Exposure-response (PKPD) analysis demonstrates predicted exposure for clinical efficacy with pridopidine 45 mg bid dose

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Background

- Pridopidine is a novel small molecule in clinical development for HD and ALS with **a selective high affinity and agonistic activity at the Sigma-1 receptor (S1R).**
- The S1R is enriched in brain areas implicated in HD (basal ganglia and cortex).
- The S1R is an endoplasmic reticulum (ER) protein located at the mitochondrial interface, modulating diverse cellular processes **crucial for neuronal function and survival.**
- S1R activation by pridopidine induces **beneficial effects** in multiple neurodegenerative disease models.
- S1R agonist activity is characterized by a **biphasic dose response curve** in preclinical and clinical studies.
- Pridopidine demonstrates the expected biphasic effects.
- Pridopidine **45 mg bid is the most efficacious dose** in clinical trials
  - In HART and MermaiHD, 45 mg bid, the highest dose tested, was most efficacious for improving Total Motor Score (TMS).
  - In the PRIDE-HD trial, the lowest dose tested, 45 mg bid was the most efficacious for maintaining Total Functional Capacity (TFC).

Maurice, EODD 2021; Naia et al., Neurotherapeutics 2021; Ionescu et al, Cell Death Dis 2019; Ryskamp et al, Front. Neurosci. 2019; Smith-Dijak et al.,Front Cell Neurosci 2019, Ryskamp et al, NBD. 2017 ; McGarry et al., JHD 2020; Garcia de Yebenes et al, Lancet Neurol. 2011

Biphasic response curves are well-established for S1R agonists

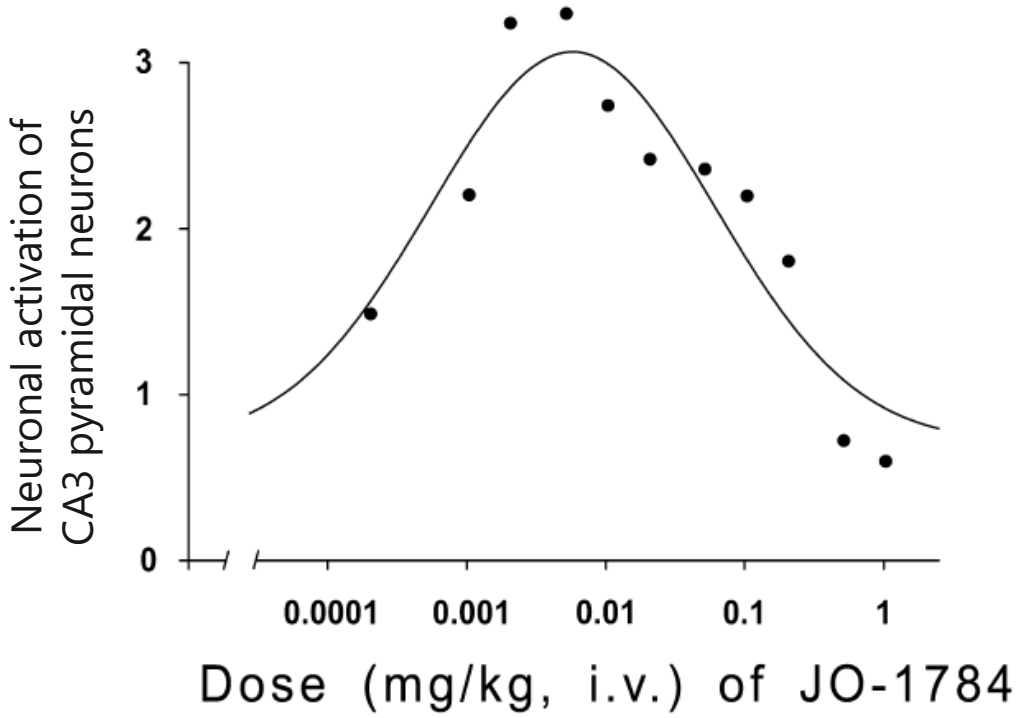
- "An important consideration for S1R agonists is the biphasic dose-response curve is typically observed in biological responses" (Maurice, 2021)
- "S1R agonists are typically characterized by a bell-shaped *(biphasic)* dose response curve in various experimental paradigms…" (Lucas et al., 2008)
- "Bell-shaped *(biphasic)* dose–response curves are a common finding in studies regarding the effect of sigma-1 receptor agonists" (Van Waarde et al., 2011)
- "In behavioral models, drugs with high affinity and specificity for S1R such as BD-737 and (+)3-PPP generate bell-shaped *(biphasic)* response curves…" (Bergeron et al., 1995)
- " A biphasic bell-shaped *(biphasic)* dose response curve has been observed for sigma ligands in various behavioral, biochemical and electrophysiological paradigms." (Bermack and Debonnel 2005)

Maurice, EODD 2021 Apr;16(4):373-389; Lucas et al., Int J Neuropsychopharmacol 2008; 11(4):485-95; van Waarde et al., Behav Brain Res. 2011; 221(2):543-54; Bergeron et al., Naunyn Schmiedebergs Arch Pharmacol. 1995 Mar;351(3):252-60; Bermack and Debonnel, J Pharmacol Sci 2005; 97(3):317-36;

The S1R agonist Igmesine (JO-1784) demonstrates biphasic dose response in preclinical and clinical studies

Preclinical

Neuronal activation by igmesine at optimal dose of 0.01 mg/kg



Lower and higher doses show reduced effects

Clinical

Optimal efficacy of igmesine at 25 mg, reduced efficacy at 100 mg

Change from baseline in Total Hamilton Depression Rating Scale (HAMD)

	Placebo	*Igmesine 25 mg*	*Igmesine 100 mg*
Outpatients			
Baseline	26.0 ± 2.6	26.0 ± 3.0	26.3 ± 2.7
Endpoint	13.9 ± 8.0	10.5 ± 6.7*	14.1 ± 9.1

*** p=0.003 vs placebo**

Phase 2, randomized placebo-controlled trial, 6 weeks, n=358

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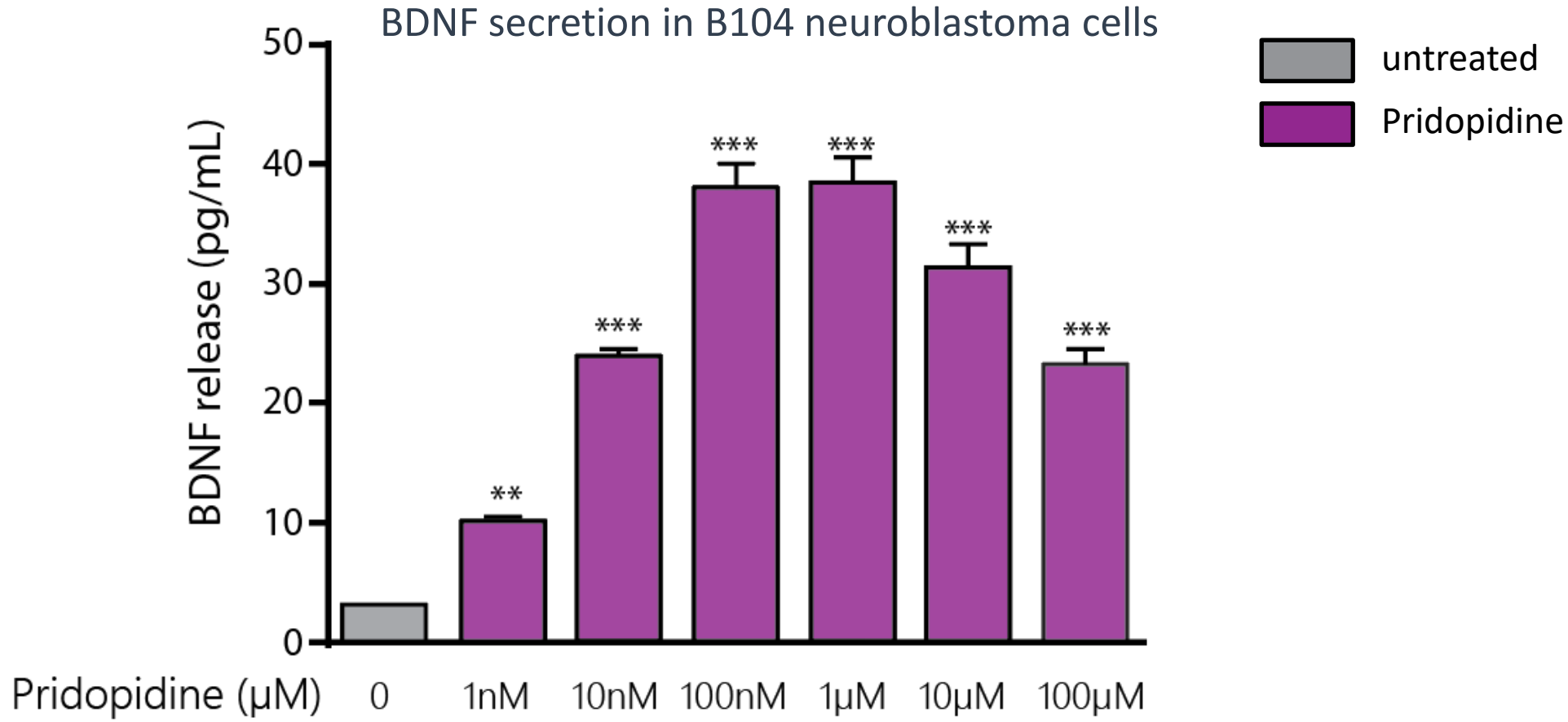
Bermack and Debonnel, J Pharmacol Sci 2005

Pande et al., European Neuropsychopharmacology 1999; Volz and Stoll, Pharmacopsychiatry 2004

Maximal effect of pridopidine on BDNF secretion seen at 100 nM and 1µM

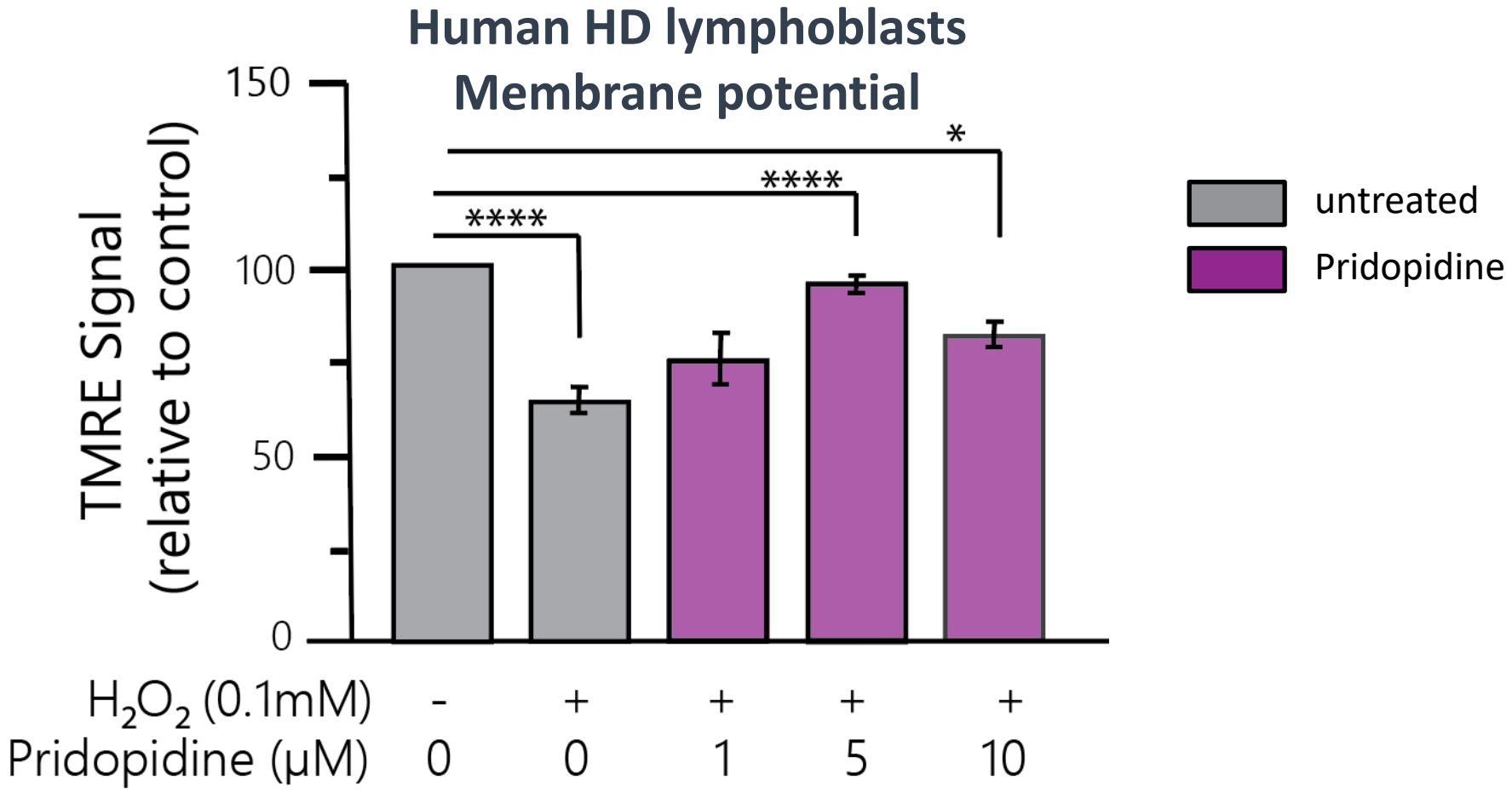
Higher and lower doses are less effective



B104 cells, 5 days pridopidine treatment. BDNF release measured by in situ ELISA.
Data is mean ± sem; *p<0.05; ** p<0.01; *** p<0.001 by one way ANOVA with a Dunnett's post-hoc test.

Source: Internal report #16102

Pridopidine restores mitochondrial membrane potential in human HD lymphoblasts (CAG 67/15) with maximal effect at 5µM



Higher and lower doses show reduced effects

Human lymphoblasts HD patient NA04724, TMRE measured by flow cytometry (n=4).*p<0.05, **p<0.01, ***p<0.001 by two-way ANOVA with a Tukey's post hoc test.

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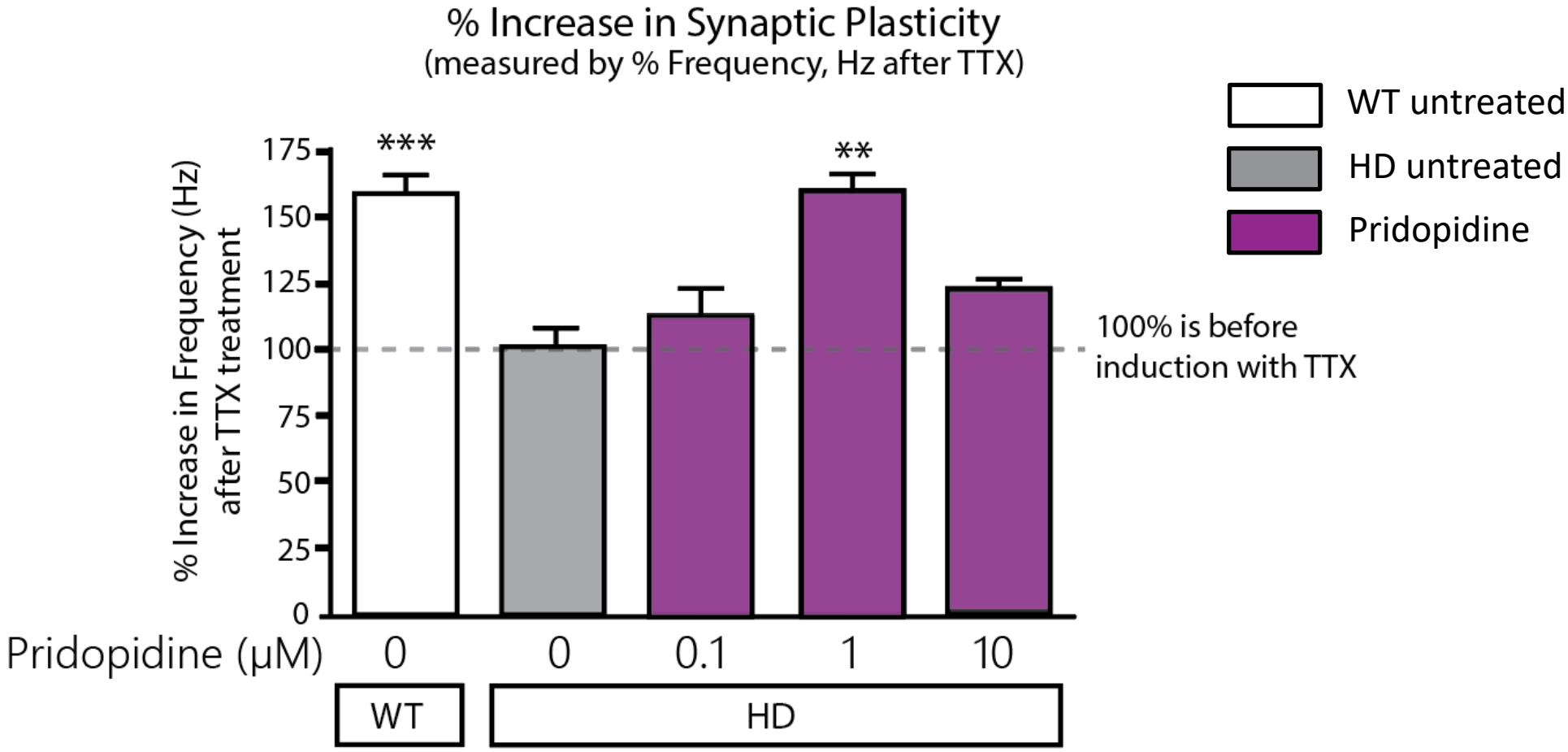
Naia et al, Neurotherapeutics, 2021

Pridopidine ↑ synaptic plasticity with strongest effect at 1µM



Higher and lower doses show diminished effects

TTX (Tetrodotoxin) -induced Homeostatic Synaptic Plasticity (HSP) as measured by miniature Excitatory Post Synaptic Current (mEPSCs) frequency (Hz)

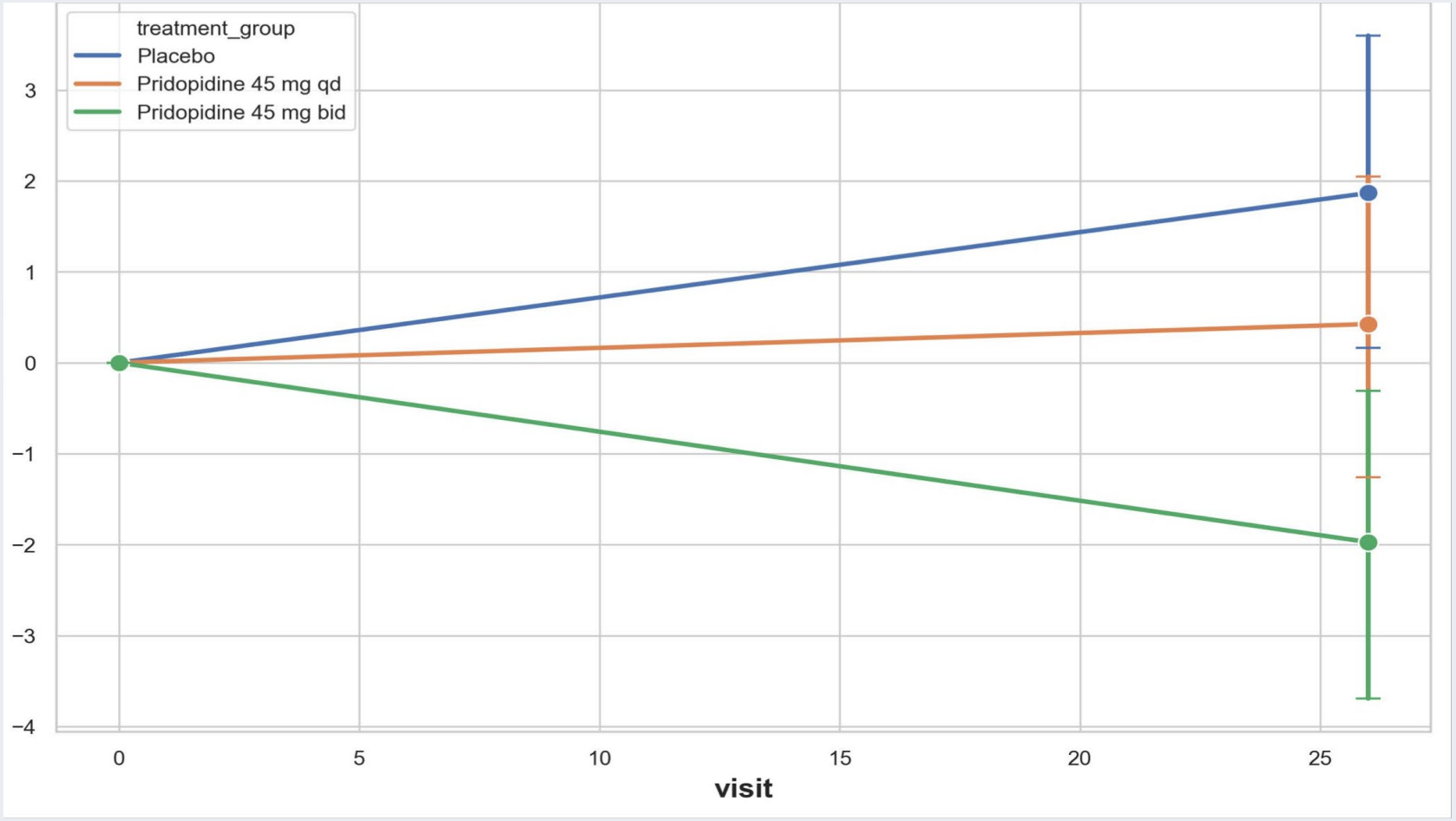
Source: Smith-Dijak et al. Front Cell Neurosci 2019

N=4 culture batches, **p < 0.01, ***p<0.001 Bonferroni post hoc t-test

Pridopidine demonstrates the classic biphasic dose response curve in clinical studies

MermaiHD: 45 mg bid shows better TMS improvement compared to 45 mg qd at week 26

Early HD



Placebo
n=68

45 mg qd
n=82

45 mg bid
n=75
ΔTMS vs placebo:-3.4
P=0.004

Analysis by Blackfynn, based on actual data (no missing data modeling); early HD: TFC 7-12

From: Garcia de Yebenes et al, Lancet Neurol. 2011 Dec;10(12):1049-57

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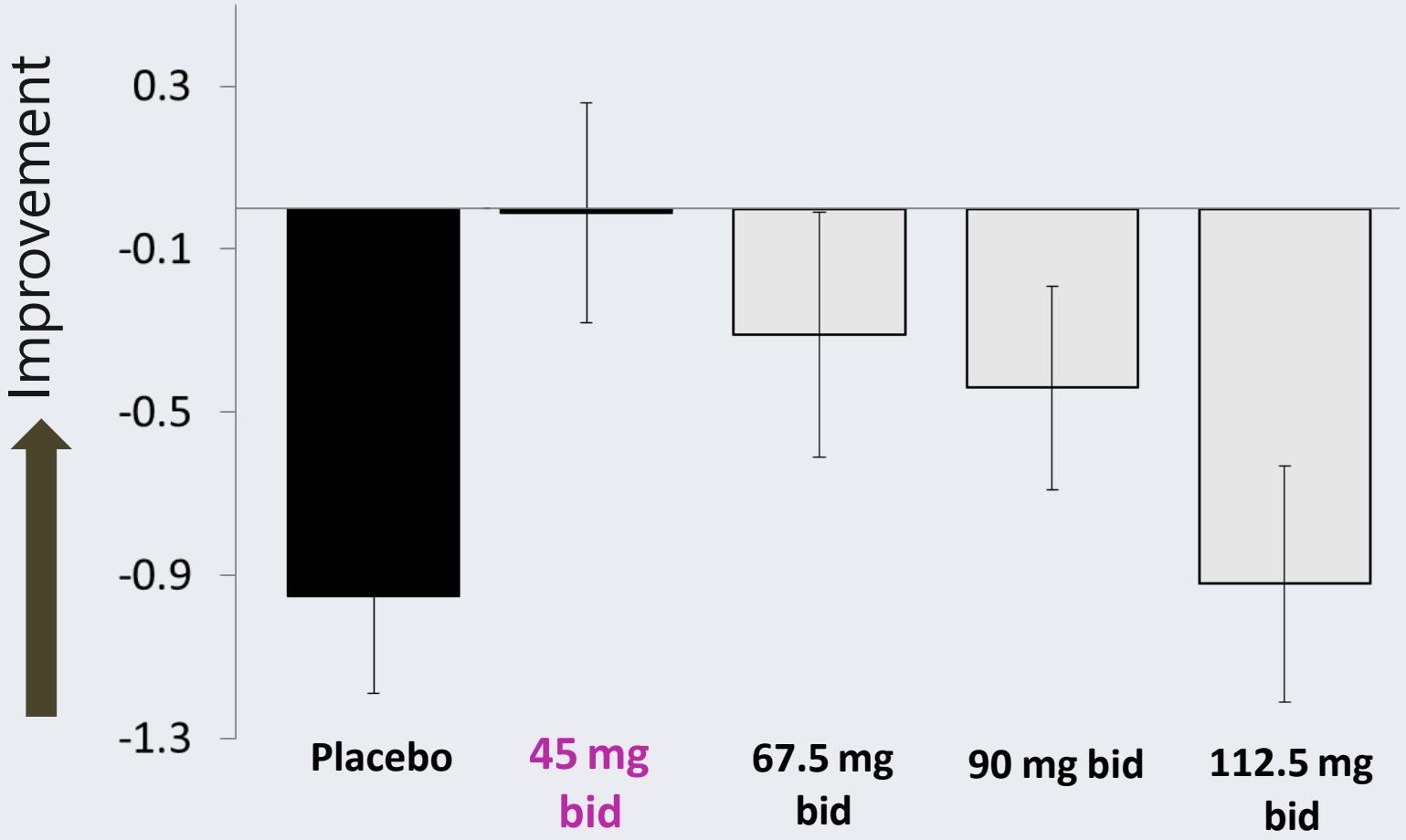
45mg bid is the most efficacious dose for maintaining TFC in early HD patients

PRIDE HD, 52 weeks
Early HD



Adj. means ± SEM

Early HD (TFC 7-10)

Source: PRIDE-HD CSR

94% of patients on 45 mg bid show exposure between 7-19 mg*h/mL (PRIDE-HD)

Number (%) of patients per treatment group

AUC mg*h/ml	45 mg bid	67.5 mg bid	90 mg bid	112.5 mg bid
7-19	34/36 (94%)	8/27 (30%)	4/34 (12%)	1/23 (4%)
20-34	2/36 (6%)	19/27 (70%)	20/34 (59%)	14/23 (61%)
35-80	0	0	10/34 (29%)	8/23 (35%)
Total	36 (100%)	27 (100%)	34 (100%)	23 (100%)

In PRIDE-HD, pridopidine doses of 45, 67.5, 90 and 112.5 mg bid were tested over 52 weeks. To evaluate pridopidine exposure-response relationship for TFC, individual plasma exposure (area under curve, AUC) was plotted against TFC score at 52 weeks

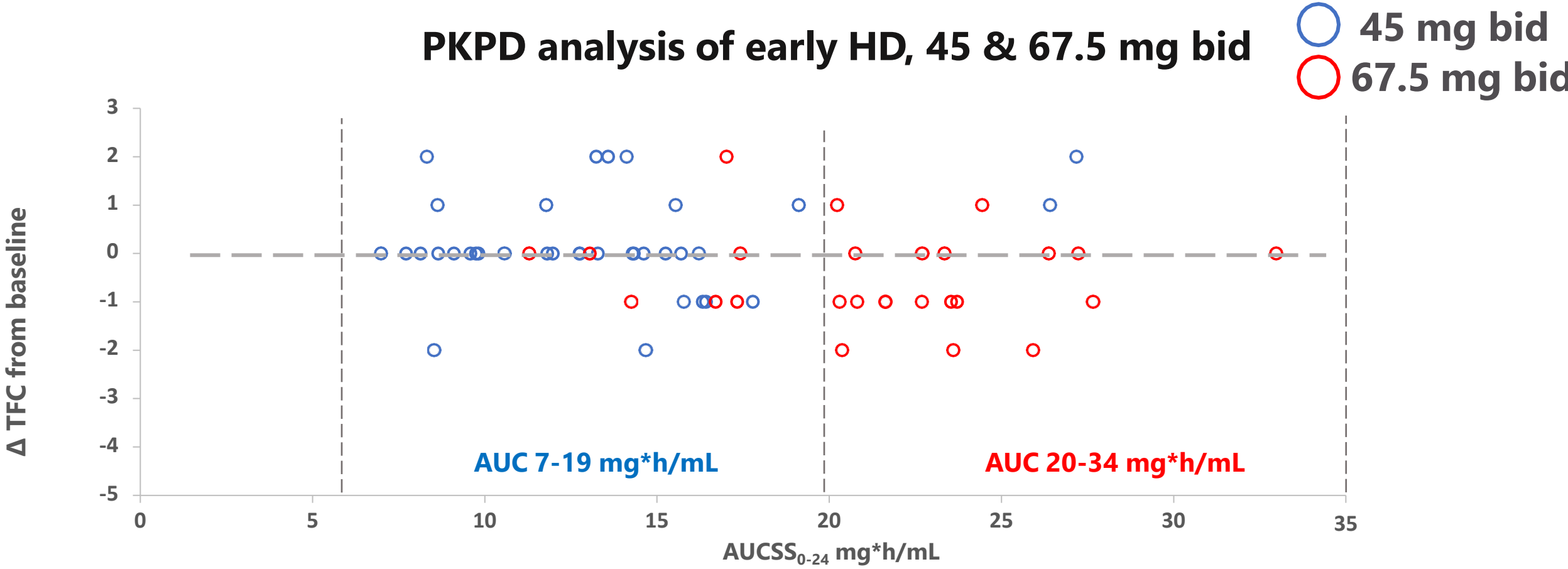
*n represents a subset of patients for whom PK data was available

Dose relationships to maintenance or improvement in TFC (ΔTFC ≥ 0)

N of patients with AUC 7-19 mg*h/mL	45mg bid N=34	67.5mg bid N=8	90mg bid N=4	112.5mg bid N=1
% of patients with ΔTFC ≥ 0	28/34 **(82%)**	5/8 **(62.5%)**	2/4 **(50%)**	1/1

At 45 mg bid 28/34 (82%) of patients with AUC 7-19 mg*h/mL show maintenance or improvement in TFC (TFC≥ 0)

Little overlap in exposure between 45mg bid and 67.5mg bid



45 mg bid: 94% (34/36) of patients have AUC between 7-19 mg*h/mL

67.5 mg bid: 70% (19/27) of patients have AUC between 20-35 mg*h/mL

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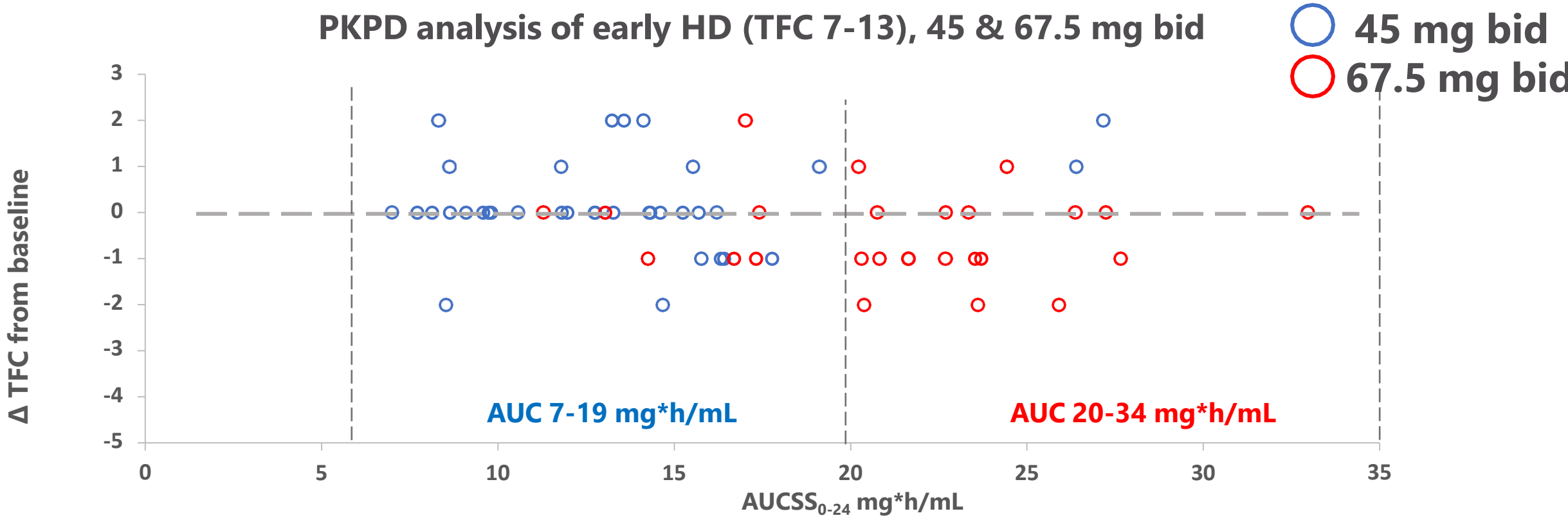
$AUCSS_{0-24}$ – area under the plasma concentration-time curve over the last 24-h dosing interval, at steady state

Most patients (33/42, 78.5%) with AUC between 7-19 mg*h/ml on both 45 and 67.5 mg bid show maintenance or improvement in functional capacity (ΔTFC ≥ 0)



% of patients with AUC 7-19 mg*h/mL showing (ΔTFC≥0)

- **82%** (28/34) on 45 mg bid
- **62.5%** (5/8) on 67.5 mg bid

Summary: Pridopidine 45 mg bid yields the optimal exposure for clinical efficacy as measured by changes in TFC

- **The majority of patients with plasma exposure of AUC 7-19 mg*h/mL demonstrate TFC ≥ 0**
- 94% (34/36) of patients on 45 mg bid pridopidine demonstrate AUC 7-19 mg*h/mL
- 82% (28/34) of patients on 45 mg bid with AUC 7-19 mg*h/mL demonstrate maintenance or improvement in TFC
- Higher doses yield higher exposures
  - Less association with maintenance of TFC