The OLE Portion of the PROOF-HD Trial Shows Persistent Benefits of Pridopidine on Function, Cognition, and Motor in Huntington's Disease

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Pridopidine is an investigational therapy under development for Huntington's Disease, ALS, and other neurodegenerative diseases. It is currently not approved by any regulatory agency.
This presentation is for general information purposes only; it is not a substitute for professional medical advice.

What is Pridopidine?

Investigational drug in clinical development for **Huntington's Disease (HD) and Amyotrophic Lateral Sclerosis (ALS)**

Administered orally twice a day (bid) in morning and evening

Binds and specifically activates the **Sigma-1 receptor (S1R)**

Extensive clinical experience including long-term (up to 7 years) with the clinically used dose of **45 mg bid** shows a **safety and tolerability profile comparable to placebo***

*Majority of safety data is from patients with HD. Additional safety data from patients with ALS, Parkinson's disease, schizophrenia and healthy volunteers.
McGarry et al., J Huntingtons Dis. 2020;9(2):173-184; McGarry et al., J Huntingtons Dis. 2020;9(4):371-380; Darpo et al., Neurol Ther. 2023 Apr;12(2):597-617; Hayden, M., et al. (2024). AAN Annual Meeting, Denver, CO, USA, American Academy of Neurology; Geva M., et al. (2024) ENCALS, Stockholm, Sweden.

Background

- The S1R is highly expressed in the brain stem, spinal cord, basal ganglia and cortex, brain areas primarily affected in HD and ALS
- S1R activation by pridopidine demonstrates neuroprotective effects in preclinical models by enhancing mitochondrial function, autophagy and BDNF signaling, among other cellular processes[1-4]
- Human Positron Emission Tomography (PET) imaging shows selective and robust (>90%) occupancy by pridopidine at 45 mg bid, the dose evaluated in PROOF-HD[5]
- The safety and efficacy of pridopidine for treating HD was evaluated in the Phase 3 randomized clinical trial PROOF-HD[6,7]

1. Geva et al., Hum Mol Genet. 2016 25(18):3975-3987; 2. Naia et al, 2021 Neurotherapeutics 18(2):1017-1038; 3.Wang et al., Autophagy. 2022 4:1-26; 4. Lenoir et al., Neurobiol Dis. 2022; 173:105857; 5. Grachev et al, EJNMMI, 2021 48(4):1103-1115; 6. McGarry et al., JHD 2020; 9(2):173-184; 7. Darpo et al., Neurol Ther 2023; 12(2):597-617

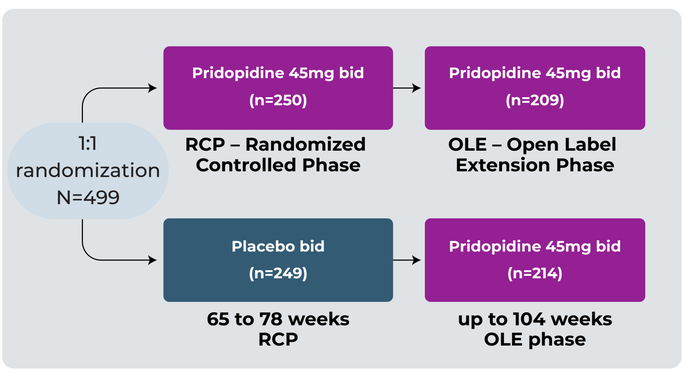
HD is a rare, progressive disease with high unmet need

- Only limited symptomatic treatment for chorea available (VMAT2 inhibitors and neuroleptics off label)
- High unmet need for new therapies impacting progression, function, cognition and motor abilities
- Predictable longitudinal decline in measures of global disease progression (cUHDRS), function (TFC), cognition (SWR) and motor (Q-Motor) functions
  - Improvements in any of these measures are not normally observed
- No drug to date has shown any sustained benefits in these clinical measures

Pridopidine is the first drug to show clinically meaningful benefits across numerous measures of disease progression

PROOF-HD: Pridopidine Outcome On Function in HD

A Phase 3 Global, Randomized, Double-Blind, Placebo-Controlled Study



Primary efficacy endpoint
Change from Baseline to week 65 in the UHDRS-Total Functional Capacity (TFC)

Safety
Incidence and severity of (S)AEs

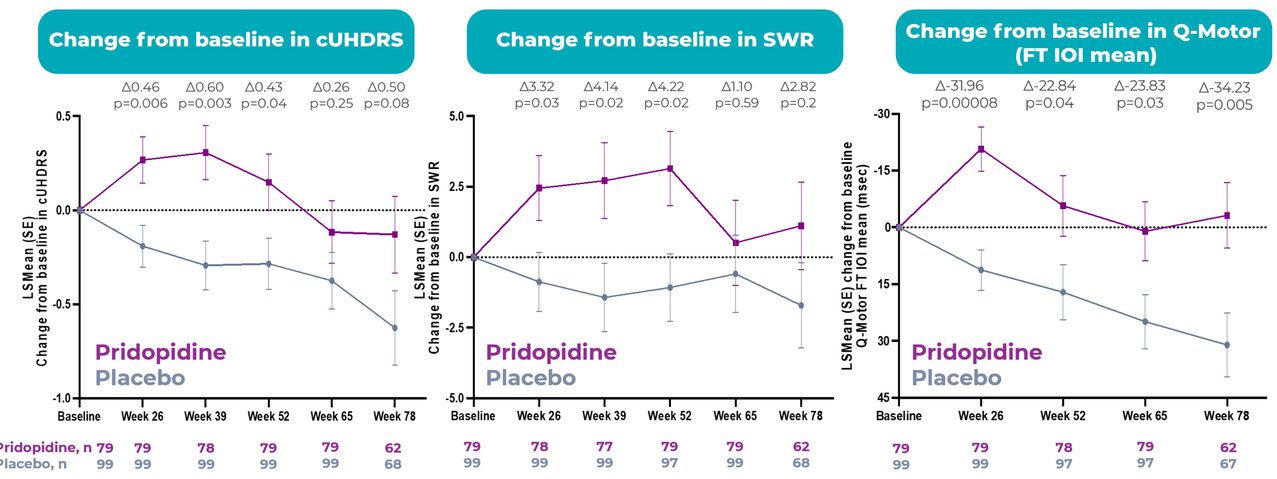
Secondary endpoints
Change from Baseline to week 65 in composite UHDRS
(cUHDRS: TFC, TMS, SDMT, SWR)

Prespecified analyses
Exclusion of participants on neuroleptics and chorea medications (ADMs)

- Groups were well balanced with regard to demographics and clinical characteristics
- Primary and secondary efficacy endpoints were not met in the full analysis set

TFC: Total Functional Capacity TMS: Total Motor Score, SDMT: Symbol Digit Modalities Test, SWR: Stroop Word Reading, cUHDRS: Composite Unified Huntington's Disease Rating Scale; ADMs: antidopaminergic medications; Reilmann R et al., Nat Med. 2025 Sep 5. Epub ahead of print.

PROOF-HD: pridopidine shows meaningful clinical benefit in cUHDRS, cognitive and motor scales in patients not taking ADMs



Per-protocol population; Nominal p-values; Feigin, A. (2025, Apr 6-9) AAN Annual Meeting, San Diego, CA, USA, American Academy of Neurology; cUHDRS : composite Unified Huntington's Disease Rating Scale, SWR: Stroop Word Reading, FT: finger tapping, IOI: inter-onset interval; Reilmann R, et al., Nat Med. 2025 Sep 5. Epub ahead of print.

OLE Analysis

- **Primary Efficacy population:**
  - Not taking ADMs during DBP and OLE
  - Subjects who completed 78 weeks of RCP
- **Endpoints:**

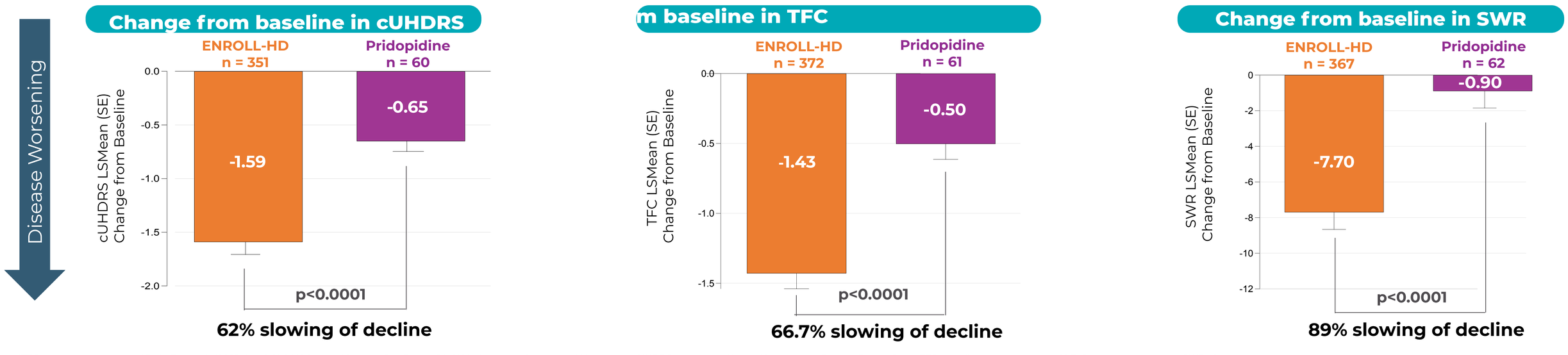
Persistence of effect in **cUHDRS, TFC & SWR** to week 104 (2 years, OLE wk 26)
- Pridopidine-to-pridopidine group
- Compared to propensity matched historical controls (**Enroll-HD** and **TRACK-HD**)

Persistence of effect in **Q-Motor** to week 104 (2 years, OLE wk 26)
- Compared to propensity matched historical control (**TRACK-HD**)

DBP: double-blind period, OLE: Open-label extension, FT-IOI: Finger tapping inter onset interval, SWR: Stroop word reading

Pridopidine has sustained and significant long-term benefit in progression (cUHDRS), function (TFC) and cognition (SWR) compared to natural history matched controls

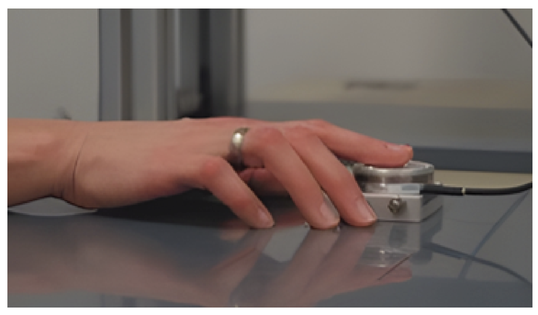
PROOF vs Enroll-HD (observational registry, Enroll-hd.org)



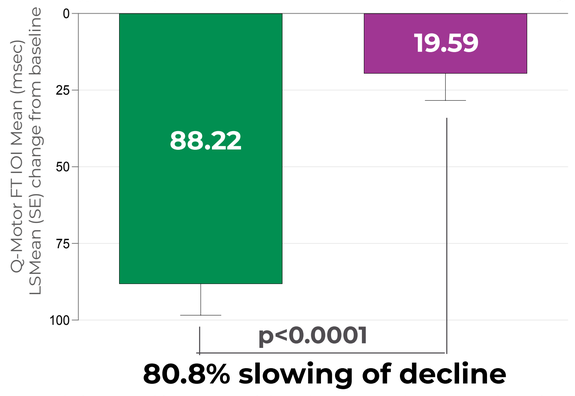
mITT Population, not taking ADMs; Feigin, A. (2025, Apr 6-9) AAN Annual Meeting, San Diego, CA, USA, American Academy of Neurology; cUHDRS: composite United Huntingtons Disease Rating Scale; TFC: total functional capacity; OLE: Open-label extension, SWR: Stroop word reading

Pridopidine has sustained and significant long-term benefit in fine motor function (Q-Motor finger tapping) compared to natural history matched controls

- Q-Motor has unique properties that overcome inherent challenges in categorical rating scales
- Q-Motor is objective, centrally read, displays a lack of inter and intra-rater variability, shows high reliability, minimal orn o placebo response & correlation with clinical and imaging outcome measures



PROOF vs TRACK-HD[1]
(prospective observational study)



mITT Population, not taking ADMs; Feigin, A. (2025, Apr 6-9) AAN Annual Meeting, San Diego, CA, USA, American Academy of Neurology;
OLE: Open-label extension FT: finger tapping; IOI: inter-onset-interval

[1] Tabrizi et al. Lancet Neurol. 2011 Jan;10(1):31-42)

Summary

PROOF-HD results show consistent and sustained beneficial effect in patients not taking ADMs

- Pridopidine did not meet primary or key secondary endpoints in all patients
- Pridopidine shows benefits in HD on clinical progression, cognition and motor, in patients not taking antidopaminergic medications (ADMs)
- Pridopidine shows long-term, sustained efficacy up to 2 years
  - Significant long-term benefit is confirmed compared to a matched cohort from Enroll-HD and TRACK-HD observational studies
- The safety and tolerability profile of pridopidine is comparable to placebo (data not shown)
- Pridopidine's Market Access Authorization (MAA) is currently under review by the European Medicines Agency (EMA)

FERRER & PRILENIA are partners in co-development and commercialization of pridopidine for Europe and other select markets*
* Middle East and North African Region, the Southern African Region, the Central and South American Region, and the Commonwealth of Independent States Region

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