prilenia

Pridopidine for ALS:

Healey Platform Trial Regimen D

FAQs

1. What is pridopidine?
2. What is the Sigma-1 Receptor (S1R)?
3. Why is the S1R a good target for an ALS therapy?
4. Why test pridopidine for ALS?
5. Was pridopidine tested in people before?
6. How do you know pridopidine gets into the brain and spinal cord in people?
7. Is there any evidence that pridopidine slows progression of other diseases?
8. How do you know pridopidine is safe?

1

What is pridopidine?

What is pridopidine?

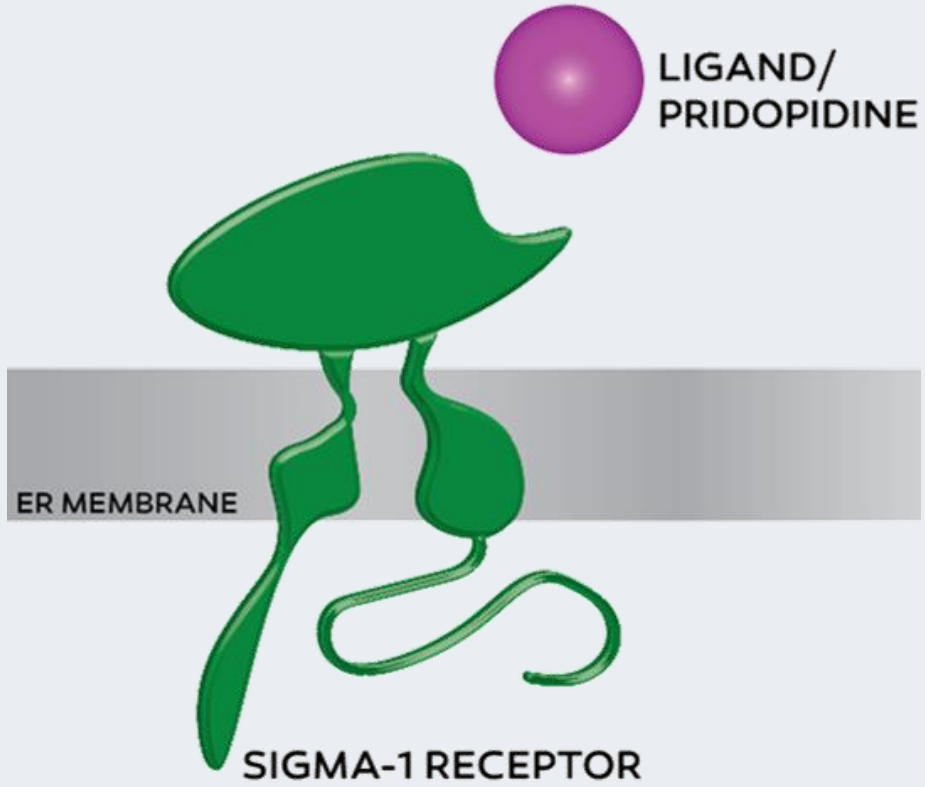
- A small molecule investigational drug in clinical trials for ALS and Huntington disease (HD)
- Pridopidine is administered orally twice a day (BID), in the morning and in the afternoon
- Pridopidine binds and specifically activates a receptor called the Sigma-1 receptor
- Pridopidine is safe and tolerable. The dose tested for ALS has a side effect profile like that of placebo in clinical studies in Huntington disease.
- In patients with Huntington disease, pridopidine is the first drug to show maintenance of total functional capacity (TFC).
- This effect is durable up to 5 years (longest time that has been analyzed to date)
- TFC is the most accepted scale used to assess HD patient function and disease progression, and is accepted by the regulatory agencies as a single primary endpoint in clinical trials

2

What is the Sigma-1 Receptor (S1R)?

What is the Sigma-1 receptor (S1R)?

- A protein highly expressed in the brain and spinal cord, particularly in motor neurons
- Plays an important role in the cell's response to stress
- Activation of the S1R has neuroprotective effects:
  - Reduces degeneration and death of neurons
  - Enhances neuronal health and function by increasing energy production and clearance of toxic proteins
  - Increases neuronal connectivity
  - Reduces cellular stress and neuroinflammation



3

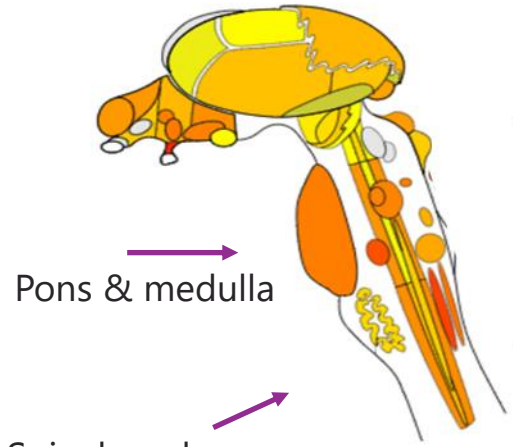
Why is the S1R a good target for ALS?

High distribution of S1R in brain areas implicated in ALS

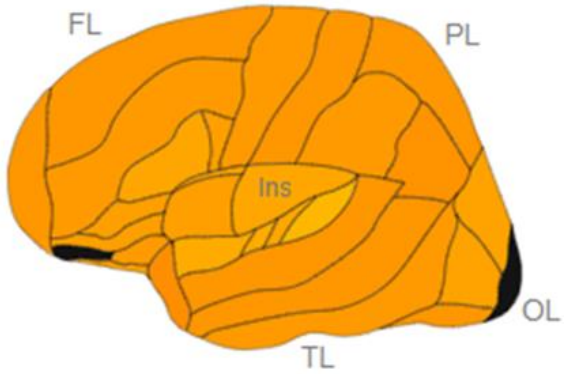
S1R is highly expressed in the brain stem, spinal cord and cortex

High expression of S1R mRNA:

Brainstem and Spinal Cord



Cortex



low high

Human validation: Genetic mutations in S1R cause ALS

The S1R gene

Complete Loss of function mutations located near the ligand binding site → cause Juvenile ALS

Partial loss of function mutations → cause late-onset ALS

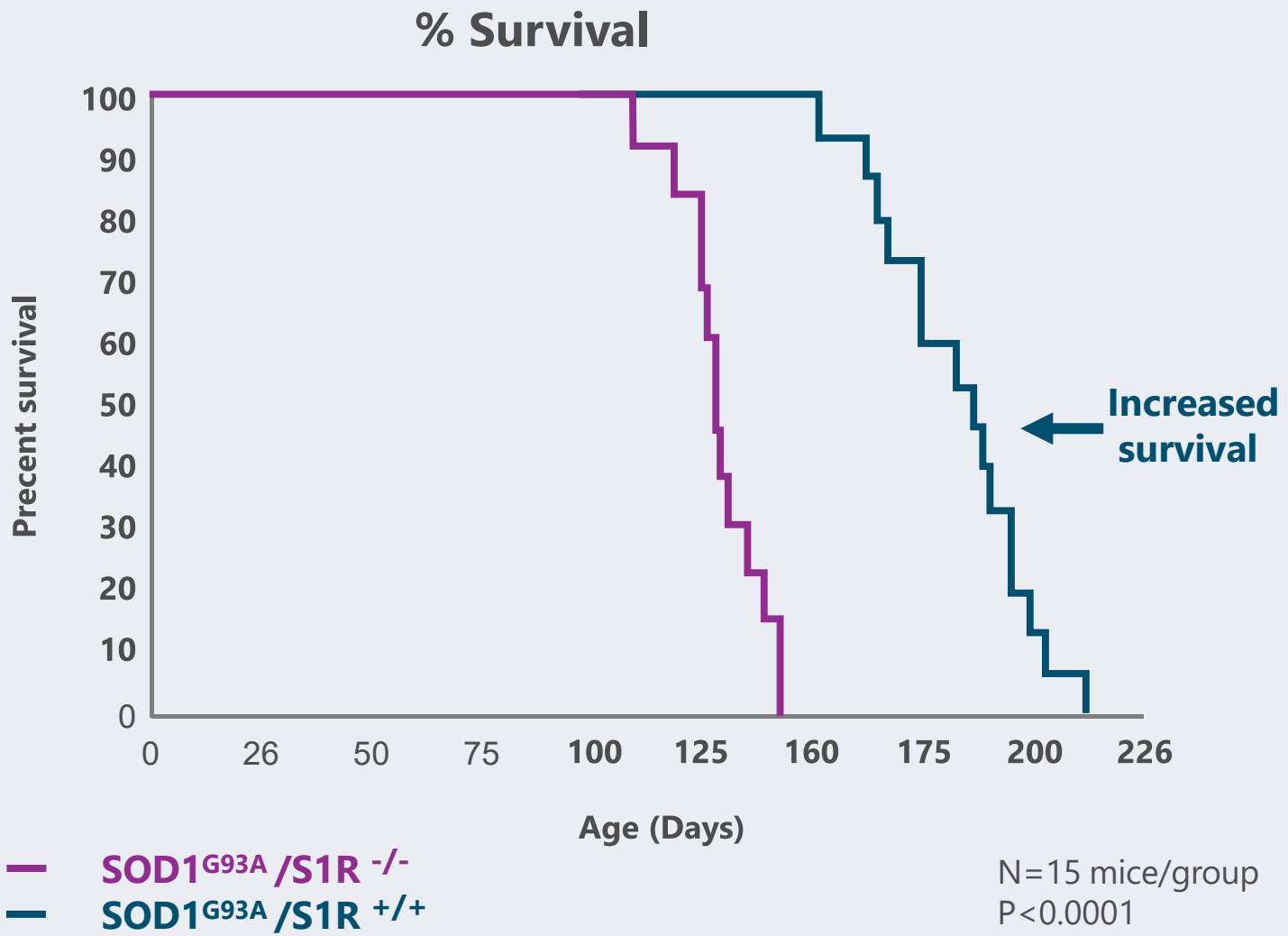
- ER signal motif
- Trans-membrane motif
- Ligand binding motif

Al-Saif et al., 2011; Watanabe et al., 2016; Izumi et al., 2018

Adapted from Watanabe et al, 2016

Lack of S1R exacerbates disease progression in ALS mice

- Mice with a mutation in the SOD1 gene are a common model used in ALS research
- Removing the S1R gene (S1R-/-) from SOD1 mice accelerates disease progression and decreases survival (in purple)

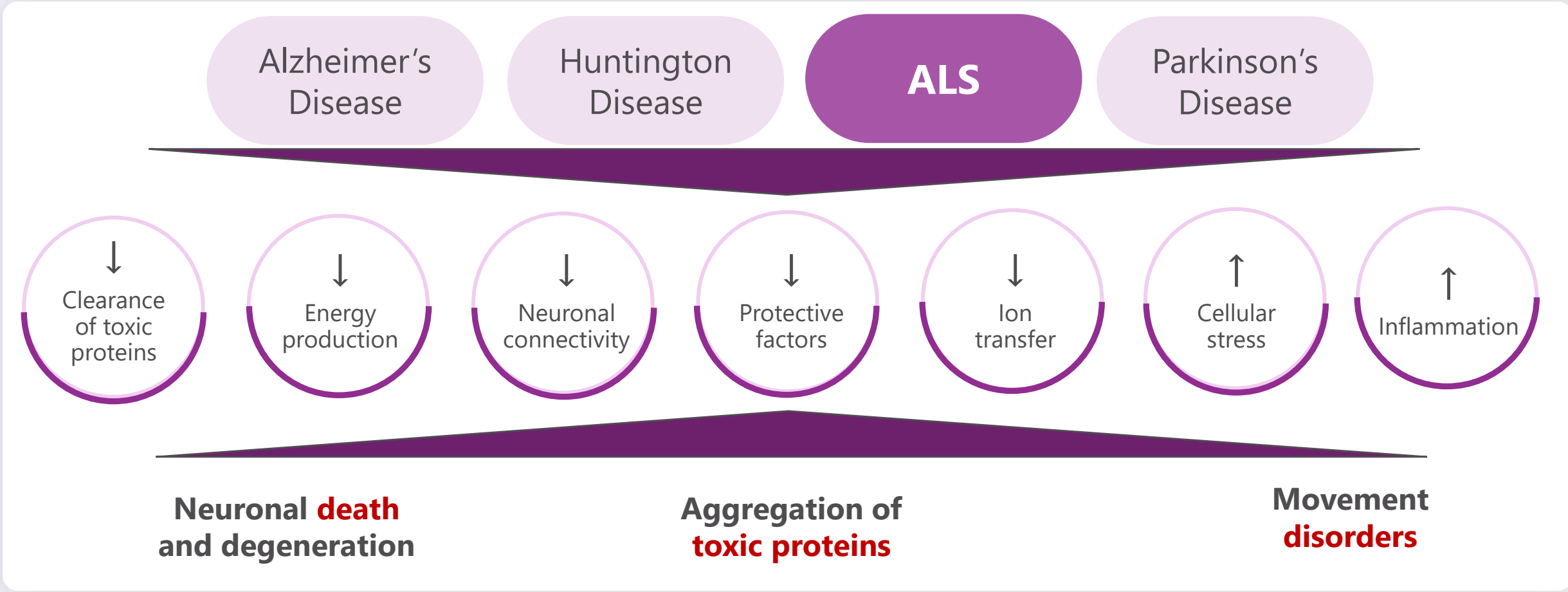


Mavlyutov et al, Neuroscience (2013)129–134

4

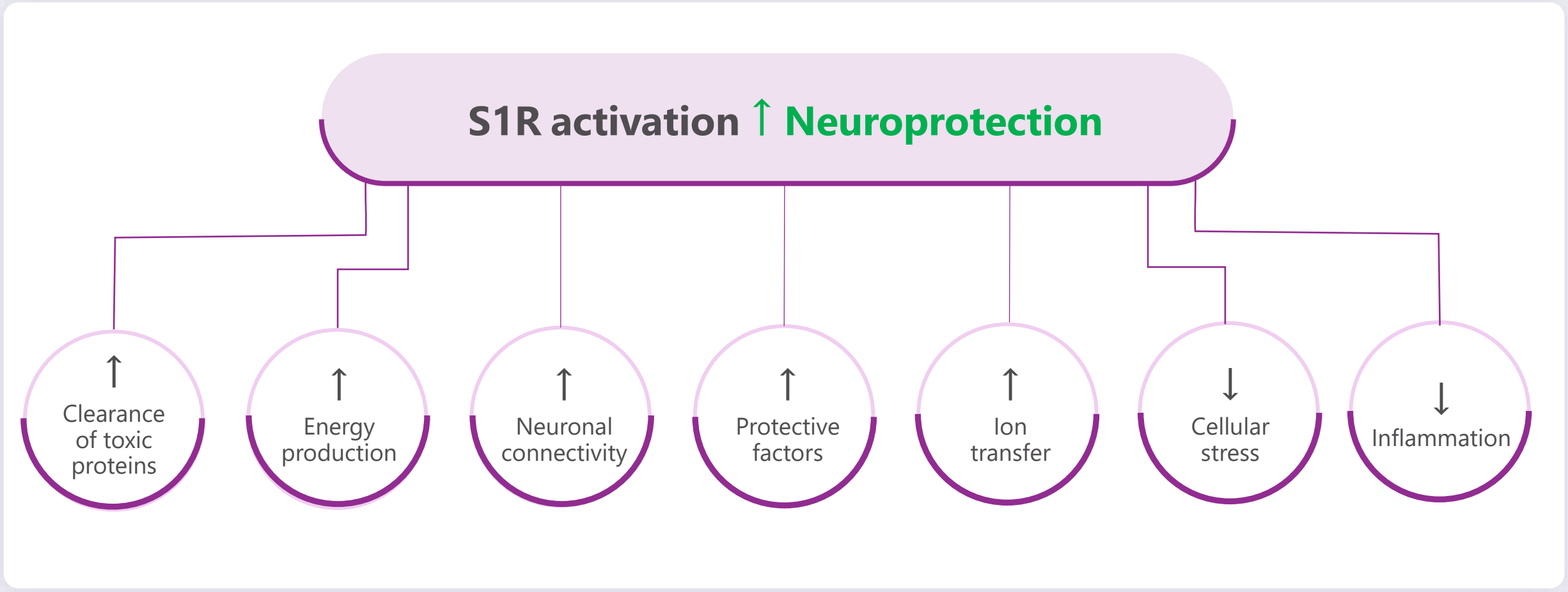
Why test pridopidine for ALS?

Multiple cellular pathways are similarly affected in ALS and other neurodegenerative diseases



Activation of the S1R positively affects all of these pathways

Pridopidine activation of the S1R positively influences **multiple pathways** that lead to neuroprotection

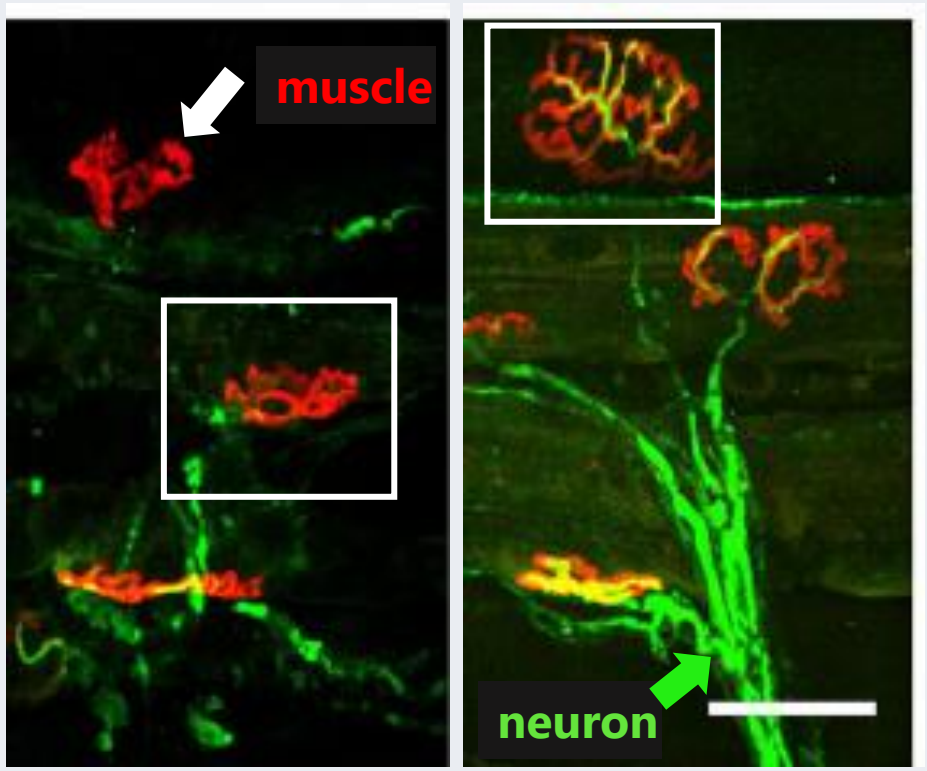


1. Christ et al, Cells. 2019; 2. Tesei et al, Frontiers in Pharmacology. 2018; 3. Hayashi and Su, Cell. 2007; 4. Tsai et al, PNAS. 2009; 5. Hayashi et al, Trends in Cell Biol. 2009; 6. Fujimoto et al, Synapse. 2012; 7. Xu et al, Psychopharmacology. 2014; 7. Kourrich et al, Trends Neurosci. 2012; 8. Ryskamp et al, Front. Neurosci. 2019; 9. Pal et al, Eur J Pharmacol. 2012. 10. Ryskamp et al, NBD. 2017 11.Allen Brain Atlas Data Portal

Pridopidine rescues the neuron-muscle connection in ALS mice

- The neuron-muscular junction (NMJ) is the connection between neuron and muscle
- In ALS mice, the NMJ is disrupted (left)
- Pridopidine rescues this connection (neuron + muscle labeling shows as yellow on the right)

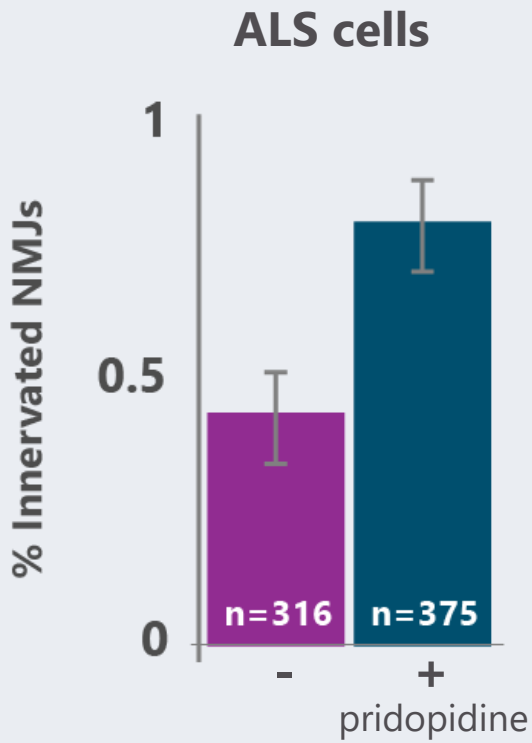
Ionescu et al., Cell Death & Disease 2019



Muscle

Neuron

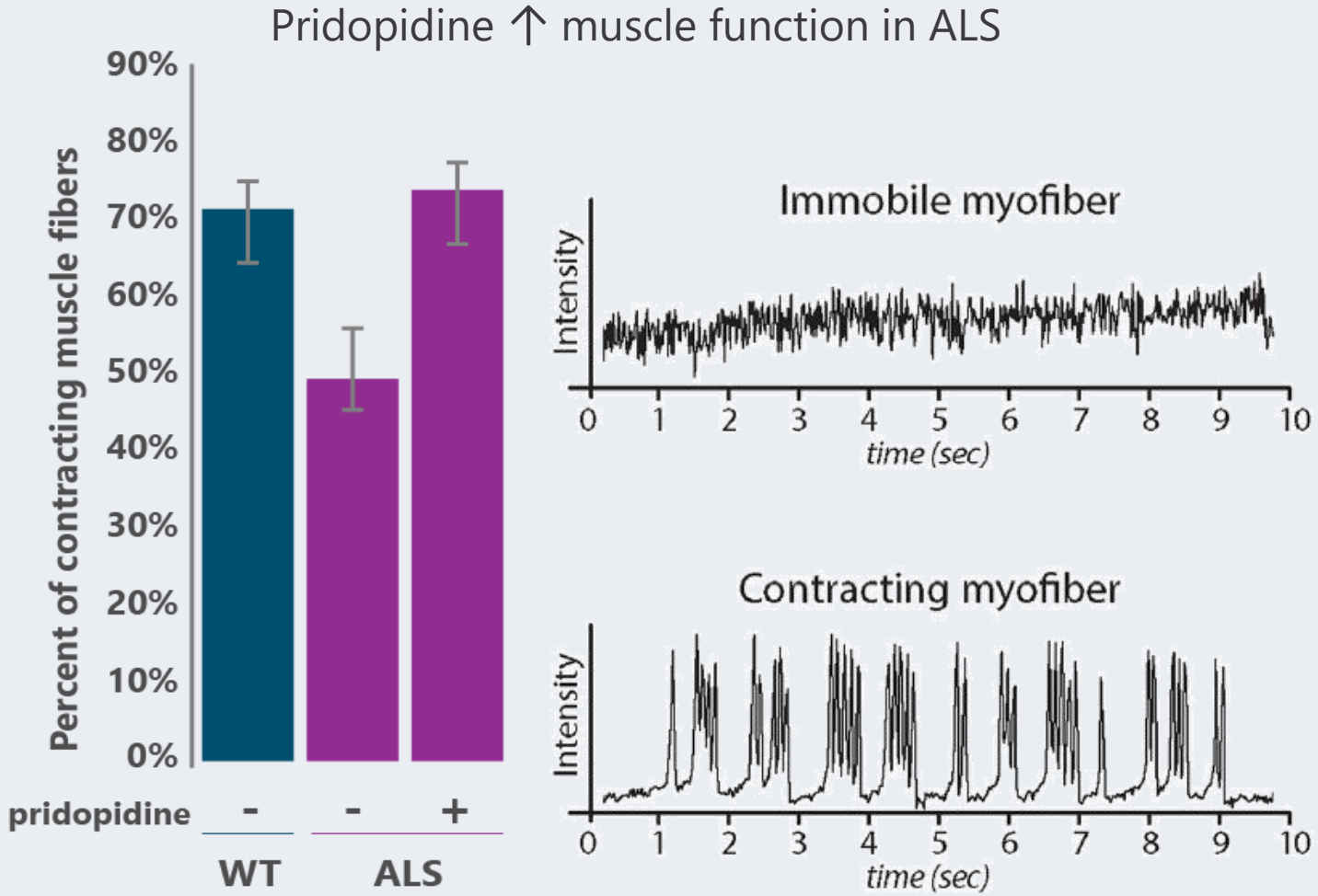
NMJ Connection (neuron + muscle)



SOD1 G93A ALS model mice

Pridopidine rescues the neuron-muscle function in ALS cells

- Healthy cells show high muscle contractility (blue, left bar)
- Disruption of the neuron-muscle connection in ALS cells → less muscle contractility (purple, middle bar)
- Pridopidine rescues muscle contractility in ALS (purple, right bar)



Ionescu et al., Cell Death & Disease 2019

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Was pridopidine tested in people before?

Yes.

Pridopidine has been tested in

>1300 people

the majority of them Huntington disease patients

To date

22 Clinical studies have been performed

for pridopidine, with some of these running for 5+ years

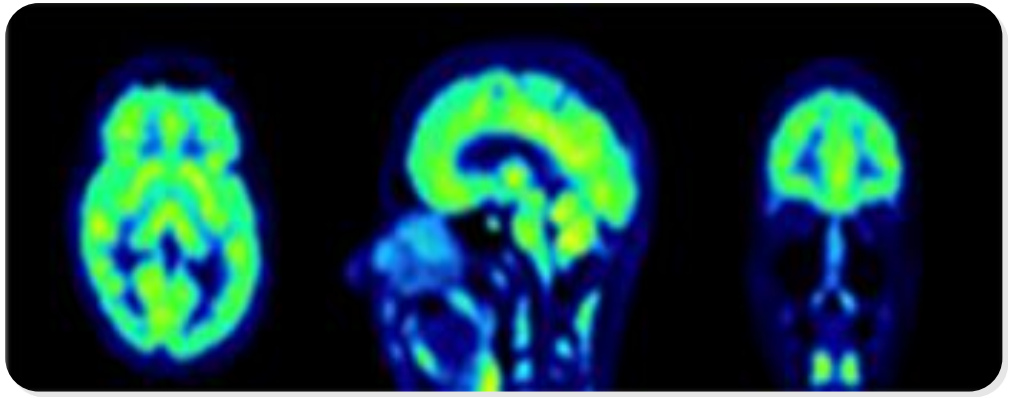
6

How do you know pridopidine gets into the brain and spinal cord in people?

Pridopidine gets into the brain and spinal cord and binds the S1R at the clinical dose

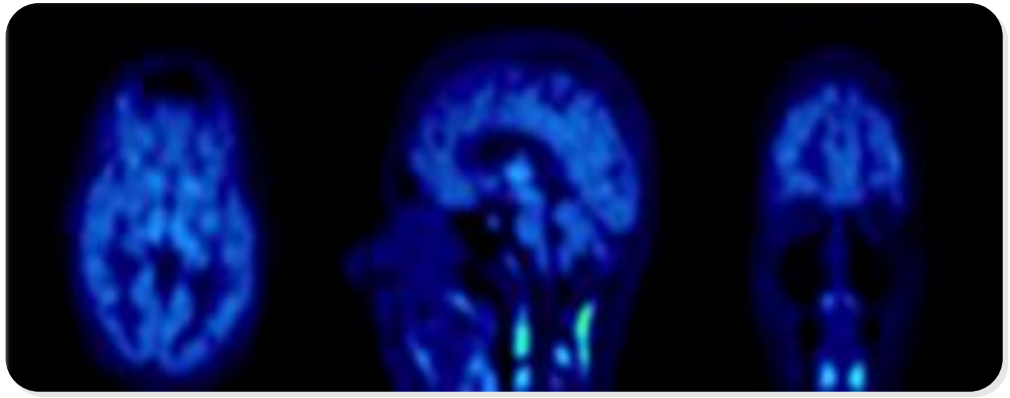
18F-Fluspidine (labeled drug that binds the S1R) S1R occupancy

Without pridopidine



- We can radioactively label **fluspidine**, a known **S1R** binding drug
- We can then view this labeled drug in the brain

With pridopidine



- Pridopidine prevents fluspidine binding to the **S1R** after an oral dose
- Prevention of labeled fluspidine binding in the brain by pridopidine shows its **strong and selective binding** to the S1R

Grachev et al; NEMJJ 2020

7

Is there any evidence that pridopidine slows progression of other diseases?

Pridopidine is the only drug that has shown a beneficial effect on Total Functional Capacity (TFC) in HD

- TFC is a scale that assesses disease progression and functionality in HD patients
- In HD patients pridopidine maintained functional capacity compared with placebo

	45 mg BID
N	59
Wk52 Δ to placebo	1.16
p value	0.0003

Early Stage HD Week 52 (BL TFC ≥7)

Patients on placebo deteriorate by 1 point /year

Patients on pridopidine did not deteriorate

McGarry et al., 2020 Journal of HD,

HD shares many similarities with ALS:

HD patients and families highlight decreased **functional capacity** as a **major burden on daily life**

Participants strongly emphasized the **burden of HD** left them **unable to perform many, if not all daily activities**

The **13-point TFC scale** captures changes in HD patients' capacity to continue working, driving, performing household activities, **eating (due to fear of choking), feeding themselves, dressing themselves, walking,** getting out of bed, and completing simple tasks

Participants noted that they have become increasingly or fully **dependent on others** for care, as HD symptoms worsened

FDA – The Voice of the Patient: Huntington's Disease - 2015

Years of research, in both the lab and the clinic show beneficial effects of pridopidine for treating neurodegenerative disease.

This effect is significant and durable.

8

How do you know pridopidine is safe?

Pridopidine has an extensive safety and tolerability profile

Extensive clinical experience

>1300
subjects

in total of ~1300
patient years

The majority of this has been in Huntington disease (HD)

45mg BID exposure
The dose to be tested in ALS

>1000 patient years

in 981 patients

Doses ranging from

10 mg → to → 112.5 mg

twice a day (BID)

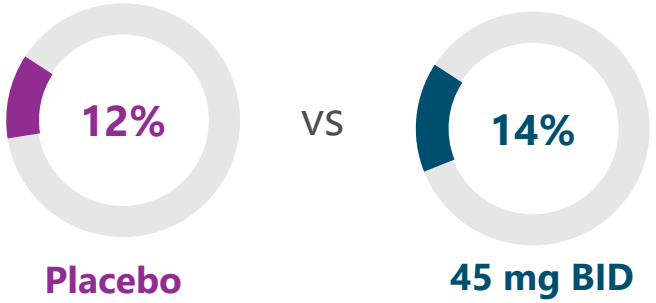
Safe and tolerable

- Including **long term safety data** (>5 years) in HD population
- Side effect profile comparable to placebo

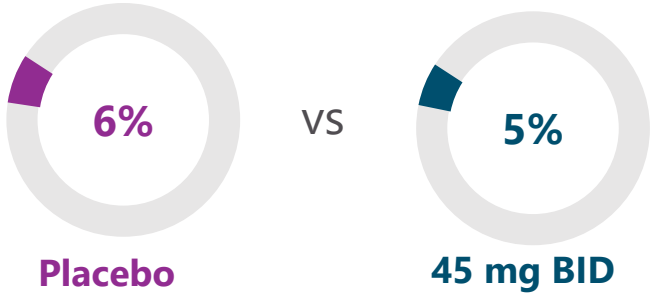
Similar incidence of side effects at 45 mg BID as placebo

Most common side effects: placebo vs 45 mg BID

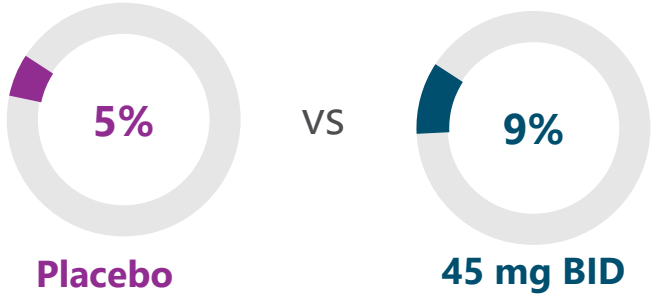
Falls



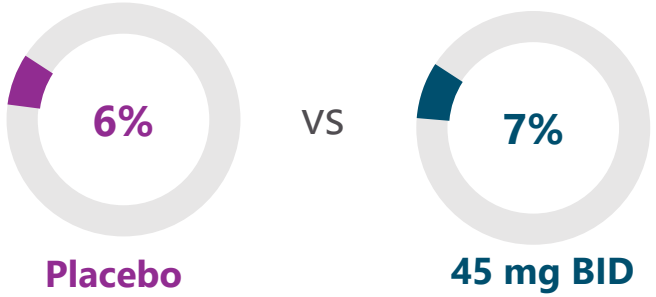
Nausea



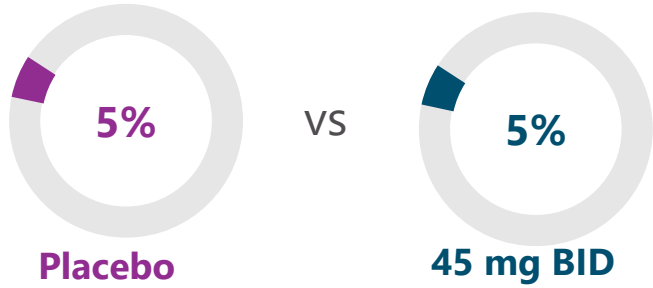
Nasopharyngitis



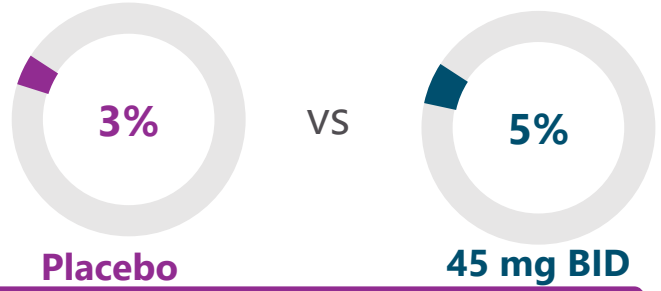
Diarrhea



Headache



Dizziness



Pridopidine 45 mg BID side effect profile is comparable with placebo

Integrated safety dataset from placebo-controlled HD trials (HART, MermaiHD and PRIDE-HD)

Pridopidine is a highly selective Sigma-1 receptor (S1R) activator for the treatment of ALS

Validated target

S1R genetic loss of function mutations cause ALS in humans

Lack of S1R ↑ progression in ALS mouse model

Neuroprotective in animal models

↑ Neuronal survival

↑ Neuron function

↑ Muscle contractility

↓ Muscle atrophy

Human target engagement

Robust and selective S1R binding in the brain and spinal cord

Safe and tolerable

Extensive safety data in >1300 patient years

45 mg BID shows placebo-like safety and tolerability

Compelling evidence supports therapeutic potential of pridopidine in ALS