

# Pridopidine for HD:

PROOF-HD Phase 3 clinical trial





Huntington's Disease is a rare, inherited neurodegenerative disorder



Pridopidine is an oral investigational drug with good safety and tolerability, and potential beneficial effects for the treatment of HD



The safety and efficacy of pridopidine are being evaluated in the PRGOFHD phase 3 clinical trial



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# What is Huntington's Disease ?



### HD is a rare, inherited neurodegenerative disorder





- Caused by expanded CAG repeats in the Huntingtin gene, which interferes with the gene's normal function.
- Neurons in the brain degenerate and die, causing a decrease in neuronal connections.
- Loss of neuronal connections results in functional, motor, cognitive, emotional and behavioral symptoms.
- Total Functional Capacity is the accepted clinical measure of disease progression.



# HD influences multiple cellular pathways that cause neuronal dysfunction





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



Participants strongly emphasize the **burden of HD** leaves them **unable to perform many daily activities** 



Patients become increasingly **dependent on others** for care, as HD progresses



### "Any beneficial effect in the TFC would be considered clinically meaningful."

Karl D. Kieburtz, M.D., M.P.H - Professor, University of Rochester and President at Clintrex LLC

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





# What is pridopidine?



### What is pridopidine?

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A small molecule investigational drug in clinical trials for Huntington's disease (HD) and ALS.

### $\bigcirc$

Pridopidine is safe and tolerable. The dose tested in PROOF-HD has a side effect profile similar to placebo.

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Pridopidine is administered orally twice a day (BID), in the morning and in the evening.

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Pridopidine binds and specifically activates a receptor called the Sigma-1 receptor (S1R).

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In patients with Huntington's disease, pridopidine is the first drug to show maintenance of total functional capacity (TFC). This effect may be durable up to 5 years (longest time that has been analyzed to date).

### Pridopidine is administered orally twice a day



### Pridopidine is packed in **small easy to swallow** capsules





# What is the Sigma-1 Receptor (S1R)?



### What is the Sigma-1 receptor (S1R)?

- A protein highly expressed in the **brain**
- Plays an important role in the cell's **response to stress**
- Activation of the S1R has **neuroprotective** effects:
  - $\downarrow$  degeneration and death of neurons
  - Enhances neuronal health and function by ↑ energy production and clearance of toxic proteins
  - ↑ neuronal connectivity
  - $\mathbf{\downarrow}$  cellular stress and neuroinflammation





# Why is the S1R a good target for HD therapy?



### High expression of S1R in the areas affected by HD







Pridopidine activation of the S1R in HD 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 HD neurons from dying in HD models**

### **Pridopidine** ↓ **neuronal cell death**



\*\*\* p < .001, ANOVA with Bonferroni post-hoc test

Healthy N586 22Q/HD N586 82Q

Eddings et al, Neurobiology of Disease 2019



### Pridopidine increases neuronal connectivity in HD neurons



#### Spines connect between two neurons

#### **Pridopidine ↑ neuronal connectivity in HD neurons**





# How do you know pridopidine gets into the brain?



# Pridopidine gets into the brain and binds the S1R at the therapeutic dose

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

#### Without pridopidine



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

Grachev et al; NEMJJ 2020

#### 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





# Was pridopidine previously tested in people?







## Pridopidine has been tested in

>1300 ที่ที่ที่ที่ดี 🗄

the majority of them Huntington's disease patients



To date Many Clinical studies have been performed

with pridopidine, some of these running for  $5 + \frac{5}{years}$ 





# How do you know pridopidine is safe?



### Pridopidine has an extensive safety and tolerability profile

45mg BID exposure The majority of this has been **Extensive clinical experience** The dose tested in PROOF-HD in Huntington's disease (HD) >1000 patient years in total of  $\sim 1300$ in 981 patients patient years Including **long term safety data Doses ranging from** Safe and tolerable (>5 years) in HD population  $10 \xrightarrow{to} 112.5$ Side effect profile comparable to placebo ma twice a day (BID)

### Similar incidence of side effects at 45 mg BID as placebo







# Is there any evidence that pridopidine slows decline in function in HD patients?



### Pridopidine is the only drug that has shown maintenance of Total Functional Capacity (TFC) in HD

Total Functional Capacity is the accepted clinical measure of disease progression



### **Durability of Effect:**

### Patients treated with pridopidine may show less TFC decline over 5 years

**Pridopidine beneficial effect on TFC may be maintained over 5 years** 







### Years of research, in both the lab and the clinic show potential beneficial effects of pridopidine for treating Huntington's Disease





# What can I expect during the trial?



### PROOFHD assesses the effect of pridopidine on TFC



**Phase 3 trial**, double-blind, placebo-controlled 2-arm trial



480 early HD patients will be randomized to receive either **pridopidine 45 mg bid** or **placebo** (240 patients per arm)



Primary objective is to evaluate the effect of pridopidine on **functional decline** at 65 weeks using the UHDRS-TFC scale



There will **be in-clinic visits** and **virtual** (phone) visits to assess the safety and efficacy of pridopidine

Patients who complete the double-blind study can enroll into the open label study and receive pridopidine (no one will receive placebo)



### **North American** PROOFHD **sites**





### **European** PROOFHD sites





Confidential



### **Questions?**

### We will be happy to hear from you!

Email: info@prilenia.com

For more information: <u>www.prilenia.com</u> <u>https://huntingtonstudygroup.org/proof-hd/</u>



