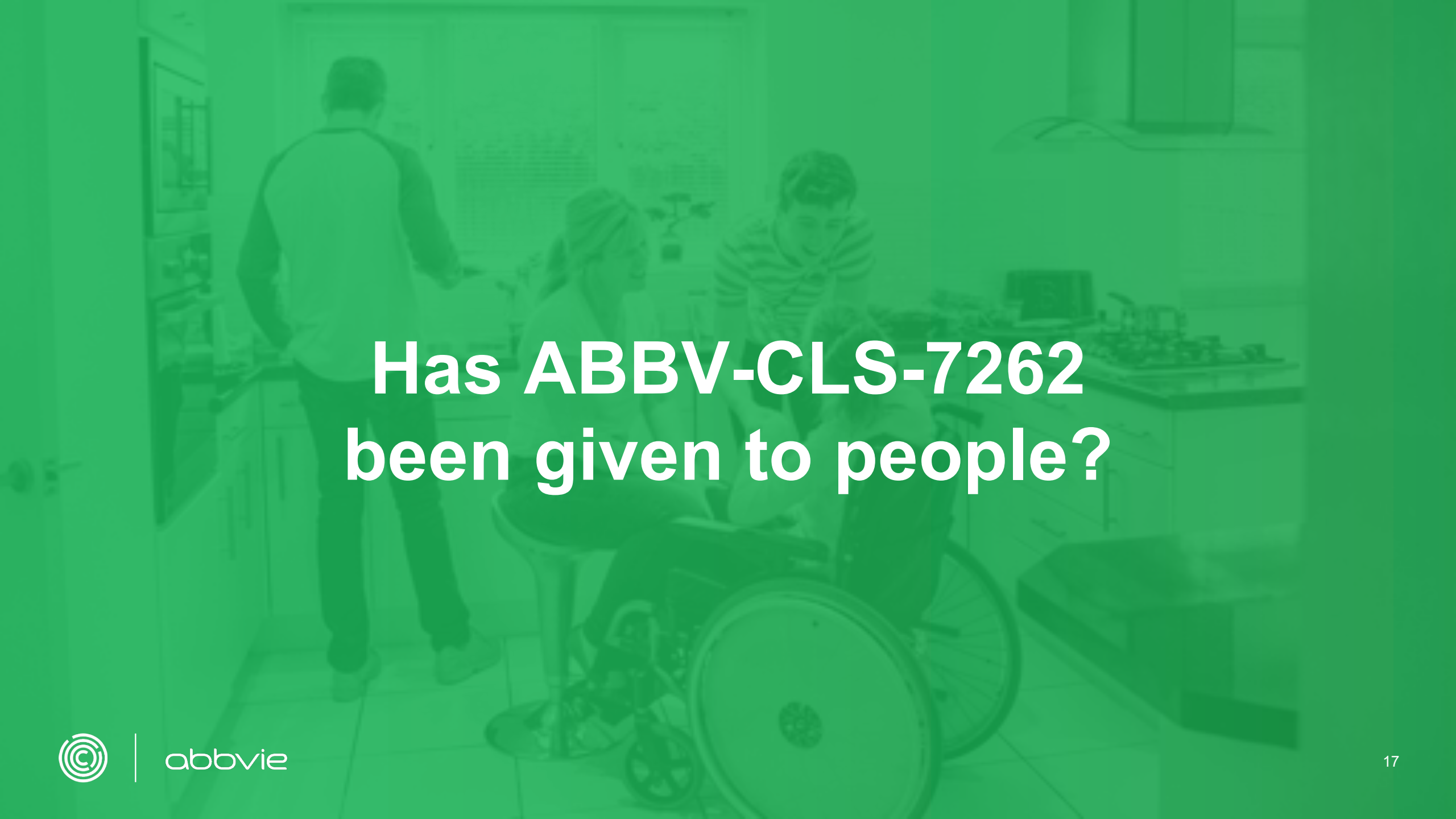
eIF2B activators may help motor neurons survive harmful stress conditions by:

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 granule | TDP-43



Has ABBV-CLS-7262 been given to people?

Results from the first study in healthy people

ABBV-CLS-7262, our clinical eIF2B activator, has been given to over

100

HEALTHY VOLUNTEERS

ABBV-CLS-7262 has favorable drug properties; it can be administered by mouth once a day

ABBV-CLS-7262 was safe across a wide range of doses.

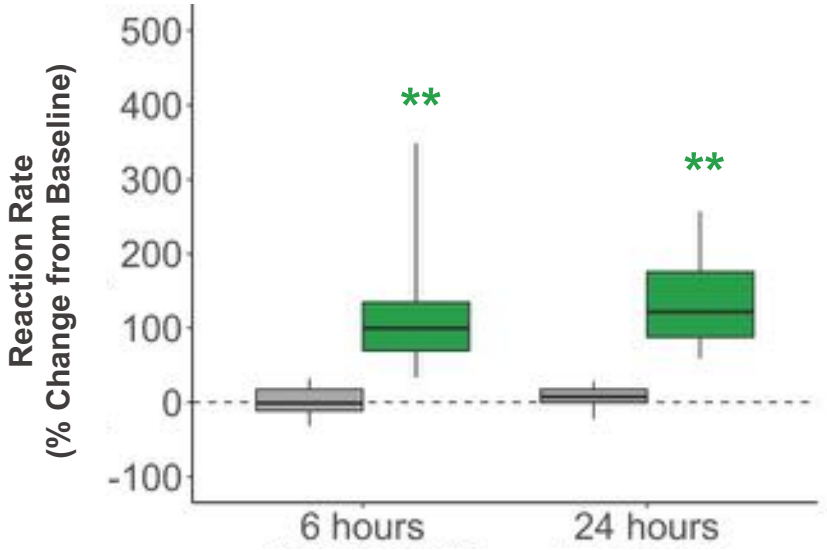
Adverse events were *non-serious* and generally similar between people treated with ABBV-CLS-7262 and placebo

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

The drug entered the cerebrospinal fluid and was present at concentrations that can fully activate eIF2B

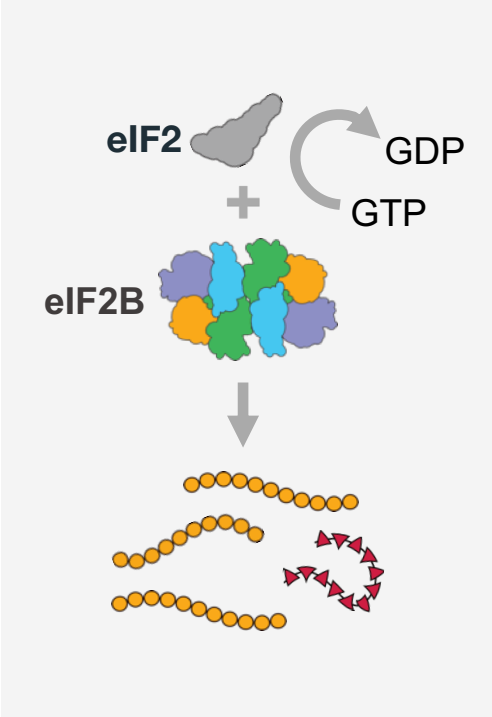
ABBV-CLS-7262 increased eIF2B activity and inhibited the ISR in blood cells collected from trial participants

ABBV-CLS-7262 enhances the enzyme activity of eIF2B

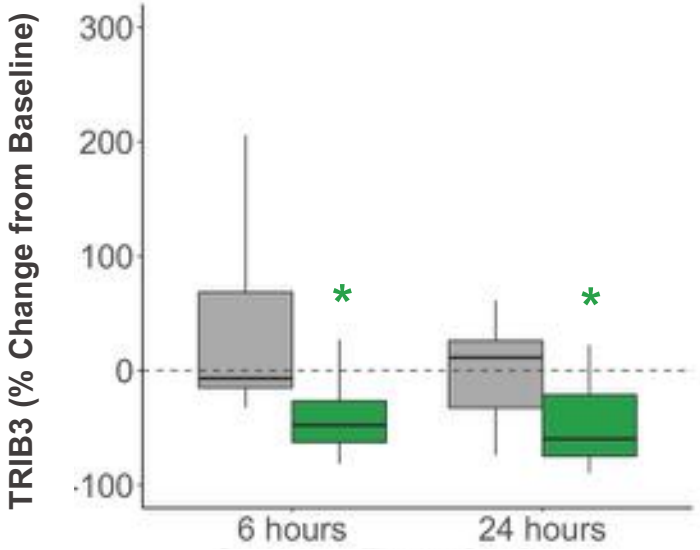


Sampling Time after Dosing

** p≤0.001 vs. Placebo



ABBV-CLS-7262 suppresses the ISR stress gene TRIB3



Sampling Time after Dosing

* p≤0.05 vs. Placebo

Placebo ABBV-CLS-7262

Has ABBV-CLS-7262 been given to people with ALS?

Preliminary safety information from an ongoing study in people with ALS

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

ABBV-CLS-7262
has been given to

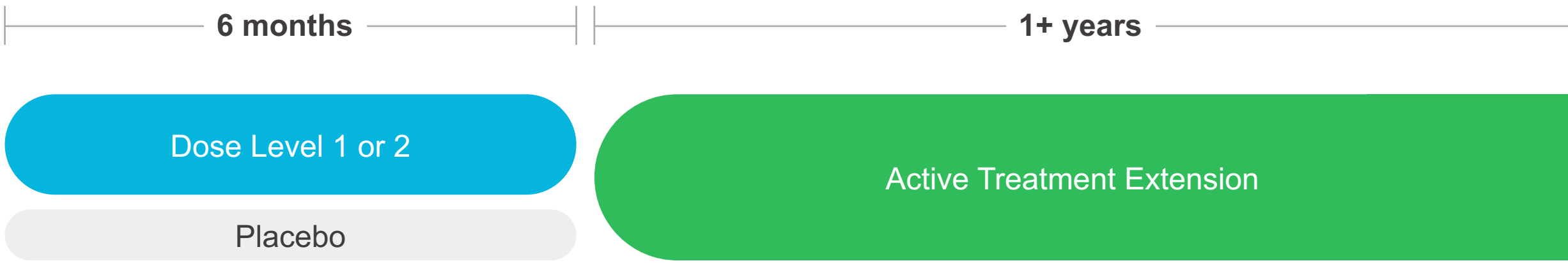
31

PEOPLE WITH ALS

Some participants have been treated for more than a year

*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 will be the next regimen (F) in the Healey ALS Platform Trial



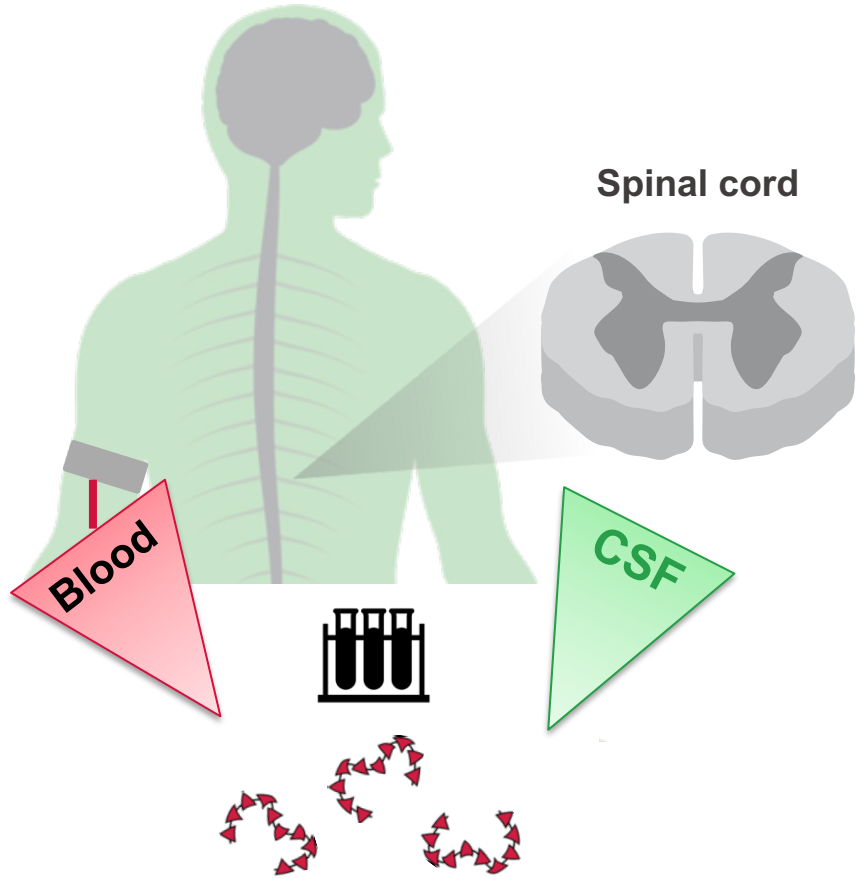
ABBV-CLS-7262 will be taken by mouth once daily

Participants will be randomly assigned to receive active drug or placebo in a 3:1 ratio

All participants will receive active drug for at least 1 year

Participants will be randomized to 1 of 2 dose levels,
both of which are predicted to be pharmacologically active

Biomarker collection in Regimen F will expand our understanding of ALS



Cerebrospinal fluid (CSF, fluid surrounding the brain and spinal cord) is collected by lumbar puncture at the beginning of the trial and at the end of the RCT

Blood will be collected periodically

These samples will measure biomarker concentrations to better understand:

- The biology of ALS and role of the ISR
- The effect of ABBV-CLS-7262 on the ISR in the brain and spinal cord
- Which people with ALS may respond better to ABBV-CLS-7262

In summary…

ABBV-CLS-7262 is ready to be evaluated as a new potential treatment for ALS

Problem	Calico
ISR is activated in ALS	ABBV-CLS-7262 is a potent inhibitor of the ISR by binding to, and activating, eIF2B
Aggregates of the protein TDP-43 are observed in most ALS cases	ABBV-CLS-7262 dissolves stress granules containing TDP-43 which may reduce formation of new TDP-43 aggregates
Drugs tested in ALS clinical trials must have their intended biological effect in people	Blood cells from people given ABBV-CLS-7262 show increased eIF2B activity and reduced ISR
The right dose needs to be administered in clinical trials	ABBV-CLS-7262 was measured in the CSF at levels predicted to be pharmacologically active at tolerated doses
Our understanding of ALS is incomplete	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

Questions

Learn more about Calico and our clinical trials:

calicolabs.com/patients

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