Pridopidine Maintenance of Total Functional Capacity (TFC) is Associated with Stabilization of Plasma Neurofilament Light (NfL) Levels

Michal Geva[1], Deniz Akinc Abdulhayoglu[2], Noga Gershoni-Emek[1], Paul Goldberg[1], Charles Li[3],

Jennifer Dreymann[3], Bruno Boulanger[2] and Michael R. Hayden[1,4]

1 Prilenia Therapeutics
2 PharmaLex Belgium SA Mont-St-Guibert, Belgium
3 Teva Pharmaceutical Industries Ltd
4 CMMT, University of British Columbia, CA

PHARMALEX
CONFIDENCE BEYOND COMPLIANCE

prilenia

Neurofilament Light (NfL) protein is a measure of ongoing axonal injury

- NfL protein is released from neurons following axonal injury

- In HD, NfL levels in plasma and CSF are ↑ **with disease progression**

- Plasma NfL in HD patients **correlates with longitudinal decline of cognition and brain atrophy**

- Plasma NfL is ↓ **upon successful treatment** in other neurodegenerative diseases (e.g MS)

Axonal injury/ degeneration

Neurofilament
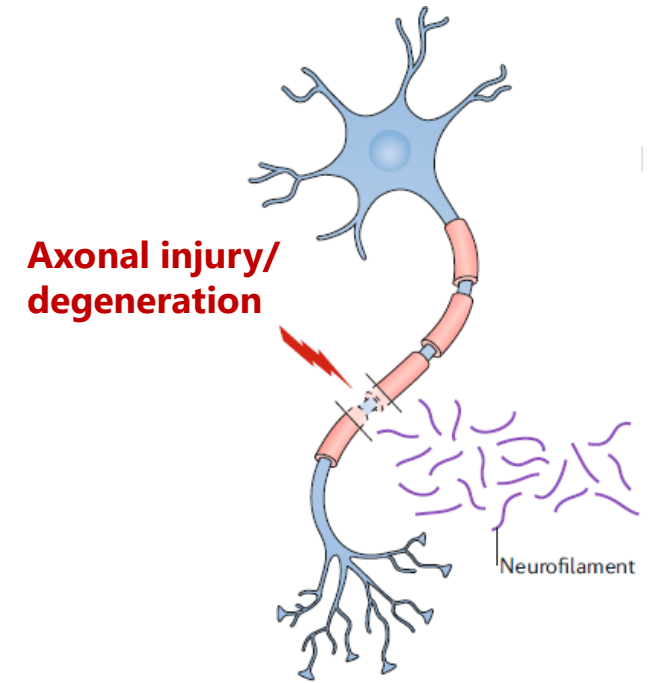
> *"NfL can be regarded as a measure of ongoing neurodegeneration and reductions in NfL are associated with clinical effectiveness of treatment"*
> *Oskar Hansson, Nature Medicine, June 2021 (954–963)*

1. Byrne et al., Sci. Transl. Med. 2018 2. Petzold et al. 2005 3. Byrne LM et al. 2017 4. Kuhle, J. et al. Neurology 2019 5.Khalil et al., Nat Rev NeuroSci 2018

prilenia

Pridopidine

- An oral drug candidate in **clinical development for HD (phase 3 PROOF-HD trial)** and ALS (phase 2/3 Healey platform trial).

- **Selectively activates the Sigma-1 receptor (S1R),** which is highly expressed in the brain.

- The S1R regulates several **cellular processes essential to neuronal function and survival.**

- **Pridopidine activation of the S1R exerts neuroprotective effects** in multiple preclinical models including HD and ALS.

- In PRIDE-HD (phase 2 trial in HD), post hoc analysis demonstrates that **pridopidine 45 mg bid maintains Total Functional Capacity (TFC)** at 52 weeks in early HD patients (Δ to placebo 1.16, p=0.0003).

- **TFC is a validated, regulatory-accepted measure of HD stage and clinical progression.**
  - Measures important functional abilities of a patient to perform day-to-day activities such as dressing, eating and managing finances.

prilenia

Increasing plasma NfL concentration is associated with HD disease progression
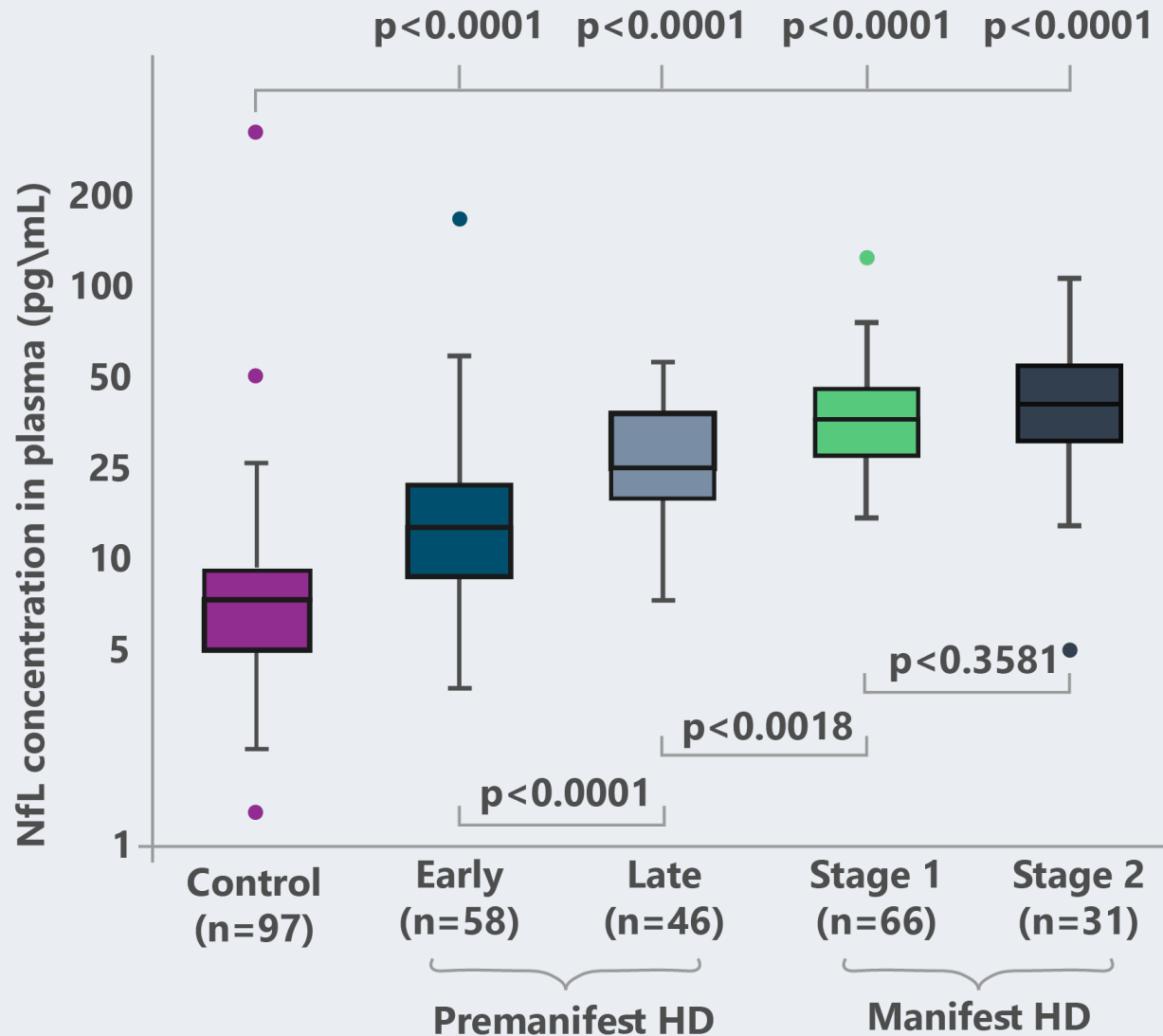
Plasma NFL levels:

- ↑ in premanifest patients vs. healthy controls

- ↑ with disease progression

Methods

- At the time of PRIDE-HD design (2012), NfL was not yet recognized as a biomarker for disease progression in HD.
    - PRIDE did not collect plasma dedicated for biomarker analysis (plasma was collected for PK analysis).
    - Therefore, post-hoc analysis of plasma NfL was measured from participants for whom plasma was available.
    - Early HD patients with available plasma for Nfl analysis (baseline and week 52):
        - Placebo n=34, 45 mg bid n=31
    - Early HD patients with TFC data (baseline and week 52)
        - Placebo n=41, 45 mg bid n=37
- NfL levels in plasma were evaluated using SIMOA methodology.
- NfL levels were log2-transformed and the relationship between NfL and TFC was modelled on all available data using a linear mixed model.

prilenia

# No differences in demographics between placebo and 45 mg bid groups

	placebo	45 mg bid
N	**34**	**31**
Age Mean (SD)	48.94 (12.63)	51.9 (13.37)
Sex (M:F) (%)	17:17 (50:50)	16:15 (52:48)
CAG Mean (SD)	44.64 (3.08)	43.65 (4.72)

prilenia

Baseline TFC and NfL levels are similar in placebo and pridopidine 45 mg bid groups

TFC at baseline

Plasma NfL at baseline
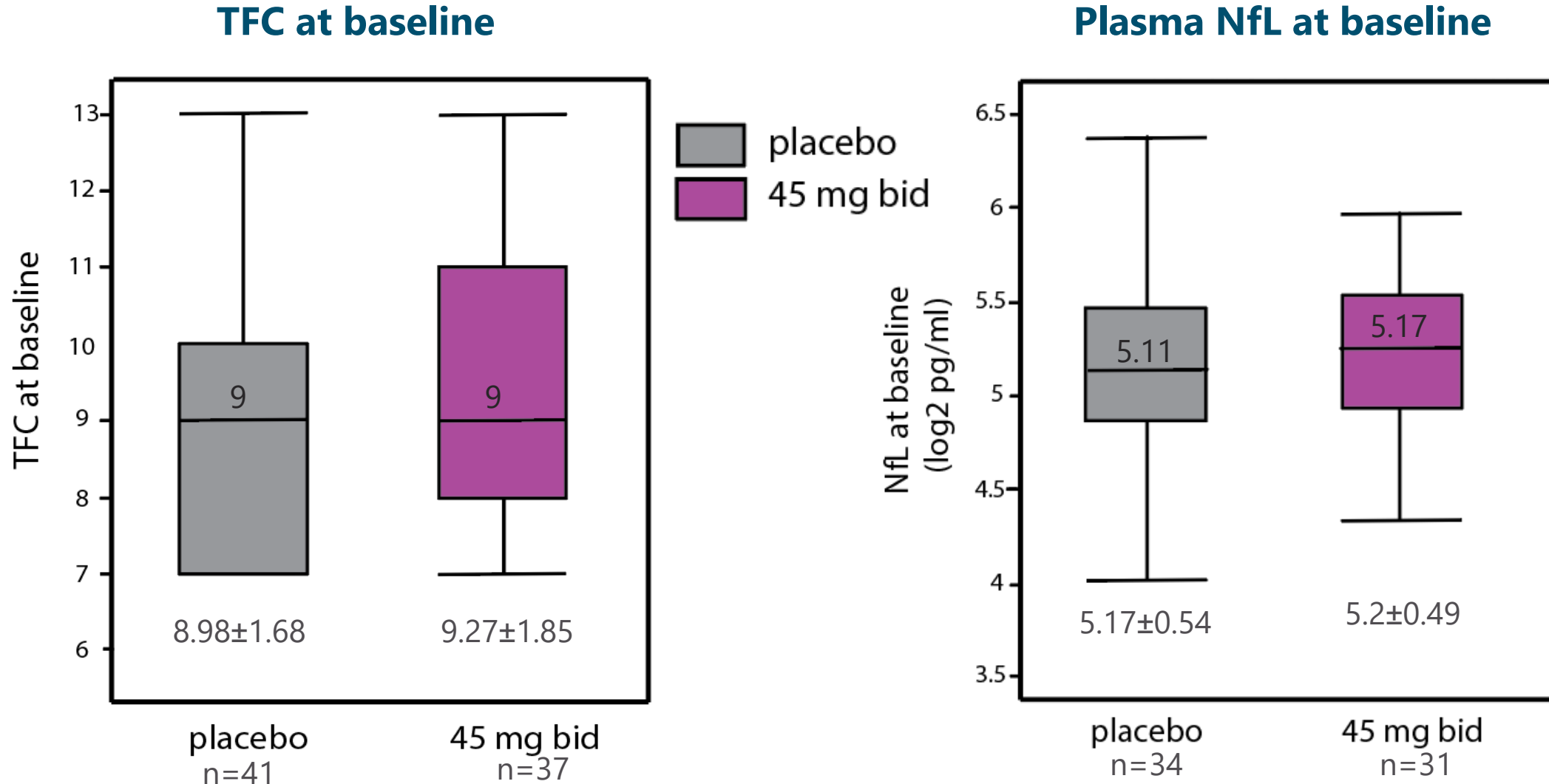
Higher CAG repeats are associated with higher NfL levels at baseline

CAG repeat is associated with baseline NfL levels, p=0.003
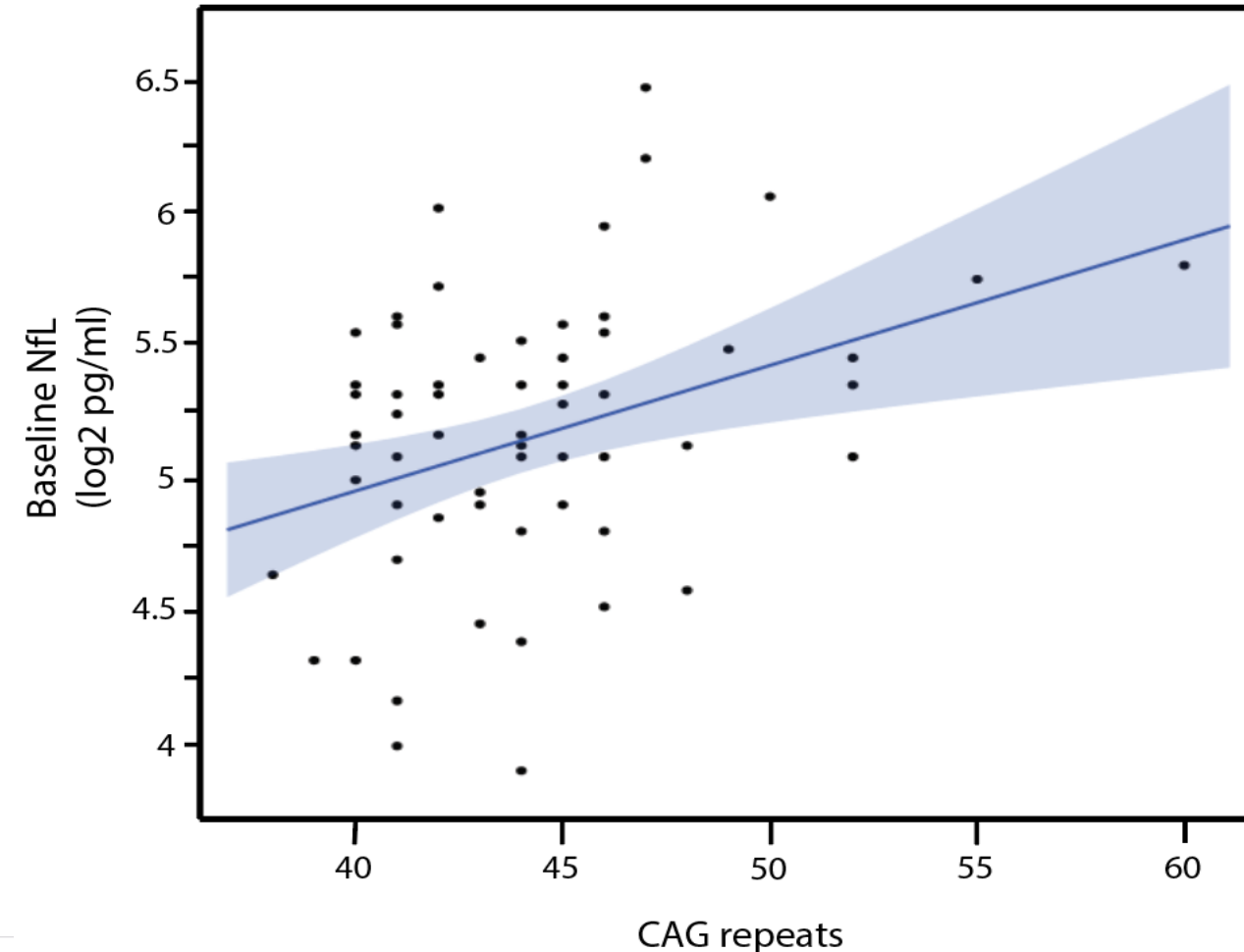
Data correlates with known association between CAG repeat number and NfL levels (Byrne et al, 2017)
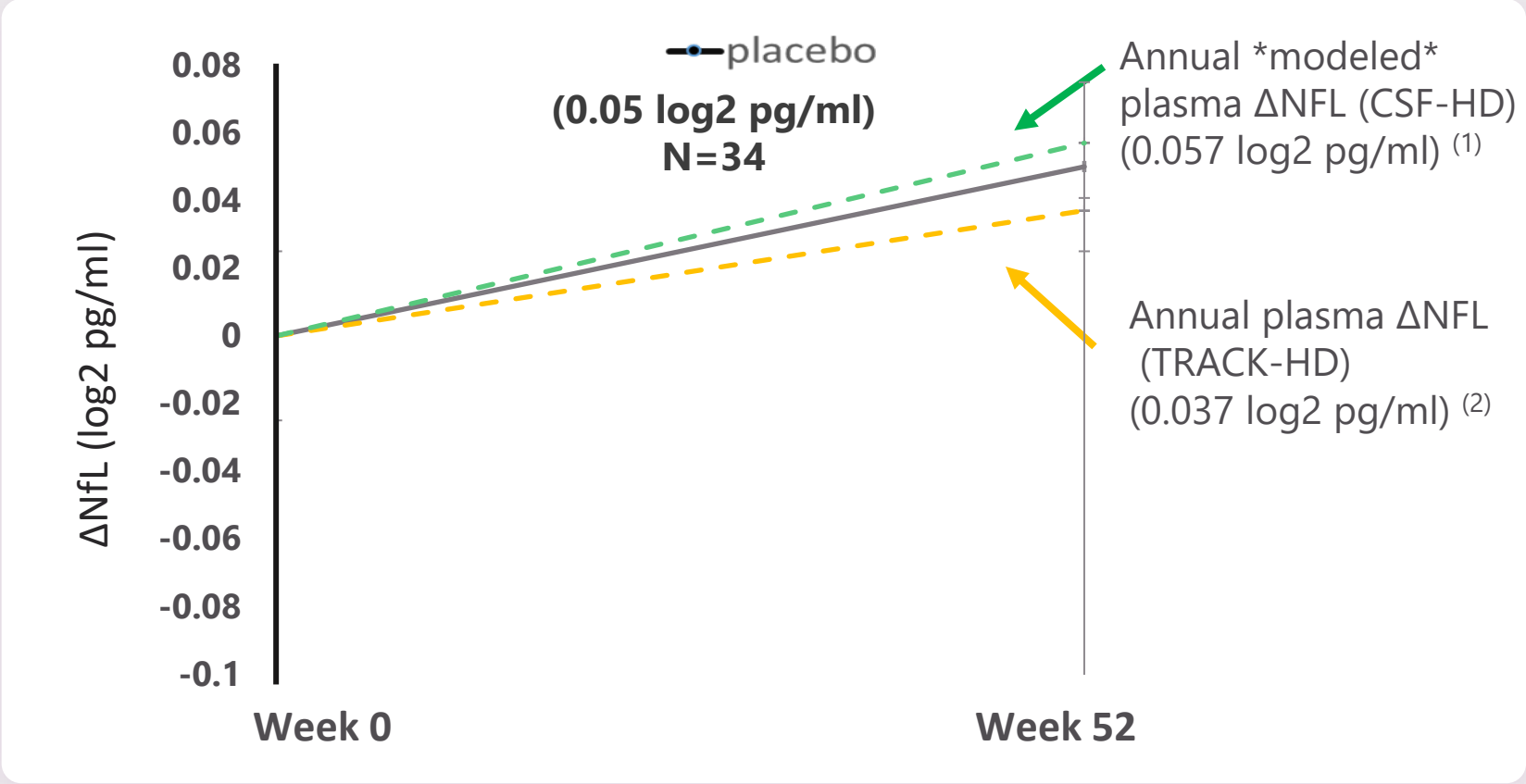
No differences in CAG values at baseline between placebo and 45 mg bid groups

Baseline data from placebo and 45 mg bid (n=65)

PRIDE-HD placebo: plasma NfL increases over time (early HD)

Annual ΔNfL in early HD patients

Annual *modeled* plasma ΔNFL (CSF-HD) (0.057 log2 pg/ml) [1]

Annual plasma ΔNFL (TRACK-HD) (0.037 log2 pg/ml) [2]

(0.05 log2 pg/ml) N=34

Week 0 — Week 52

- **Observational studies in early HD patients(TRACK-HD and CSF-HD) demonstrate an annual increase in plasma NfL levels (0.037-0.057 log2 pg/ml)**

- **Placebo group in PRIDE demonstrate a similar annual increase (0.05 log2 pg/ml)**

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

(1) Rodrigues et al., Sci Trans Med 2020; (2) Byrne et al., Lancet 2017

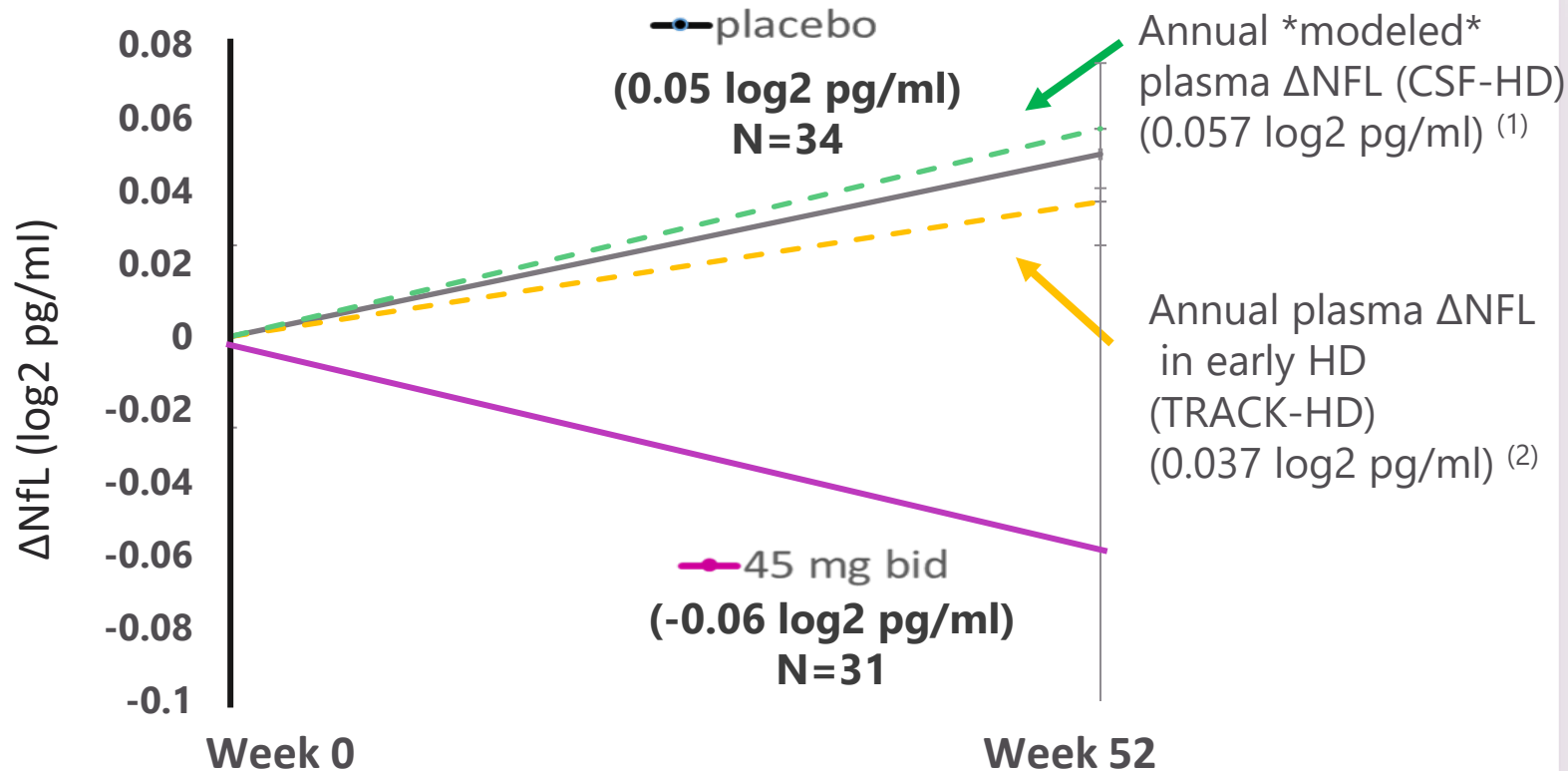# PRIDE-HD placebo: worsening in TFC is associated with an increase in plasma NfL at 52 weeks

Significant negative correlation between ΔTFC and ΔNfL, p=0.02
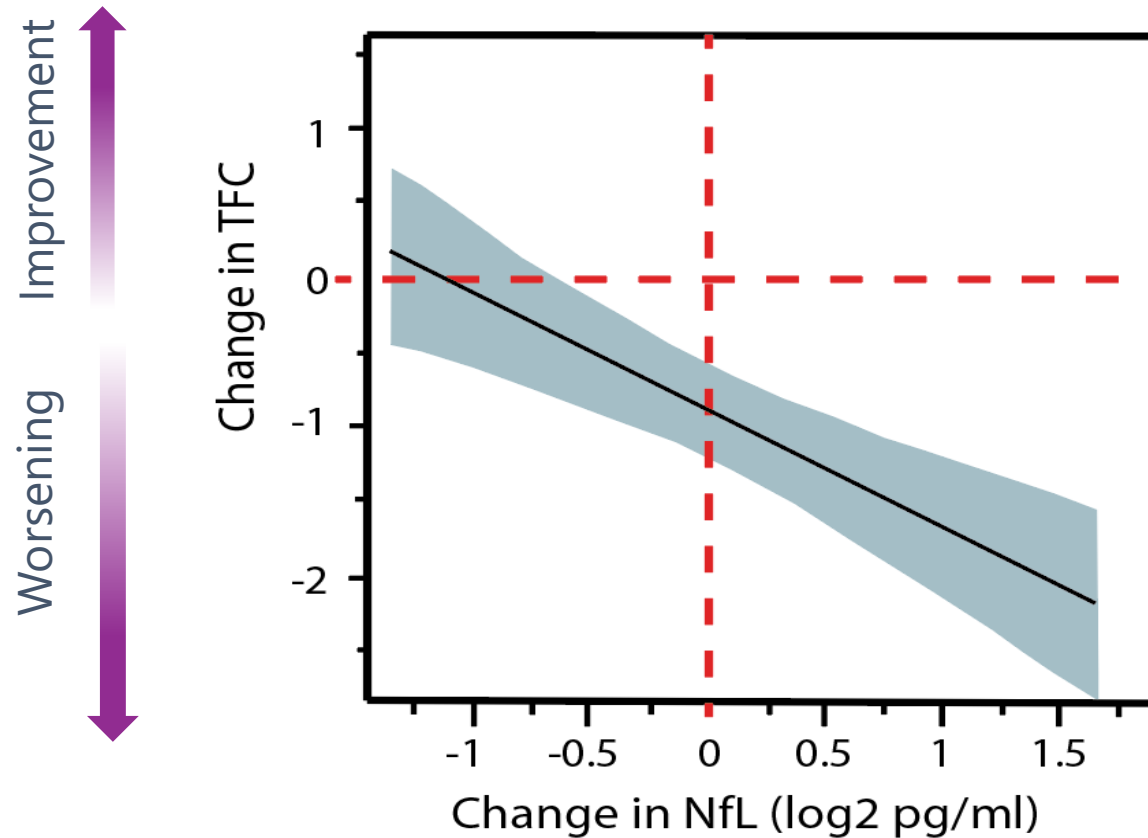
Modeled using data from placebo group, grey area indicates 95% confidence interval
N=34 for NfL; N=41 for TFC

Pridopidine 45 mg bid stabilizes plasma NfL in early HD at 52 Weeks

Annual ΔNfL in early HD patients

Pridopidine 45 mg bid stabilizes plasma NfL levels at 52 weeks (ΔNfL -0.06 log2 pg/ml)

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

(1) Rodrigues et al., Sci Trans Med 2020; (2) Byrne et al., Lancet 2017

Pridopidine 45 mg bid stabilizes plasma NfL which correlates with TFC maintenance in Early HD patients

		Δ TFC (SE) to week 52	P-value	Δ NfL (SE) to week 52 Log2 pg/ml	P-value
Early HD (TFC 7-13)	**45 mg bid**	**0.09** (0.02) n=37	**0.0006**	**-0.06** (0.07) n=34	0.2
	Placebo	**-1.0** (0.25) n=41		**+0.05** (0.1) n=31	

**Placebo ↓ -1.0 in TFC (correlates with Marder 2000)
Pridopidine maintains TFC (0.09)**

Log2 value of mean ± SEM NfL in plasma, modelled using a linear mixed model

▶ **PHARMA**LEX
CONFIDENCE BEYOND COMPLIANCE

prilenia

Pridopidine 45 mg bid maintains TFC and stabilizes NfL levels in early HD at week 52
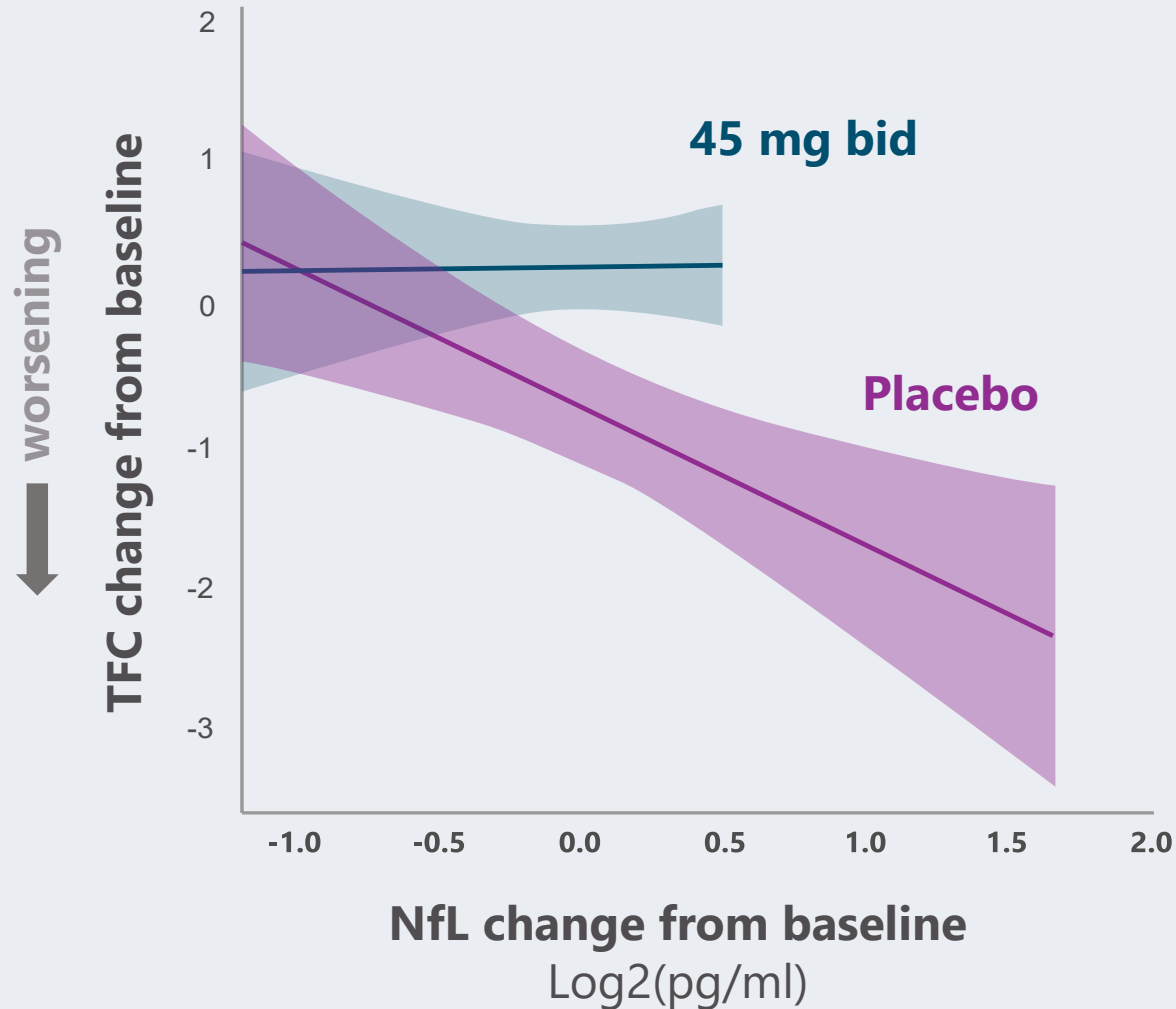
- Placebo shows a significant correlation between worsening in TFC and ↑ in NfL (negative slope, p=0.02)

- Pridopidine 45 mg bid: maintains TFC and stabilizes NfL

  o No worsening in TFC & NfL over time (no change over time)

- No increase in NfL on treatment beyond 0.5 Log2(pg/ml)

Data are mean with two-sided 95% CI
Placebo: n=34 for NfL; n=41 for TFC; 45 mg bid: n=31 for NfL, n=37 for TFC

Summary

- **We analyzed early HD patients from the PRIDE-HD phase 2 trial treated with placebo or 45 mg bid pridopidine for 52 weeks**
  - At baseline, placebo and 45 mg bid show similar demographics, similar CAG repeat number and similar plasma NfL levels
  - Higher CAG repeats correlate with higher NfL levels at baseline (p=0.003)
- **Placebo group shows the expected annual ↑ in NfL (+0.05 log2 pg/ml)**
  - → ↑ in NfL is associated with worsening (↓) in TFC (ΔTFC -1.0 at 52 weeks)
- **Pridopidine 45 mg bid stabilizes NfL at 52 weeks (-0.06 log2 pg/ml)**
  - **→ Stabilization of NfL is associated with maintenance of TFC (ΔTFC 0.09 at 52 weeks)**
- **Effect of pridopidine on TFC in early HD patients is being evaluated in the ongoing phase 3 PROOF-HD (see PROOF-HD poster)**
  - Plasma NfL is a prespecified endpoint in the PROOF-HD phase 3 trial

prilenia