The Impact of Antidopaminergic Medications on Assessment of Function, Cognition, and Motor Features on HD Outcomes

Andrés Cruz-Herranz[1], Andrew M Tan[1], Kelly Chen[1], Wei Feng[1], Randal Hand[1], Ferdinando Squitieri[2], Michal Geva[1] and Michael R Hayden[1,3]

[1] Prilenia Therapeutics B.V., Naarden, The Netherlands
[2] Huntington and Rare Diseases Unit at IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo and Fondazione LIRH, Rome, Italy.
[3] CMMT, University of British Columbia, Vancouver, Canada

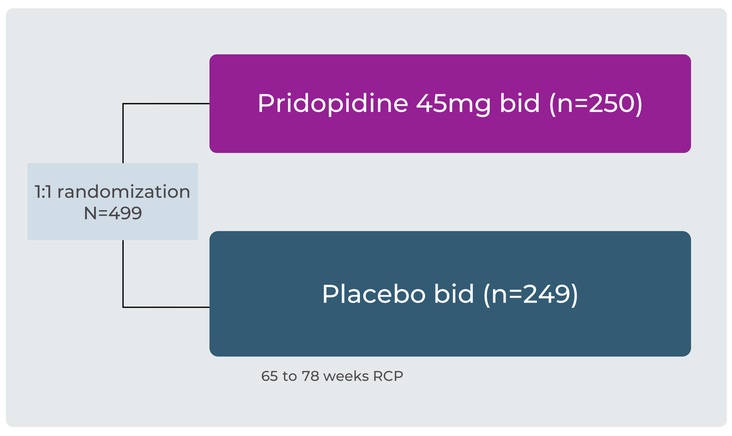
Pridopidine is an investigational therapy under development for Huntington's Disease, ALS, and other neurodegenerative diseases. It is currently not approved by any regulatory agency.
This presentation is for general information purposes only; it is not a substitute for professional medical advice.

Introduction

- Huntington's disease (HD) is a rare neurodegenerative disease, manifesting as a decline in cognitive, behavioral and motor functions
- Antidopaminergic medications (ADMs), VMAT2 inhibitors and antipsychotics, are commonly prescribed for HD patients[1,2]
  - VMAT2 inhibitors (e.g. tetrabenazine) are used to treat chorea, a key motor symptom
  - Antipsychotics are used to treat behavioral symptoms, and are often used off-label to treat motor symptoms
- Certain ADMs used to treat symptoms of HD can cause adverse effects that cannot be distinguished from disease progression[2,3]
  - Adverse effects impaired cognition, somnolence, mental state changes (eg. depression and suicidality, apathy, or emotional blunting), and extrapyramidal motor side effects (parkinsonism, dystonia, akathisia, and non-reversible tardive dyskinesia)[4,5]
- The Ph3 PROOF-HD trial evaluated the safety and efficacy of pridopidine in HD, and is the first double-blind, placebo-controlled study presenting data assessing the impact of ADMs on a placebo group
- Pridopidine is an orally-administered, investigational drug in clinical development for HD and ALS.
- It selectively binds and activates the sigma-1 receptor (S1R)
- S1R activation elicits neuroprotective effects in multiple preclinical models of neurodegenerative disease

(1) Dash & Mestre Neurotherapeutics. 2020 Oct; 17(4): 1645–1659; (2) Harris et al., J Neurol Neurosurg Psychiatry. 2020 Jun; 91(6): 622–630. (3) Tedroff et al., J Huntingtons Dis. 2015;4(2):131-40. (4) Geva et al., Mov disord. 2025 May;40(5):928-937 (5) Tan AM, et al. J Huntingtons Dis. 2025;14:16–29.

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)

PROOF HD

- 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.

Most frequently used ADMs in PROOF-HD

ADM	Drug Class	% of subjects on ADMs
Olanzapine	Antipsychotic	18%
Risperidone	Antipsychotic	18%
Deutetrabenazine	VMAT2i	13%
Tiapride	Antipsychotic	11%
Tetrabenazine	VMAT2i	9%
Aripiprazole	Antipsychotic	8%
Quetiapine	Antipsychotic	5%

Patients could be using >1 ADM; % are not cumulative

Scientific justification for ADM subpopulation selection

- Literature of HD & observational studies show that ADMs are associated with worse function, clinical progression and cognitive performance

Review article

Antidopaminergic medications in Huntington's disease

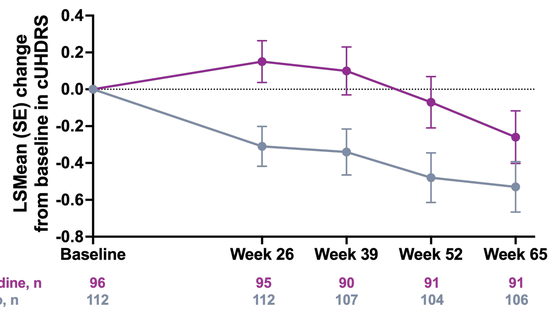
Andrew M Tan [1,2], Michal Geva [1], Y Paul Goldberg [1], Henk Schuring [1], Bernd-Jan Sanson [1], Anne Rosser [3,4,5], Lynn Raymond [6], Ralf Reilmann [7,8], Michael R Hayden [1,3], and Karen Anderson [9]

- PROOF-HD allowed for the use of ADMs as this is regarded standard of care

ADM: antidopaminergic medication; Geva et al., Mov Disord. 2025 May; 40(5):928-937

PROOF-HD: pridopidine shows clinically meaningful benefits in cUHDRS; slowing decline vs placebo in predefined subgroup of patients not taking ADMs

Treatment Difference Pridopidine vs Placebo in cUHDRS				
LSMean Diff	Δ 0.46	Δ 0.45	Δ 0.41	Δ 0.27
p-value	0.004	0.014	0.035	ns



*"We have reached consensus **that a slowing of clinical decline ≈ 0.2–0.3 points per year) equivalent to 2.4 to 3.5 mo/y of time saved from progression** can be used to **define a clinically efficacious treatment**."*

Schobel et al, 2017 American Academy of Neurology: 89:2495–2502

mITT population; Reilmann R, et al., Nat Med. 2025 Sep 5. Epub ahead of print.; ADMs: antidopaminergic medications; cUHDRS: composite Unified Huntington's Disease Rating Scale

Methods

- Participants from the placebo arm of the PROOF-HD (NCT04556656) trial either taking (n=133) or not taking ADMs (n=112) were compared across HD outcome measures.
- Mixed-effects modeling adjusted for baseline characteristics (age, sex, CAG repeat length, disease stage, and TFC), with sensitivity analyses accounting for missing data and stratification by ADM class (VMAT2 inhibitors vs. antipsychotics).

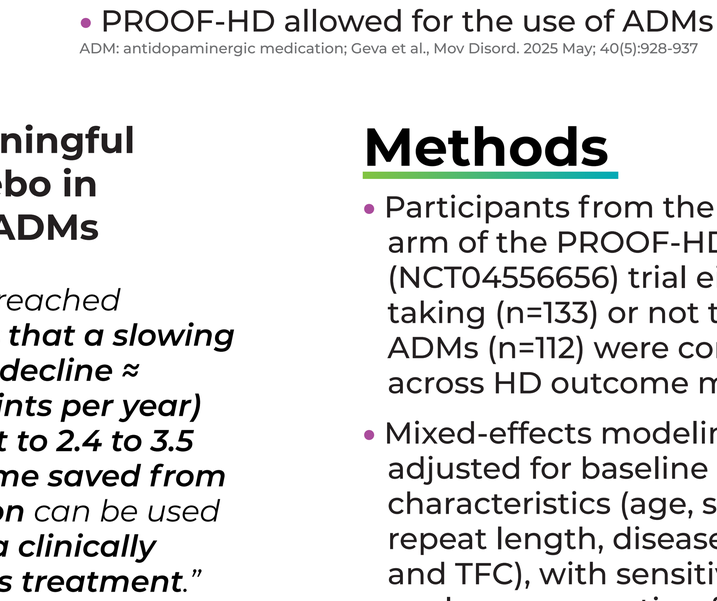
Outcome Measures

1. Composite Unified Huntington's Disease Rating Scale (cUHDRS)
   - Note: cUHDRS is a weighted combination of TFC, SDMT, SWR, and TMS (with TMS scores negatively weighted)
2. Total Functional Capacity (TFC)
3. Total Motor Score (TMS)
4. Symbol Digit Modalities Test (SDMT)
5. Stroop Word Reading (SWR)

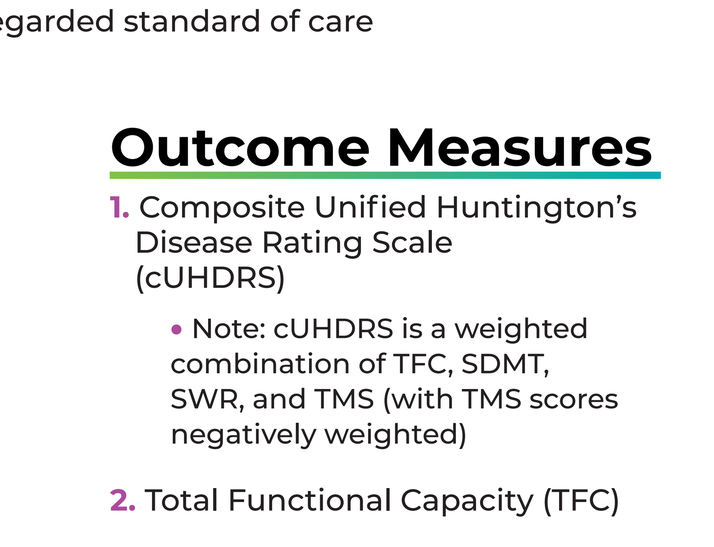
PROOF-HD: placebo subjects taking ADMs show significant faster progression in function, cognition & motor outcomes vs patients not taking ADMs

Progression (cUHDRS)

Function (TFC)



Motor (TMS)



Cognition (SWR)

Cognition (SDMT)

mITT population; **TMS:** higher scores indicate worsening; mITT population. Number of patients at baseline – on ADM: 133, off ADM: 112; Feigin, A. (2025, Apr 6-9) AAN Annual Meeting, San Diego, CA, USA, American Academy of Neurology; cUHDRS, TFC, SWR, SDMT: lower scores are worse; TMS: higher scores are worse

Summary

- Participants taking ADMs show greater declines across all measures of HD progression compared with participants not taking ADMs
- These findings underscore the impact of ADMs on HD outcomes, and highlight the need for careful consideration in patient care and clinical trial design
- Future HD trials should account for ADM use to ensure accurate assessment of disease progression and treatment efficacy

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

For more information, please contact: medinfo@ferrer.com and medinfo@prilenia.com

NP-EMEA-057-06/2025