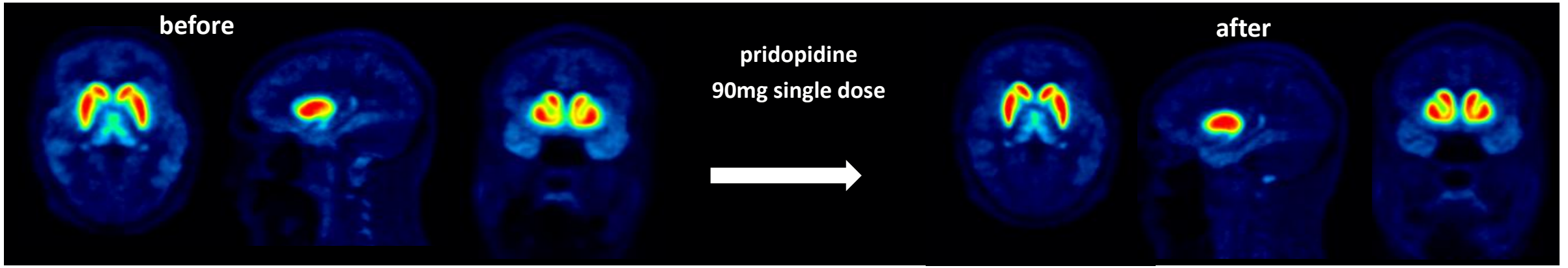
PRidopidine Outcome On Function in Huntington Disease **(PROOF-HD)**

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Arm, Multicenter Study Evaluating the Efficacy and Safety of Pridopidine in Patients with Early Stage of Huntington Disease

Human PET studies with **Fallypride (D2/D3 ligand) show no in-vivo occupancy** at prior used clinical doses (45 mg bid)

18F-Fallypride
D2/D3R occupancy



- Previously believed to be dopamine modulator with potential effect on motor symptoms
- Human PET study assessed pridopidine target occupancy at D2/D3 receptors
- Fallypride is a high affinity D2/D3 receptor antagonist
- Negligible (~3%) occupancy of D2/D3R after 90mg single dose of Pridopidine (correlates to 45 mg BID at steady state)

Grachev et al; EJNMMI 2020

Pridopidine recently shown to be a potent selective S1R agonist

- **Recently elucidated MoA** pridopidine targets the sigma-1 receptor vs. D2/D3 receptors
- This insight provides a **new development pathway** in neuroprotection across a variety of CNS indications

Pridopidine is a selective, high affinity S1R ligand with low binding affinities to other CNS receptors:

Target	Binding Ki (μM)	Fold selectivity for S1R
Sigma-1 (σ1R)	**0.057**	**1**
Adrenergic α2C	1.58	28
Dopamine D3	1.63	28.5
Serotonin 5-HT1A	3.63	64
Sigma-2 (σ2R)	5.45	96
Serotonin 5-HT2A	7.00	123
Serotonin 5-HT7	8.51	149
Adrenergic α2A	11.0	193
Histamine H3	18.3	321
Muscarinic M2	24.4	428
Dopamine D2	29.5	517.5

Selective S1R binding at low dose, 45 mg BID

High Doses ≥ 100 mg bid

18F-Fallypride -D2/D3R occupancy

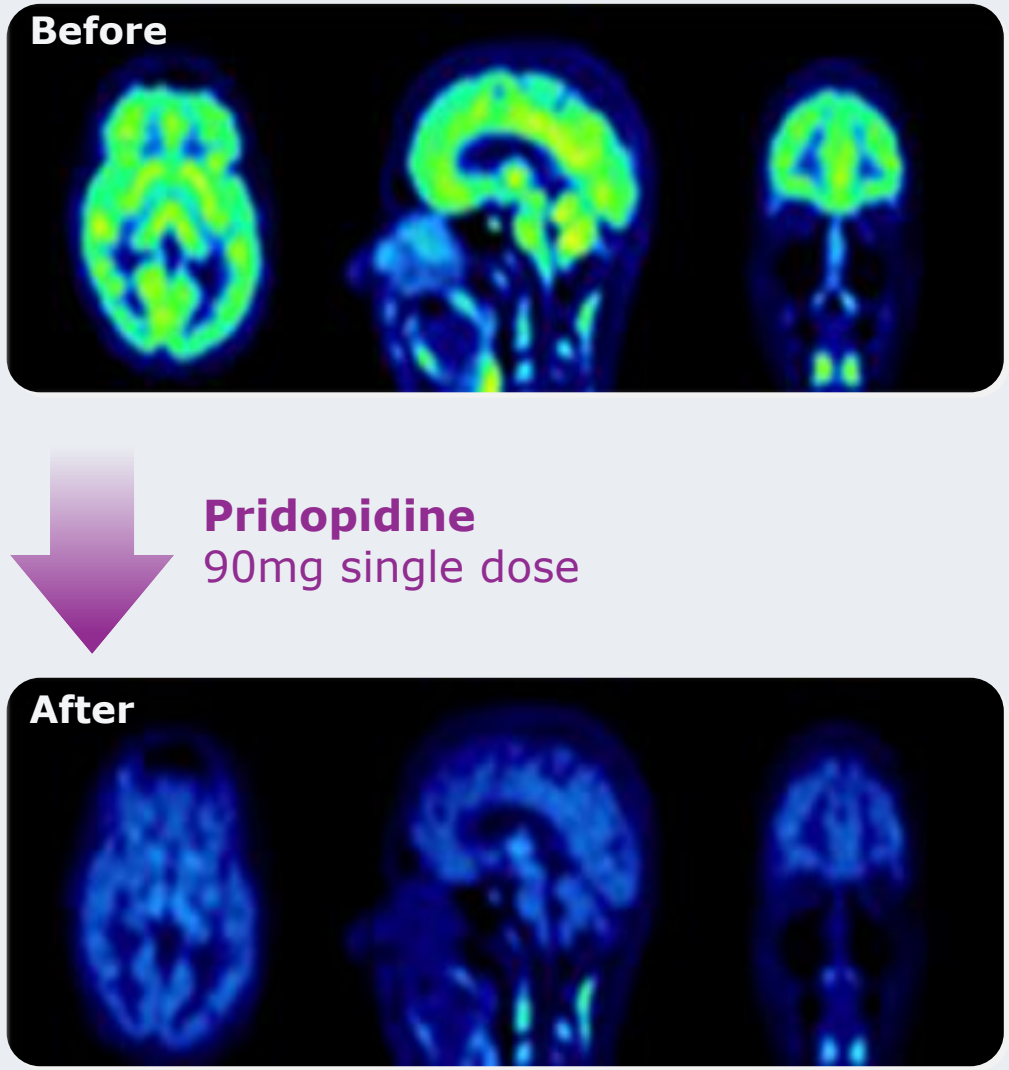
-- Source: Johnston et al, MDS, 2019.

Full S1R Occupancy Confirmed in Human PET Studies

- Human PET study assessed pridopidine target occupancy at S1R
- Complete occupancy of S1R after 90mg single dose of Pridopidine (correlates to 45 mg BID at steady state)

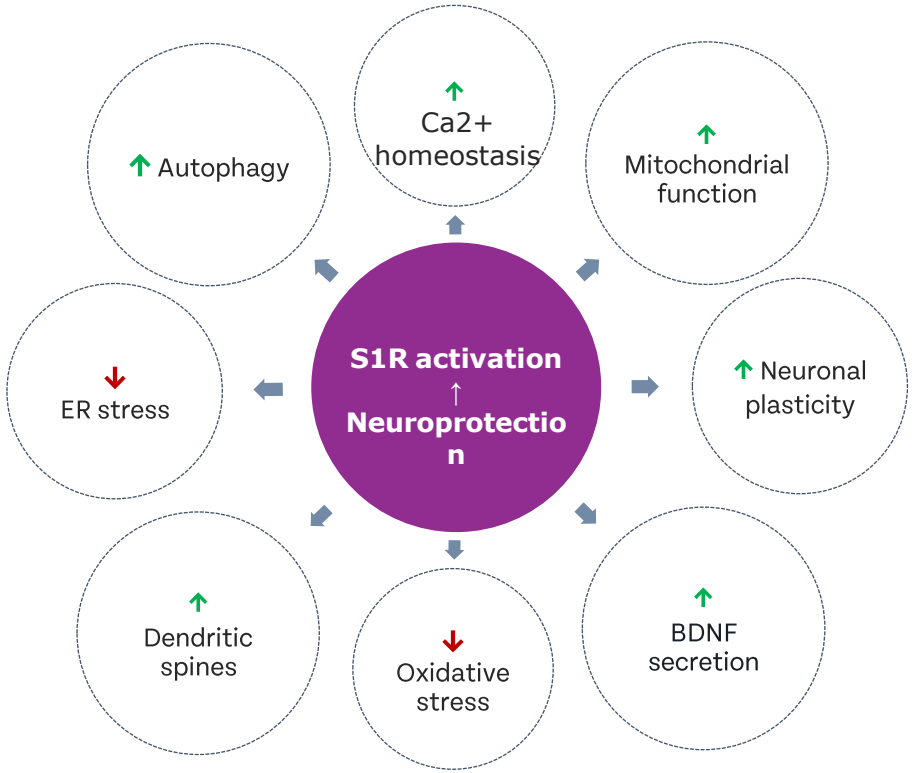
Grachev et al; EJNMMI 2020

18F-Fluspidine
S1R occupancy



S1R influences multiple pathways and is highly expressed in the CNS

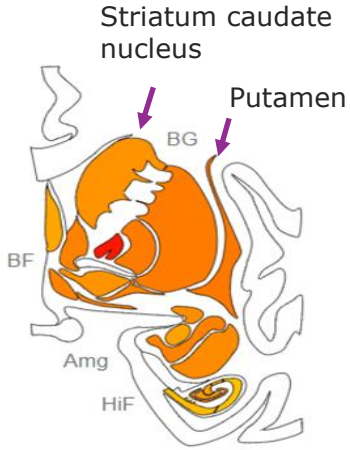
S1R Activation has Multiple Positive Downstream Effect



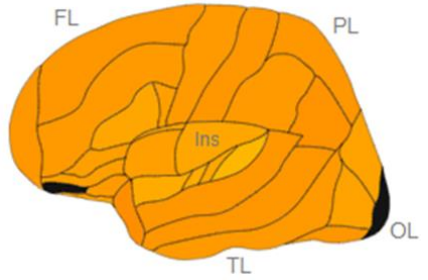
Distribution of S1R in the Human Brain

High expression of S1R mRNA:

Basal Ganglia



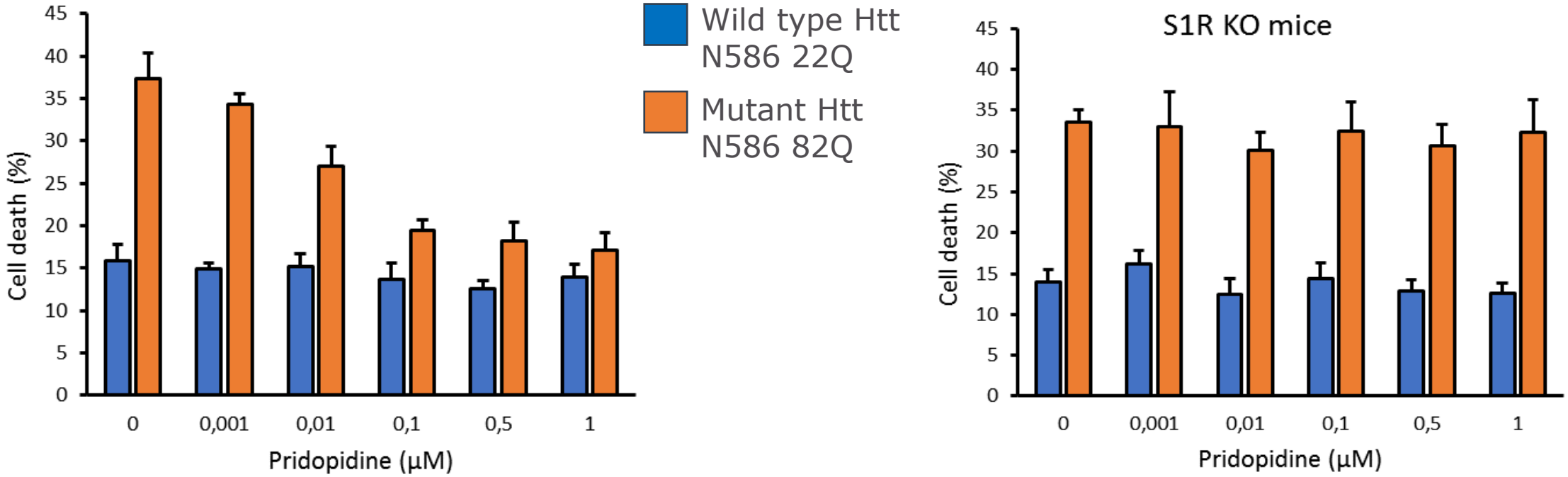
Cortex



low high

Source: Allen Brain Atlas Data Portal; https://human.brain-map.org/microarray/gene/show/10134.

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



+ S1R → neuroprotection

- S1R ~~→~~ X neuroprotection

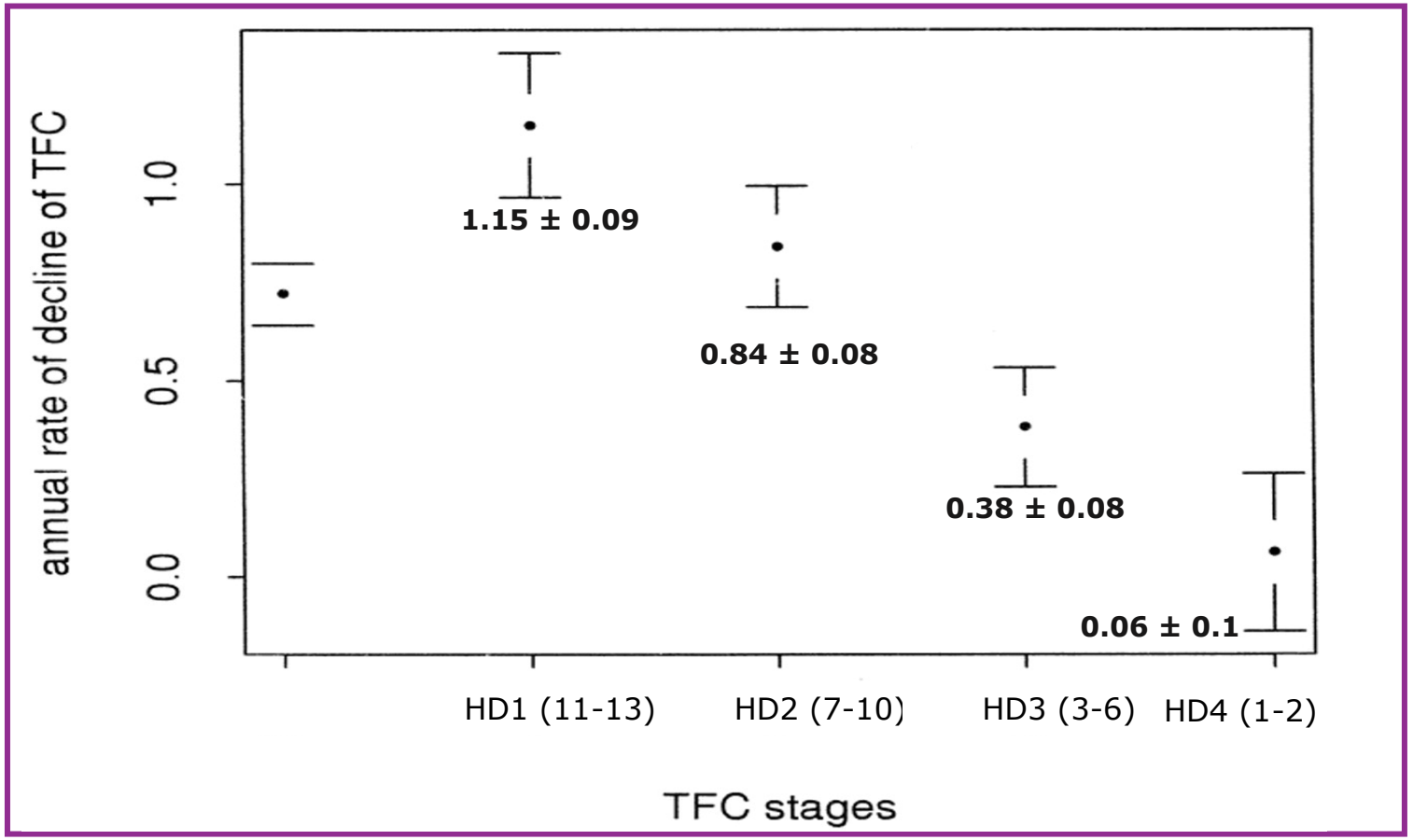
- ED50 20-50nM

Chris Ross lab
Eddings et al, Neurobiology of Disease 2019

Extensive safety and tolerability profile

- Extensive clinical experience **>1300 subjects** in total of **~1300 patient years**
- The majority of this is in Huntington Disease (HD)
- Doses ranging from mg 10 BID to 112.5 mg BID
- **Safe and tolerable**
- **45mg bid dose**
  - Exposure >1000 years in 981 patients
  - **Placebo-like AE profile**

~ 1-point decline per year in early stage HD



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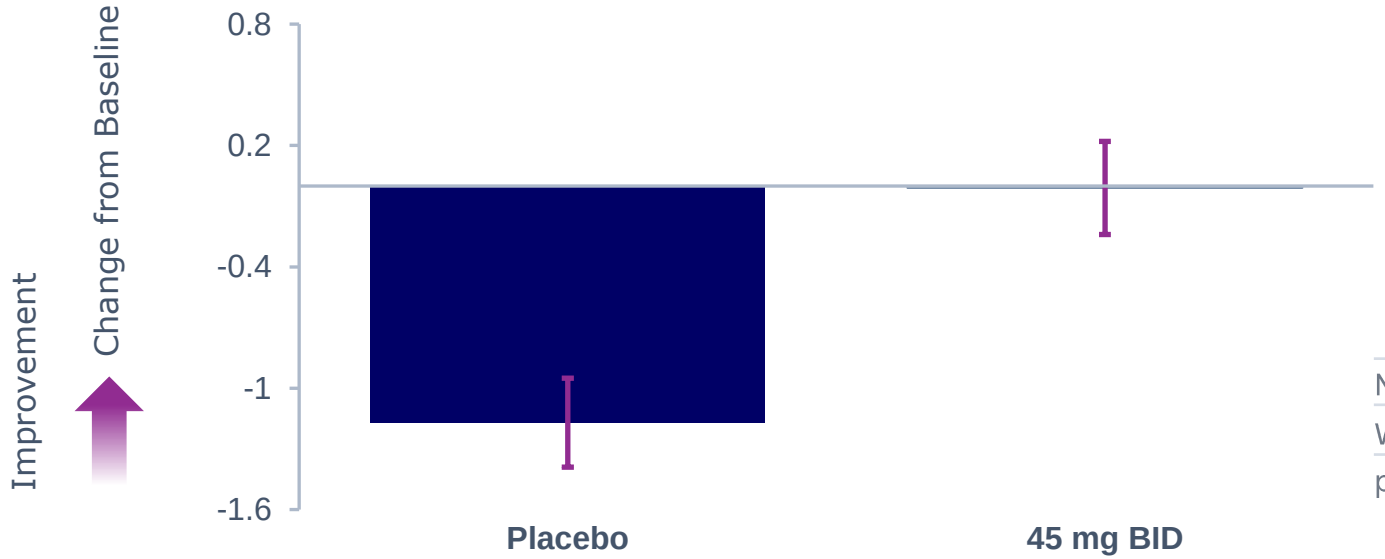
Values are Mean ± SE
All rates of decline were significantly different from one another $p<0.05$

Source: K. Marder et al. Neurology 2000;54:452

Pridopidine Maintains Functional Capacity (TFC) at 52 Weeks in HD Patients: PRIDE-HD

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

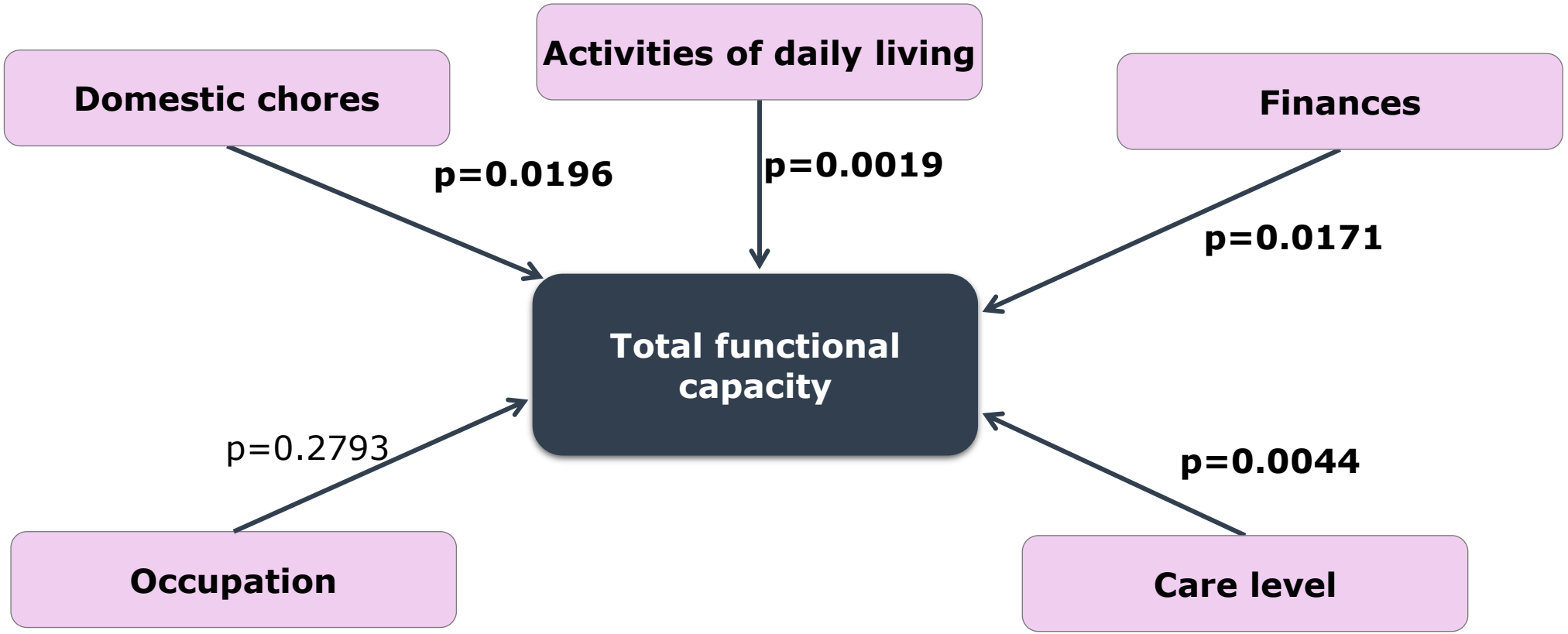
Early Stage HD Week 52 (BL TFC ≥7)



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

McGarry et al, JHD, 2020 (online ahead of print)

All TFC Domains Numerically Contributed to the Overall TFC Finding of Pridopidine 45 mg BID at Week 52 in Early Stage HD



Capacity to undertake domestic chores, activities of daily living, care level, and the capacity to manage finances were found to contribute the most

McGarry et al, JHD, 2020 (online ahead of print)

FDA "Voice of Patients":
HD patients and families highlight **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
- Participants described being unable to continue working, driving, performing household activities, eating (due to fear of choking), taking care of oneself, participating in favourite hobbies (such as biking, walking, playing on the playground), and completing simple tasks
- Participants noted that they have become increasingly or fully dependent on others for care, as HD symptoms worsened

FDA

" The UHDRS-TFC is the most clinically relevant scale to measure maintenance of functional capacity that has been determined to have the **most impact on patients' daily lives"**

FDA "Voice of Patient", September 22, 2015

PRIDE-HD (Ph 2): Beneficial Effect on Maintaining Functional Capacity in HD

- Placebo has demonstrated little to no impact on TFC decline
- Annual TFC decline of ~1/year in HD patients (in TFC 7-13) (1)

No placebo response; TFC showed progression of functional decline in all other HD studies

(1) Marder et al., Neurology 2000

	Study	Baseline TFC	Treatment	Annual TFC progression	Follow-up time
Placebo/ observational	HSG	7.5	Observational	-0.72	18 mo (median)
	HSG	Stage 2 (TFC 7-10)	Observational	-0.84	18 mo
	REGISTRY	8 (M), 7.4 (F)	Observational	-0.74 (M), 0.94 (F)	21 mo
	CARE-HD	10.3	Placebo	-1.096	30 mo
	2CARE	11.0	Placebo	-0.952	60 mo
	CREST-E	10.2	Placebo	-0.7	18-48 mo
	PRIDE-HD	**TFC 7-13**	**Placebo**	**-1.17**	**12 mo**
Treatment	CARE-HD	10.1	CoQ	-0.96	30 mo
	CARE-HD	10.0	Remacemide	-1.08	30 mo
	2CARE	10.8	CoQ	-0.906	60 mo
	CREST-E	10.2	Creatine	-0.82	18-48 mo
	Tetra-HD continuation	7.6	Tetrabenazine	-1.3	18 mo
	PRIDE-HD	**TFC 7-13**	**Pridopidine 45mg bid**	**-0.01**	**12 mo**

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

Pride-HD responder analysis:
45 mg bid shows a significant decrease in the proportion of patients having worsening of TFC (decline ≥ 1 points), at 52 weeks

Number of patients (%) with worsening of TFC

	Placebo	45 mg bid	Odds Ratio (95% CI) (GLIMMIX model)	P-value
Early HD (TFC ≥ 7) Placebo, n=41 45 mg bid, n=37	21 (51.2%)	7 (18.9%)	0.20 (0.07 - 0.56)	0.002

In early HD, 45mg bid ↓ the probability of worsening of TFC by 80% (p=0.002)

McGarry et al, JHD, 2020 (online ahead of print)

Durability of Effect:

Less TFC decline over 5 years in patients treated with pridopidine 45mg bid vs. historical placebo

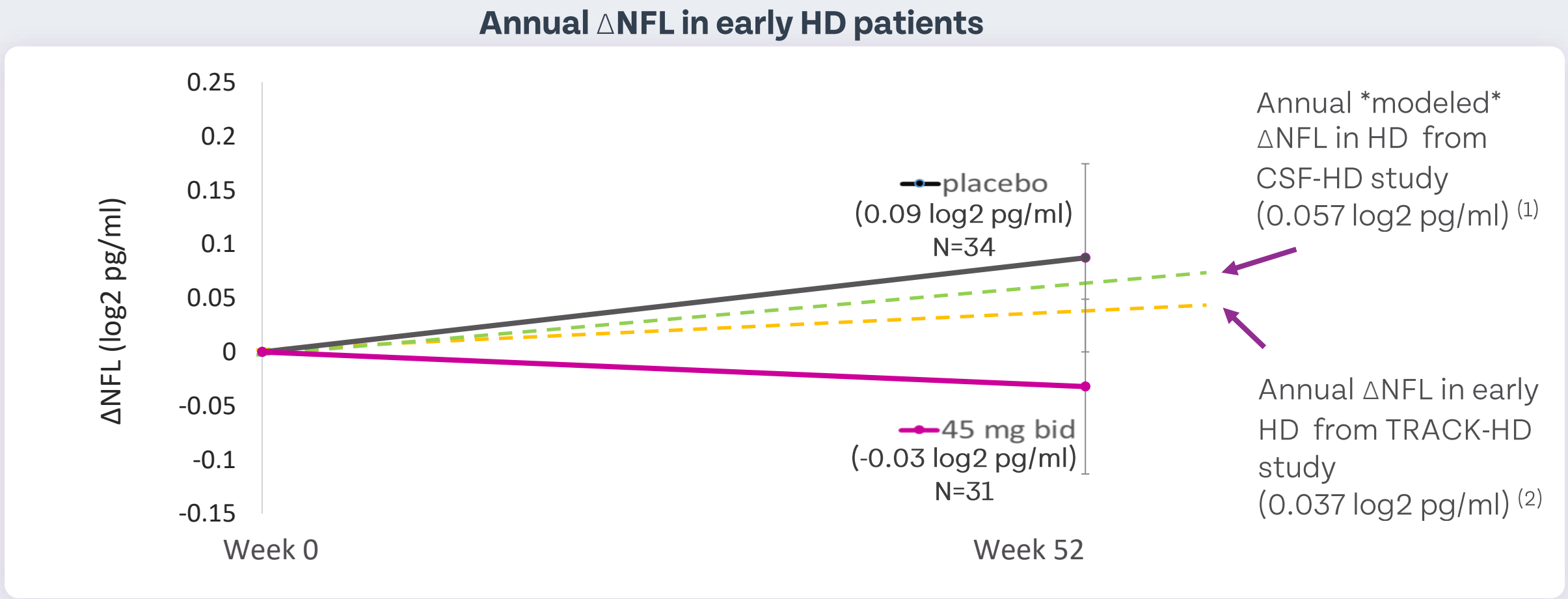
2CARE (placebo) and Open-HART (pridopidine 45 mg bid) 5 years ΔTFC from baseline

	60 months ΔTFC (SE)
2CARE, Placebo (baseline TFC 9-13) N=303	-5.0 (0.3) N=123
Open HART, pridopidine 45 mg bid (baseline TFC 9-13) N=55	-1.8 (0.5) N=19 P=0.001

Sensitivity analysis (MMRM) to model missing data confirms less TFC decline in Open-HART vs 2CARE at 48 (p=0.01) and 60 (p=0.001) months

McGarry et al, AAN 2016 (2CARE) // McGarry et al, JHD 9 (2020) 173–184

Pridopidine 45 mg bid ↓ plasma ΔNFL in early HD patients at 52 Weeks



Log2 transformed value of mean ± SEM NFL in plasma from a subset of PRIDE-HD patients

(1) Rodrigues et al., HSG 2020; (2) Byrne et al., 2017

PRIDE-HD Pridopidine 45 mg bid ↓ **plasma ΔNFL correlates to TFC maintenance** in Early HD patients

		Δ TFC to week 52 (SE)	P-value	Δ NFL to week 52 (SE) Log2 pg/ml	P-value
Early HD (TFC 7-13)	**45 mg bid** N=31	**+0.29** (0.18)	0.0005	**-0.03** (0.08)	0.2
	Placebo N=34	**-0.94** (0.28)		**+0.09** (0.09)	

Placebo ↓ -0.94 in TFC (correlates with Marder 2010)
Pridopidine maintains TFC (+0.29)

Log2 transformed value of mean ± SEM NFl in plasma from a subset of PRIDE-HD patients

PROOF HD Global phase 3 trial currently enrolling

- **A Phase 3, Parallel Arm Randomized, Double-Blind Placebo Controlled, Multicenter Study Evaluating the Efficacy and Safety of Pridopidine in Patients with Early Stage Huntington Disease**
- **2-arm study:** Pridopidine 45 mg bid vs placebo
- **Target population:** Early HD (Baseline TFC ≥7)
- **Endpoints:**
  - **Primary endpoint:** Mean change from Baseline in Total Functional Capacity (TFC) to week 65
  - Key secondary: Responder analysis – proportion of patients with no worsening (change ≥ 0 point) from baseline in UHDRS-TFC
  - Other endpoints focusing on measuring effect on other HD symptoms (e.g. motor, cognitive, quality of life)
  - Includes risk **mitigations for COVID-19** and similar situations

Partnership with the Huntington Study Group and support from highly engaged PIs and Co-PIs to drive trial success

Huntington Study Group Announces A Partnership with Prilenia Therapeutics to Conduct A Global Phase 3 Clinical Study of Pridopidine in Huntington's Disease

PROOF HD

Rochester, N.Y. — September 17, 2020 —The Huntington Study Group ("HSG"), a world leader in clinical research for Huntington's Disease (HD), announces a partnership with Prilenia Therapeutics, a clinical stage biotech company led by Michael R. Hayden, MD, PhD, to conduct **PR**idopidine **O**utcome **O**n **F**unction in **H**untington's **D**isease (**PROOF-HD)** clinical study. PROOF-HD is a global Phase 3, randomized, double-blind, placebo-controlled, parallel arm, multicenter study evaluating the efficacy and safety of pridopidine in patients with early stage HD.

PI North America:
Dr. Andrew Feigin, Chair of the HSG, Professor of Neurology at NYU Langone Health

PI Europe:
Dr. Ralf Reilmann, Founding Director and CEO, George Huntington Institute (GHI), Muenster

Co-PI North America:
Dr. Sandra Kostyk, Professor of Neurology, Ohio State University

Co-PI Europe:
Dr. Anne Rosser, Chair of EHDN, Professor of Neurology, Cardiff University