The PROOF-HD Phase 3 Study: PRidopidine's Outcome On Function in Huntington Disease

Ralf Reilmann[1], Anne Rosser[2], Sandra Kostyk[3], Michal Geva[4], Andrew McGarry[5], Yael Cohen[4], Noga Gershoni-Emek[4], Munish Mehra[4,6], C. Warren Olanow[5], Karl Kieburtz[5], Michael R. Hayden[4,7] and Andrew S. Feigin[8]

1 George-Huntington-Institut, Muenster, Germany
2 Cardiff University, Wales, UK
3 Ohio State University, Columbus, Ohio
4 Prilenia Therapeutics
5 Clintrex LLC, Sarasota, FL, USA
6 Tigermed, Gaithersburg, MD, USA
7 CMMT, University of British Columbia, Canada
8 NYU Langone Health, Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, NY, USA

Background

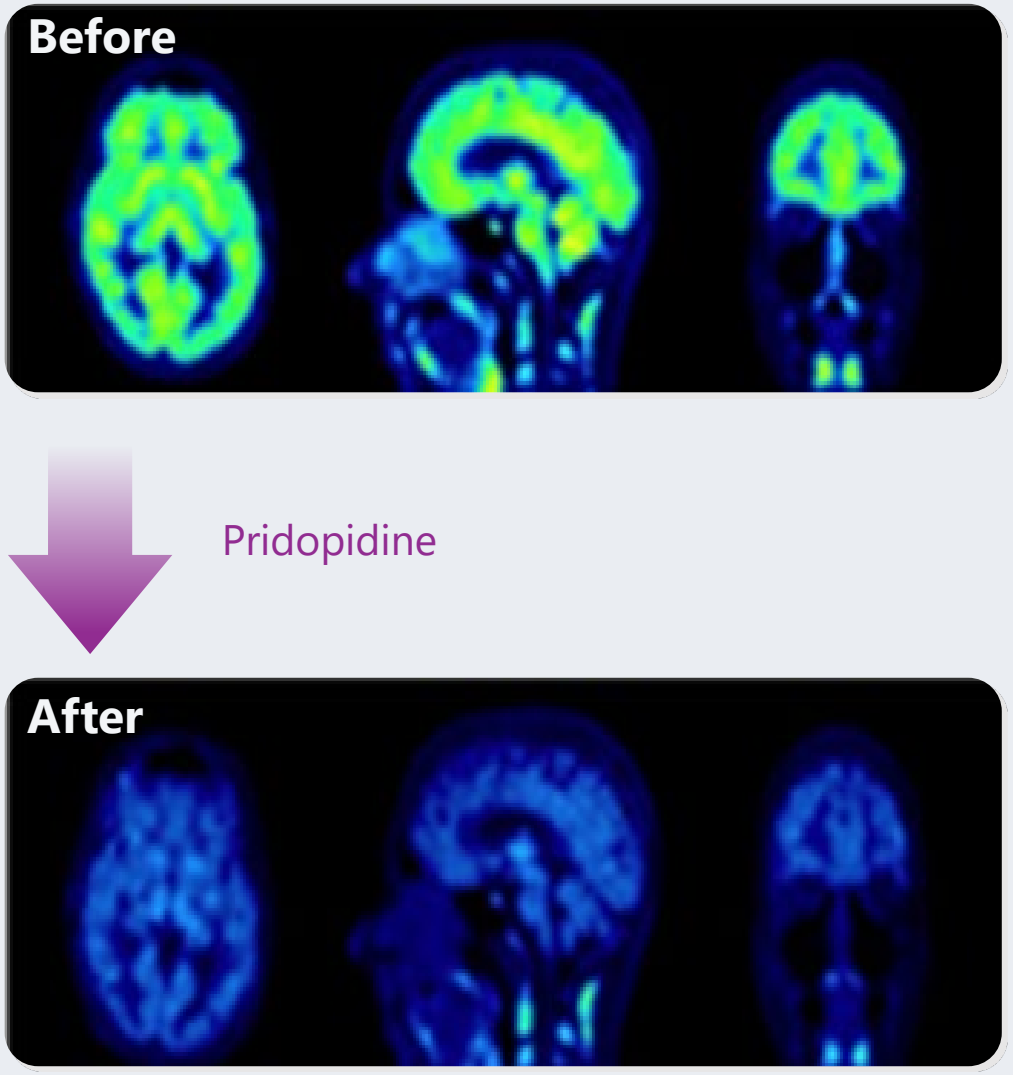
- Pridopidine is a **highly selective and potent Sigma-1 receptor (S1R) agonist.**
- The S1R is located at the ER-mitochondria interface, where it regulates diverse cellular pathways impaired in HD, including Ca^{2+} signaling, the ER stress response and mitochondrial function.
- **Human PET imaging** shows pridopidine 45 mg bid (the dose in **PROOF-HD**) has **selective and robust S1R occupancy (>90%).**
- **Long-term safety data** show pridopidine 45 mg bid is safe and tolerable, with an AE profile similar to placebo.
- To date, no therapeutic agent in HD has yet been shown to provide benefit on total functional capacity (TFC).
- In the PRIDE-HD phase 2 trial **pridopidine 45 mg bid** showed **maintenance of TFC in all HD patients at week 52 (pre-specified endpoint, p=0.0032).**
- Post-hoc analysis shows this effect is most pronounced and driven by **early-stage HD participants (nominal p=0.0003).**
- **This effect remained significant using the conservative multiple imputation with missing not at random analysis** (MNAR) (nominal p=0.016).
- Pridopidine maintenance of TFC is associated with stabilization of NfL at 52 weeks (see Prilenia's NfL poster)
- **Pridopidine 45 mg bid demonstrates improvement in Q-Motor speeded finger tapping inter-onset interval (IOI), inter-tap interval (ITI) and inter-peak interval (IPI)** at weeks 26 and 52.

Pridopidine: Confirmed in-vivo human target engagement of the S1R at therapeutic dose

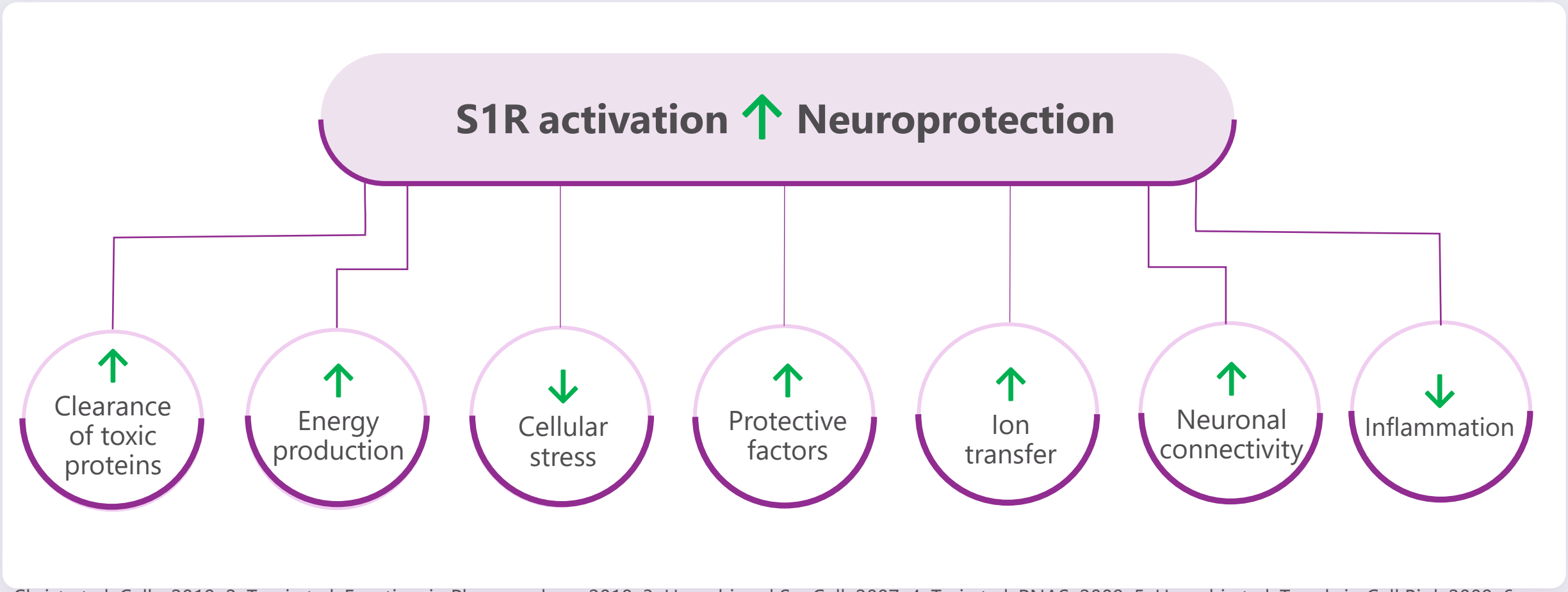
- Human PET study assessed pridopidine target occupancy at S1R
- **Complete occupancy of S1R confirmed** after 90 mg single dose of Pridopidine (correlates to 45 mg BID at steady state)
- **No occupancy of D2/D3 receptors** using dopamine ligand fallypride

Source: Grachev et al, EJNMM, 2020

18F-Fluspidine
S1R occupancy

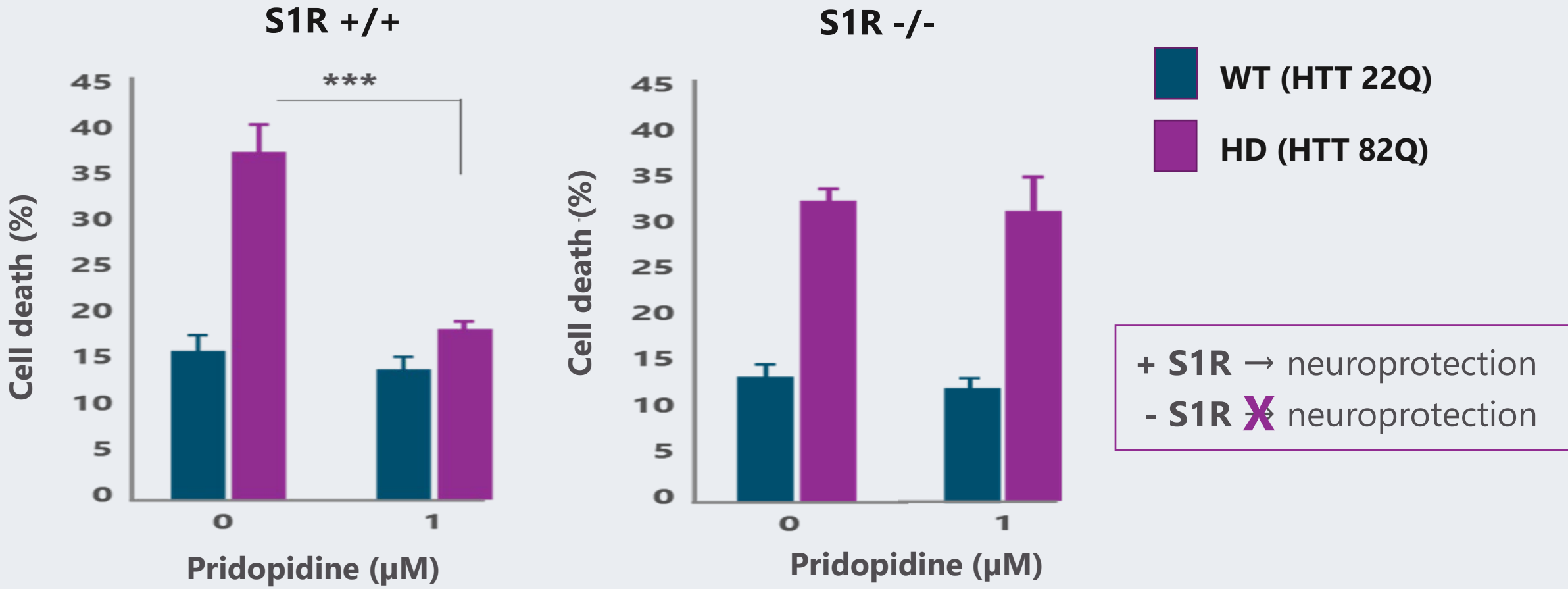


Pridopidine activation of the S1R in HD positively influences multiple pathways that lead to neuroprotection



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

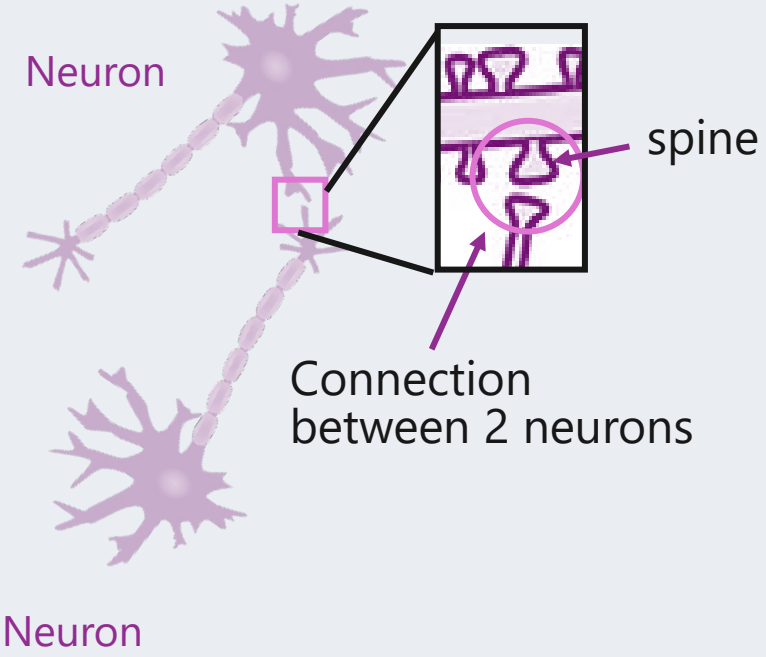
Pridopidine is neuroprotective in HD neurons, Effects not seen in the absence of S1R



Mouse striatal neurons; *** p < .001, ANOVA with Bonferroni post-hoc test

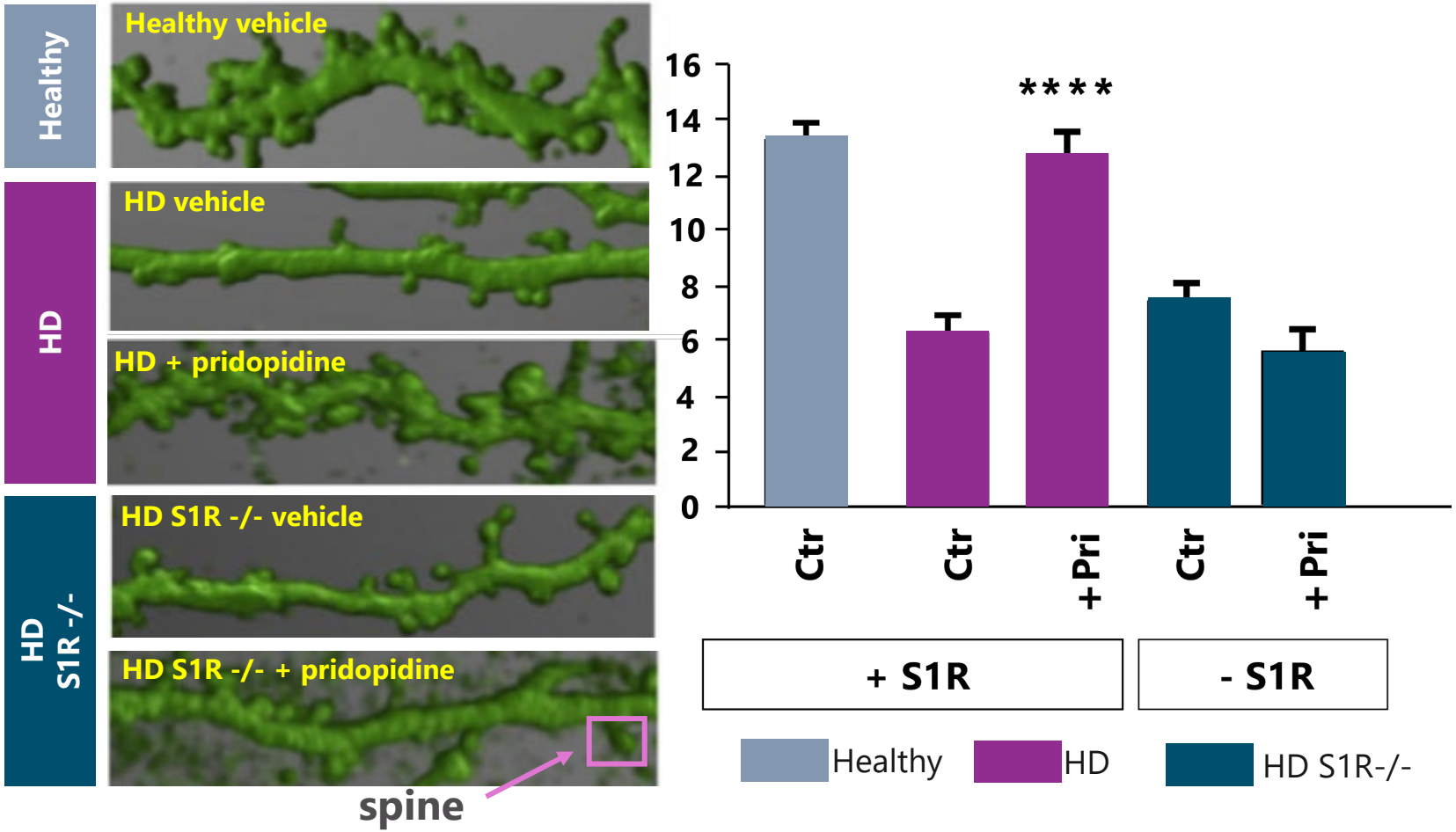
Eddings et al, Neurobiology of Disease; 2019

Pridopidine increases neuronal connectivity in HD neurons
Effects not seen in the absence of S1R (S1R-/-)



Spines connect between two neurons

Pridopidine ↑ neuronal connectivity in HD neurons



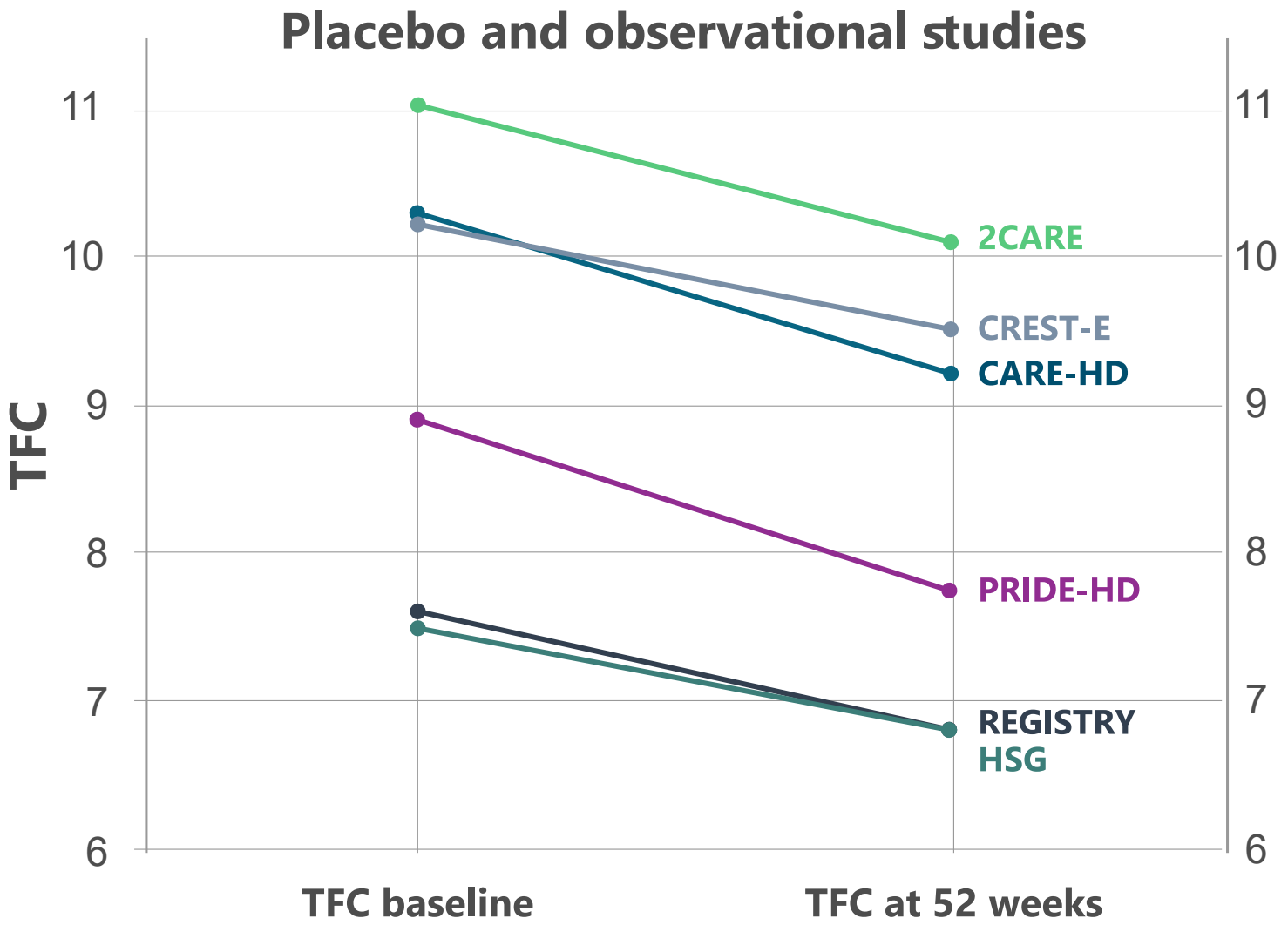
Striatal neurons from YAC128 HD mice, Pridopidine 100 nM,

Ryskamp et al., Neurobiology of Disease 2017

TFC shows a stable decline in early HD in placebo & observational studies

- **No placebo response**
- **TFC showed predictable decline in all studies**

Annual TFC decline of ~0.8-1 point/year in early HD patients (TFC 7-13) [1]

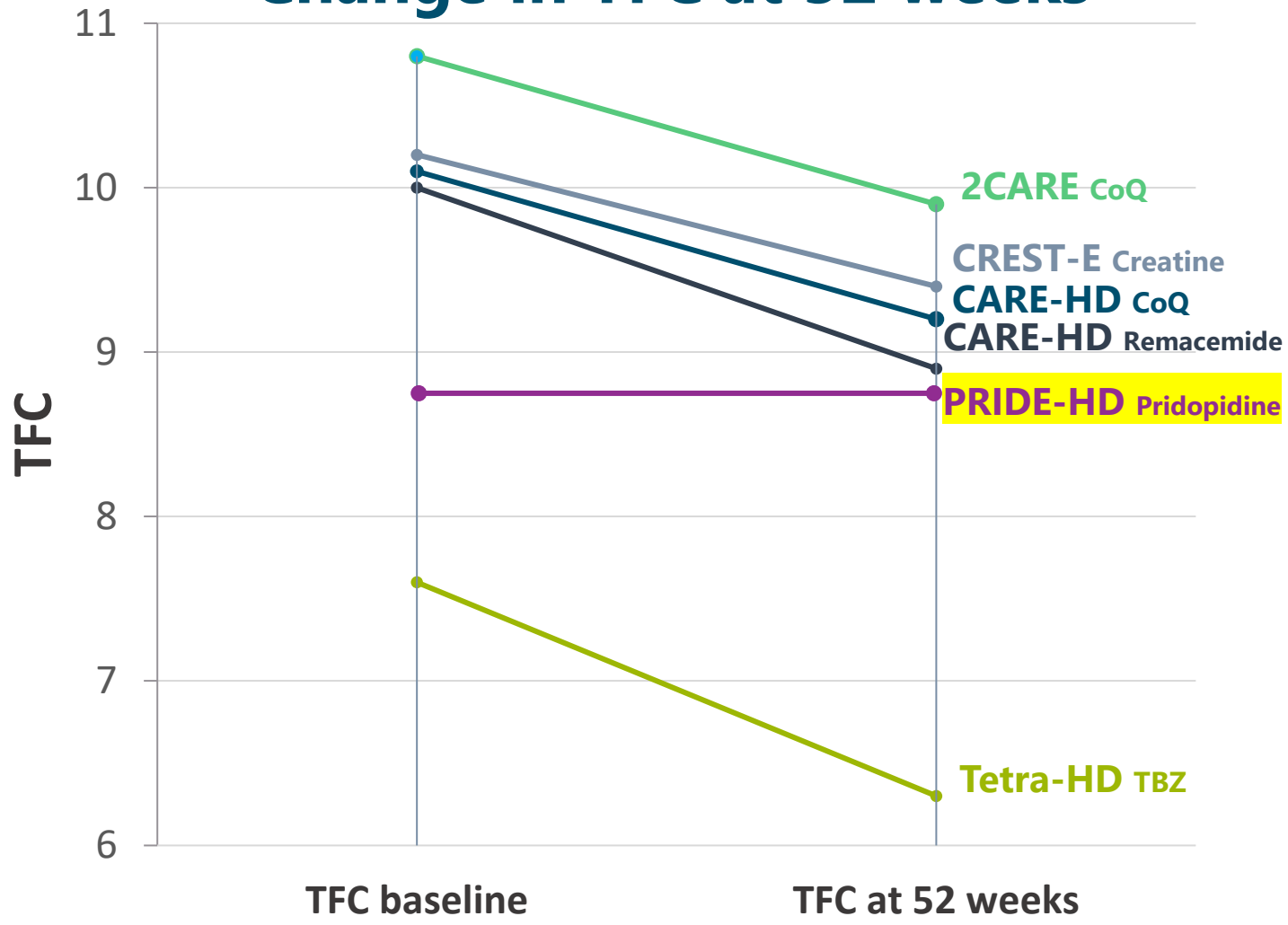


(1) Marder et al., Neurology 2000

Source: Waters et al., J. Huntington Dis 2018

Pridopidine has shown maintenance of Total Functional Capacity (TFC) in HD

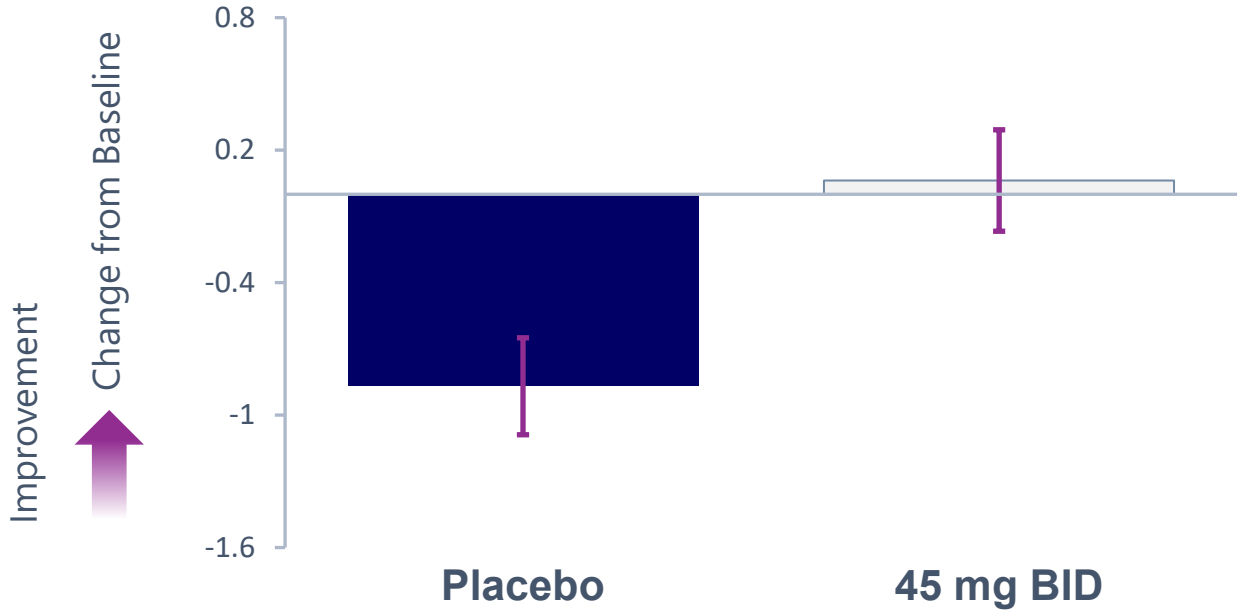
Change in TFC at 52 weeks



-- Source: Waters et al., J. Huntington Dis 2018.

PRIDE-HD: Pridopidine Maintains Functional Capacity (TFC) at 52 Weeks in HD all Patients, a pre-specified endpoint

ALL HD patients



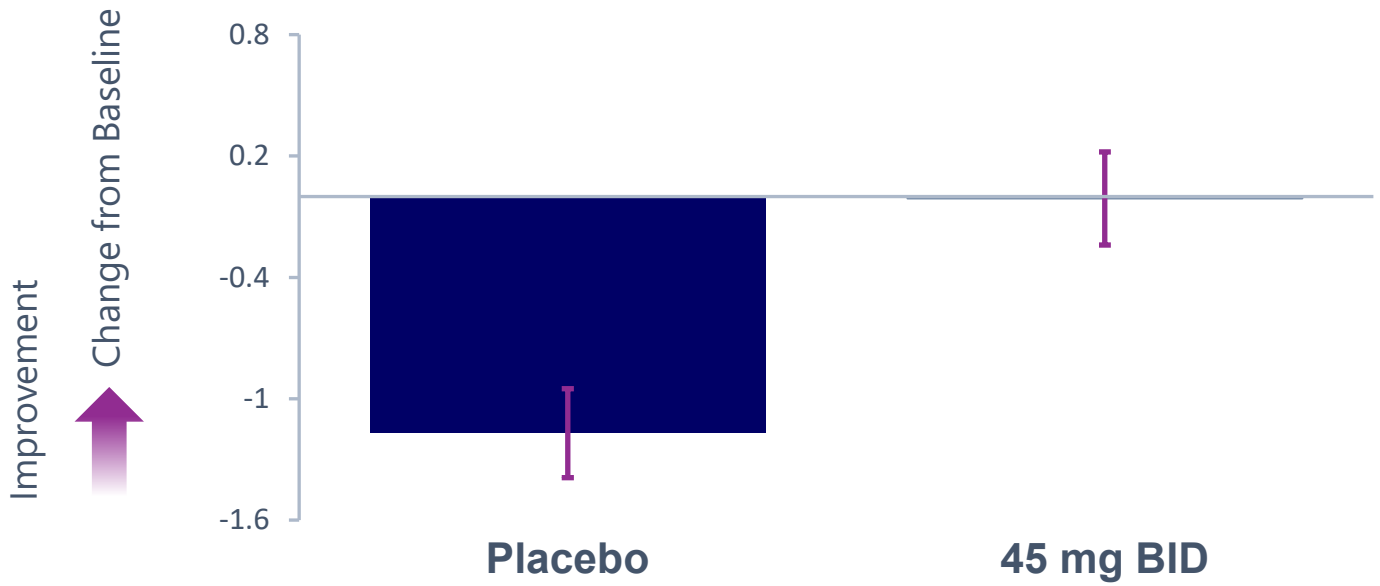
	Placebo	45 mg BID
N	81	75
Wk52 Δ from baseline	-0.83	0.04
Wk52 Δ to placebo		0.87
p value		**0.0032**

McGarry et al, JHD 2020
Analysis of correction for multiplicity confirms significance

Post hoc analysis shows that the effect of pridopidine on TFC at 52 weeks is driven by early HD Patients

The TFC Finding at Week 52 was Most Prominent in Early HD Patients

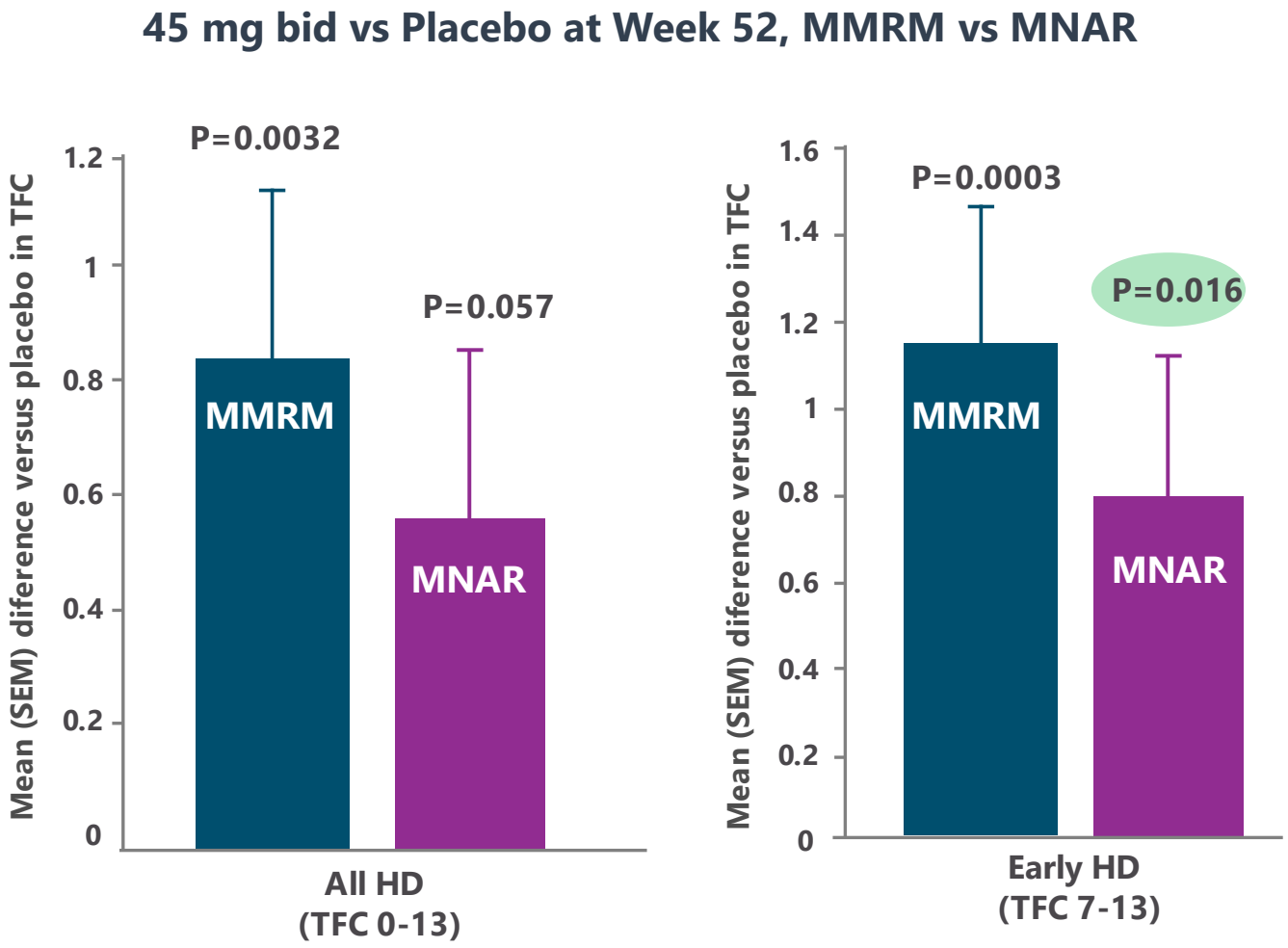
(BL TFC ≥7)



	Placebo	45 mg BID
N	62	59
Wk52 Δ from baseline	-1.17	-0.01
Wk52 Δ to placebo		1.16
p value		**0.0003**

McGarry et al, JHD 2020
Analysis of correction for multiplicity confirms significance

Effect on TFC remains significant using conservative MNAR analysis in early HD



MMRM (missing data at random)

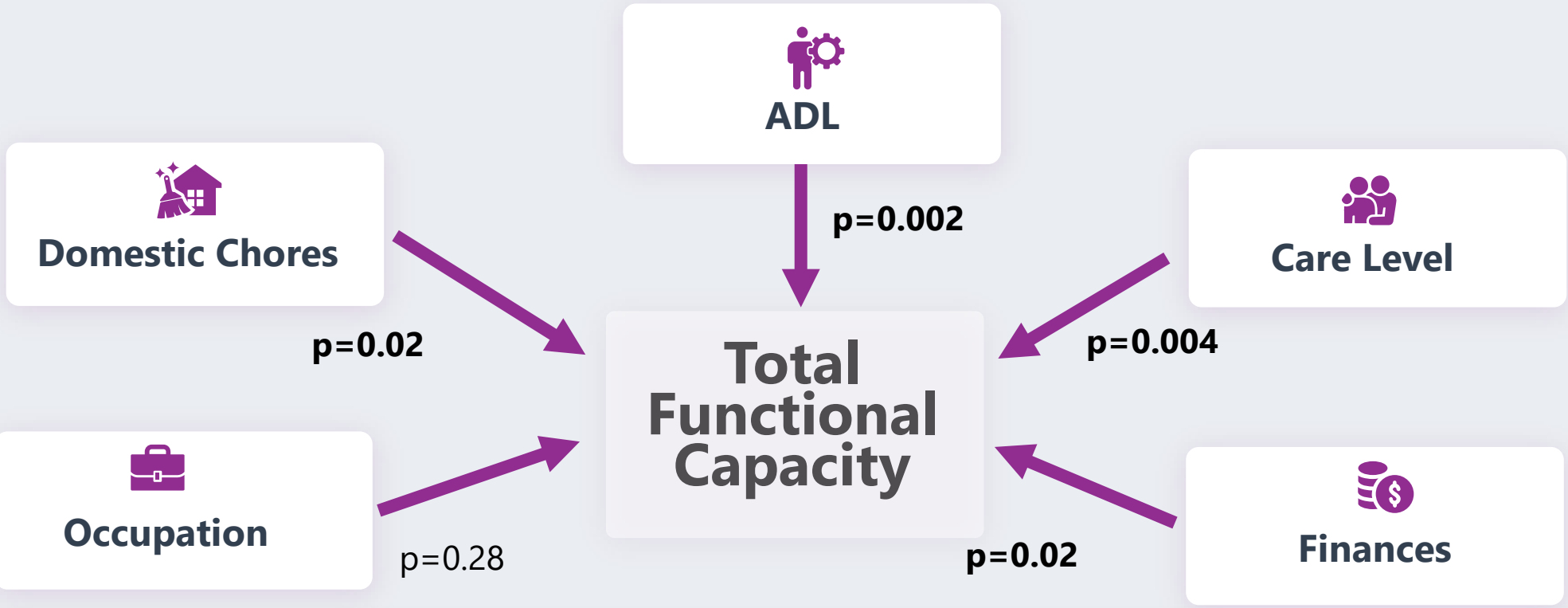
- Favored by the FDA
- Assumes dropouts behave similarly to other patients in the same treatment group.

MNAR (missing NOT at random, worst case scenario)

- Favored by the EMA
- Assumes all missing data in the active treatment group follow the trajectory of placebo.

MNAR analysis strongly supports the observed effect on TFC

All TFC Domains Numerically Contributed to the Overall TFC Finding in early HD patients



Capacity to undertake domestic chores, activities of daily living, care level, and the capacity to manage finances were major contributors

Composite Unified Huntington's Disease Rating scale (cUHDRS)

Higher score indicates overall less impairment

Total Functional Capacity (TFC)

Occupation	Finances	Domestic Chores	ADL	Care Level
0 = Unable 1 = Marginal work only 2 = Reduced capacity 3 = Normal	0 = Unable 1 = Major assistance 2 = Slight assistance 3 = Normal	0 = Unable 1 = Impaired 2 = Normal	0 = Total care 1 = Gross tasks only 2 = minimal impairment 3 = Normal	0 = Full time skilled nursing 1 = Home or chronic care 2 = Home

Total Motor Score (TMS)

124 Point scale

31 Items rating movement

Each item rated **0-4 points**

Cognition (thinking, memory processing information)

Symbol Digit Modalities Test (SDMT)

Stroop Word Reading Test (SWRT)

Pride-HD: 45 mg bid improves cUHDRS vs placebo in early HD patients at week 52

Change in cUHDRS at week 52, Pridopidine 45 mg bid vs. placebo

	Placebo Δ from baseline	45 mg bid Δ from baseline	Δ 45 mg bid vs. placebo	P-value
Early HD	-0.67	-0.07	0.6	0.04

cUHDRS score is derived from TFC, TMS and SDMT (Stroop Word Reading was not measured in PRIDE-HD)

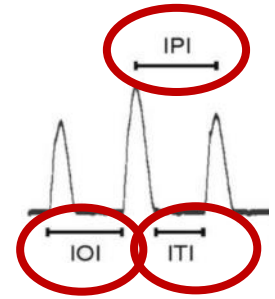
Positive change indicates improvement

Q-Motor, an objective and sensitive motor assessment for HD

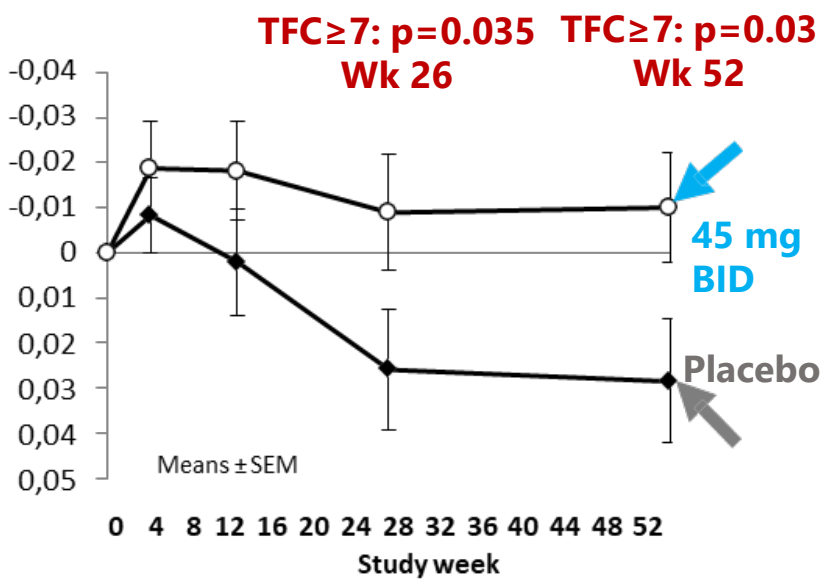
- **Q-Motor is a promising motor-assessment tool for HD patients**
  - **Highly correlates with TFC**
  - Used in >10 HD clinical trials
  - Placebo independent, objective, non-invasive, and sensitive measure
  - Centrally read; provides a standardized measurement of motor function across all sites → avoids bias introduced by raters
- **In a multicenter clinical trial in HD, Q-Motor measures were more sensitive than TMS and exhibited no placebo effects** (Reilmann and Schubert, Handb Clin Neurol, 2017;144:209-225).

Q-Motor – PRIDE-HD

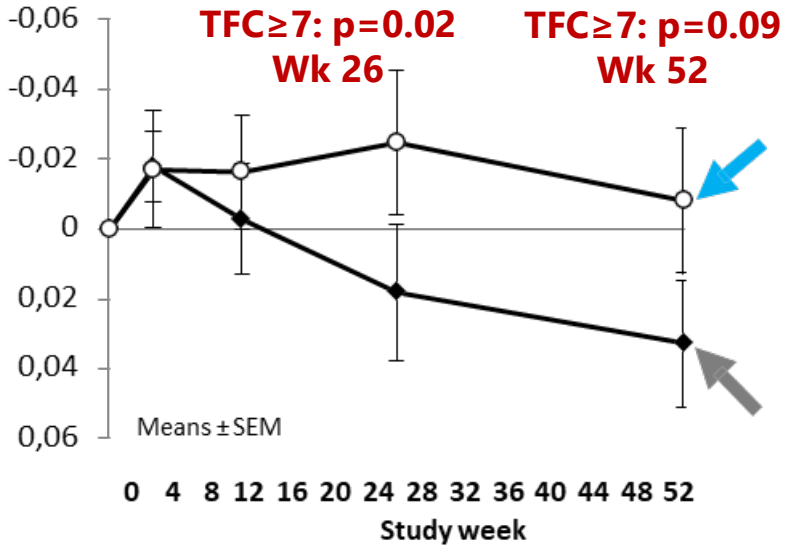
Speeded Finger Tapping
Early HD patients (TFC 7-13)



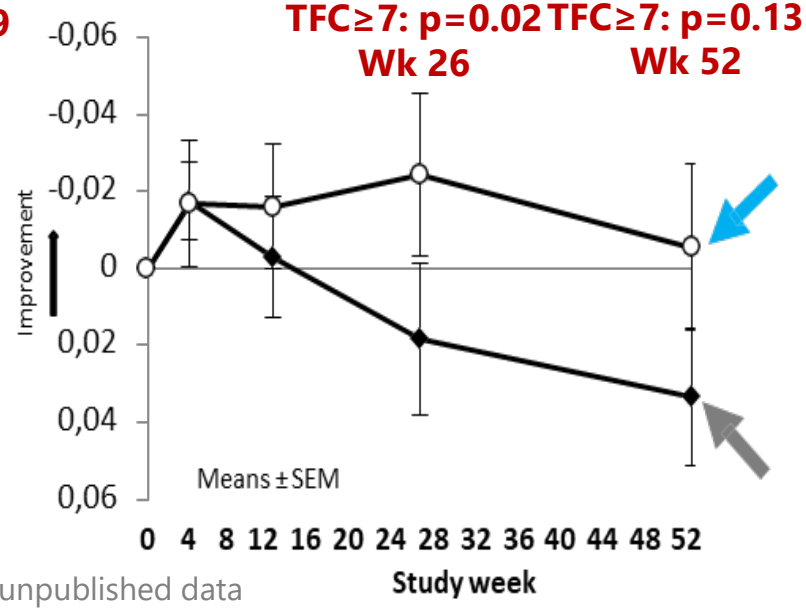
ITI – Inter-Tap-Interval-Mean (sec)



IPI – Inter-Peak-Int.-Mean (sec)



IOI – Onset-Interval-Mean(sec)

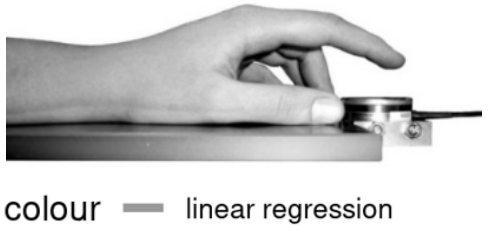


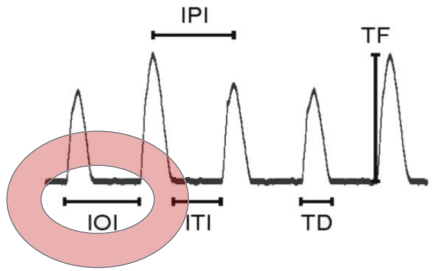
Reilmann et al., unpublished data

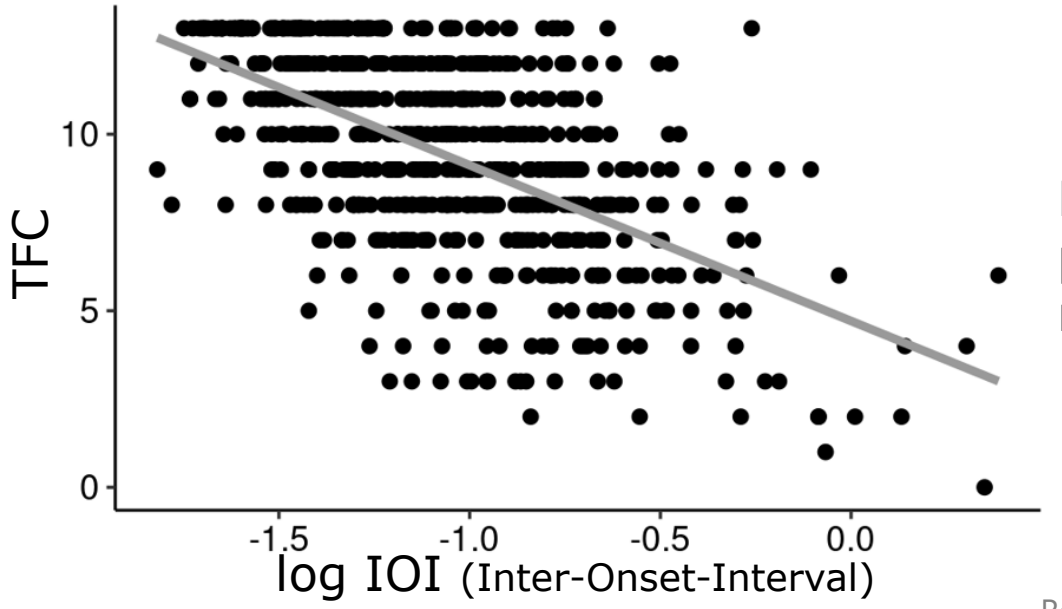
- **POC for motor improvement in HD**
- **TMS results not significant due to prolonged placebo response**

Q-Motor – PRIDE-HD

Clinical validity – relationship between Q-motor and TFC







R=0.551
p≤0.0000001
n=671

Reilmann et al., unpublished data

- TFC & Q-Motor IOI highly correlated
- Link of Q-Motor measures to function

Pridopidine has an extensive long-term safety and tolerability profile

Extensive clinical experience

>1300 subjects in total of ~1300 patient years

45mg BID exposure

>1000 patient years in 981 patients

Safe and tolerable

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

PROOF HD assesses the effect of pridopidine on TFC

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

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

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

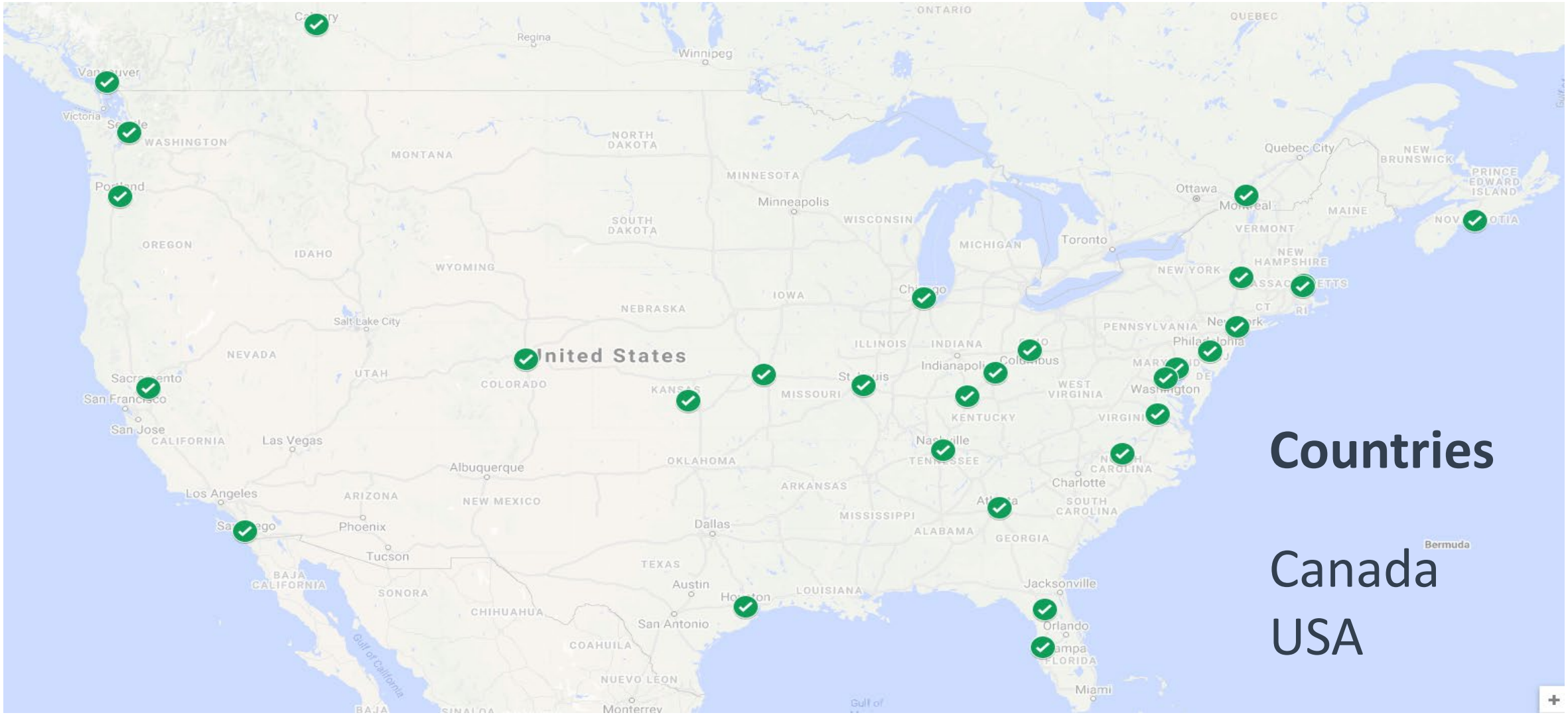
Patients who complete the double-blind study can enroll into the open label study and receive pridopidine (no one will receive placebo)

All 30 PROOF HD sites in EU activated

Countries

Austria
Czech Republic
Germany
France
Italy
Netherlands
Poland
Spain
United Kingdom

All 30 North American PROOFHD sites are activated



PROOF HD Status as of August 22, 2021

- **570** patients screened or reserved for screening
- **341** Patients randomized

  71% of the total
- Low screen failure rate (**14%)**
- No dropouts **(0%)**

  Drug is highly tolerable and safe

Currently on target to complete enrollment of 480 subjects earlier than expected, in October 2021

* **PR**idopidine **O**utcome **O**n **F**unction in **HD**