

PIVOT-HD Extension Study 24-Month Topline Interim Analysis Results

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Patient living with HD

Forward Looking Statements

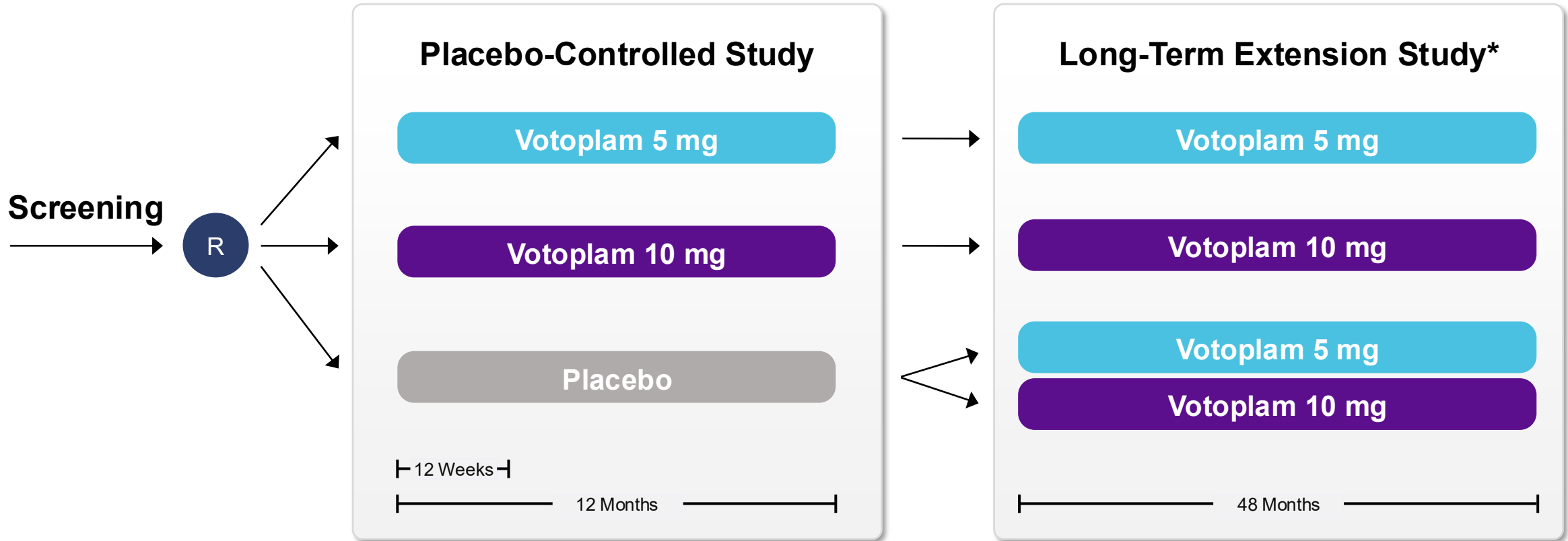
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PIVOT-HD Study Design



Primary Endpoint: Reduction in Blood HTT protein (Week 12)

*Placebo participants randomized 1:1 to 5 mg or 10 mg for LTE and all participants remain blinded to initial treatment assignment

PIVOT-HD Met Primary Endpoint of Blood HTT Lowering with Dose-Dependent Lowering Maintained at Month 12



PIVOT-HD study met primary endpoint of blood HTT protein lowering at Week 12 with durable dose-dependent lowering at Month 12



Favorable and dose-dependent trends on clinical scales at Month 12 in Stage 2 subjects



Favorable safety and tolerability profile with no treatment-related NfL increases

24-Month Interim Analysis Results

24-Month Interim Analysis Overview



Evaluate long-term clinical efficacy of voptoplam versus a propensity score–matched natural history cohort*



Assess long-term safety and tolerability profile of voptoplam



Explore blood-based and other disease associated biomarkers

*Natural history comparison was prespecified in the long-term extension protocol

Baseline Characteristics of 24-month Analysis Population

Baseline Characteristic	Stage 2		Stage 3	
	Votoplam 5 mg (N=21)	Votoplam 10 mg (N=24)	Votoplam 5 mg (N=22)	Votoplam 10 mg (N=24)
Age (years) Mean	45.6	46.7	53.2	49.2
Gender, n (%)				
Male	11 (52.4%)	11 (45.8%)	12 (54.5%)	14 (58.3%)
Female	10 (47.6%)	13 (54.2%)	10 (45.5%)	10 (41.7%)
CAG length				
Mean (SD)	44.1 (2.28)	43.8 (2.66)	43.0 (2.31)	44.3 (3.03)
Min – Max	41 – 49	41 – 50	40 – 50	40 – 50
TFC (Total Functional Capacity) Score Mean	13.0	13.0	11.6	12.0

ENROLL-HD Registry Propensity Weighted Natural History Comparator Group

ENROLL-HD is a large (>30,000 patient records), global, prospective, longitudinal observational registry for Huntington’s disease designed to systematically collect standardized natural history data. ENROLL-HD was used to create a comparator group based on key drivers of disease progression.

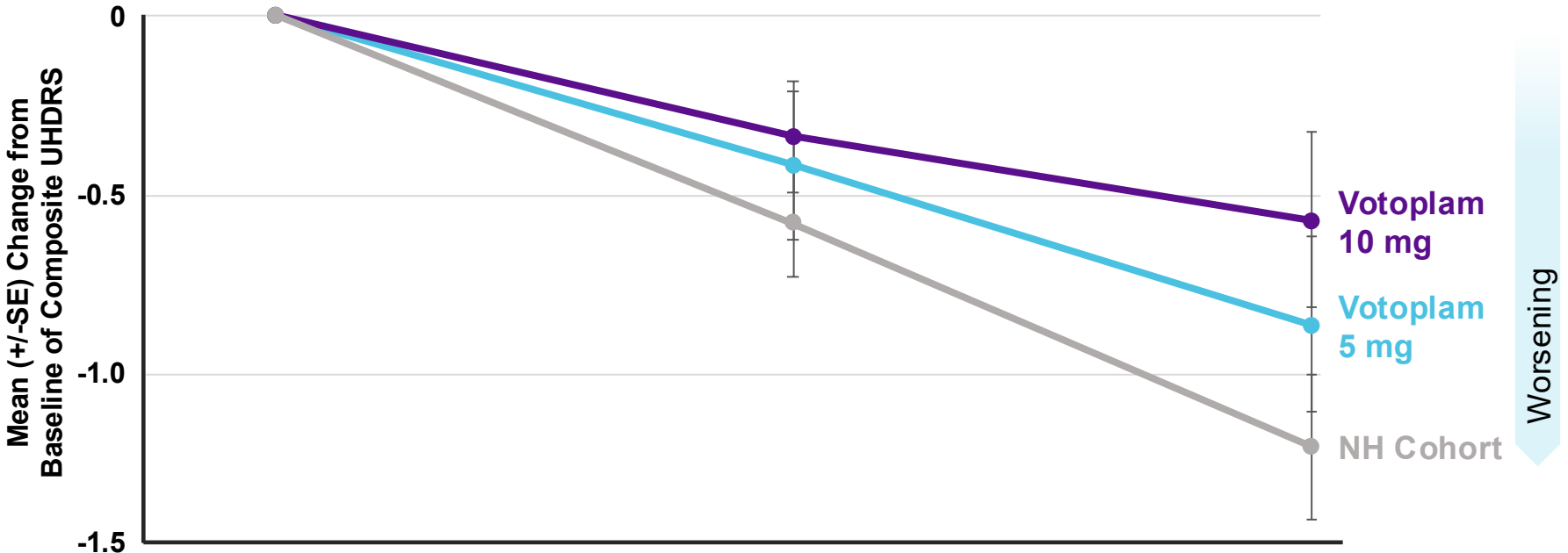
Variables Used for Identification of Natural History Cohort	
Sex	Total Functional Capacity (TFC)
Age	Symbol Digit Modalities Test (SDMT)
CAG repeats	Stroop Word Reading Test (SWRT)
Independence Score (IS)	Total Motor Score (TMS)

Natural History Cohort Well Matched to Votoplam Treated Population

Demographics and Baseline Disease Characteristics	Stage 2			Stage 3		
	Votoplam 5 mg (N=21)	Votoplam 10 mg (N=24)	NH Cohort (N=73)	Votoplam 5 mg (N=22)	Votoplam 10 mg (N=24)	NH Cohort (N=67)
Sex (% Male)	52.4%	45.8%	54.9%	54.5%	58.3%	56.7%
Age	45.6	46.7	47.0	53.2	49.2	51.2
CAG repeats	44.1	43.8	43.8	43.0	44.3	43.6
cUHDRS	14.3	14.5	14.5	11.6	11.9	11.4
Total Functional Capacity (TFC)	13.0	13.0	13.0	11.6	11.9	11.6
SDMT	41.1	38.7	39.7	31.1	31.4	30.7
SWRT	80.0	86.4	84.4	70.3	72.6	69.9
Total Motor Score (TMS)	12.9	11.2	11.4	22.0	22.3	24.4
Independence Score (IS)	100.0	100.0	100.0	89.8	91.0	88.7

Groups well matched based on Standardized Mean Difference (SMD) < 0.05 for all matching variables

Dose-dependent Slowing of Disease Progression on cUHDRS at 24 months in Stage 2 Participants

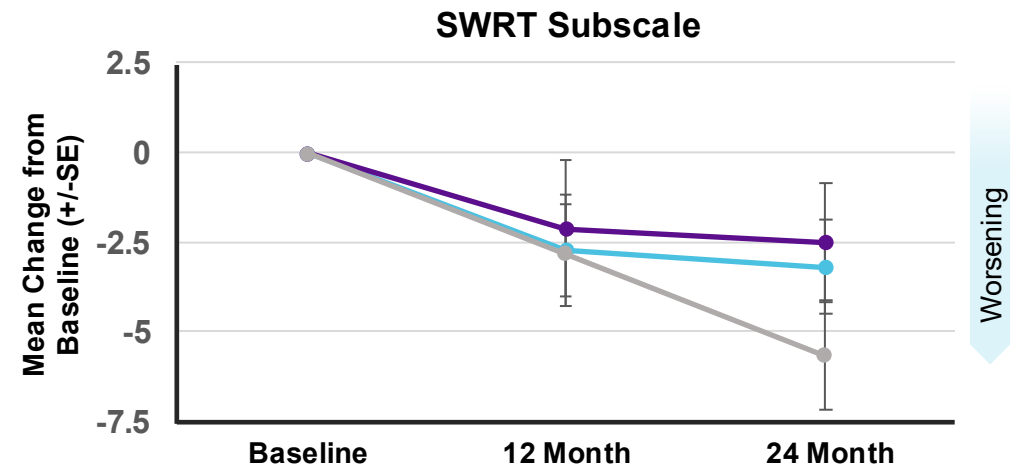
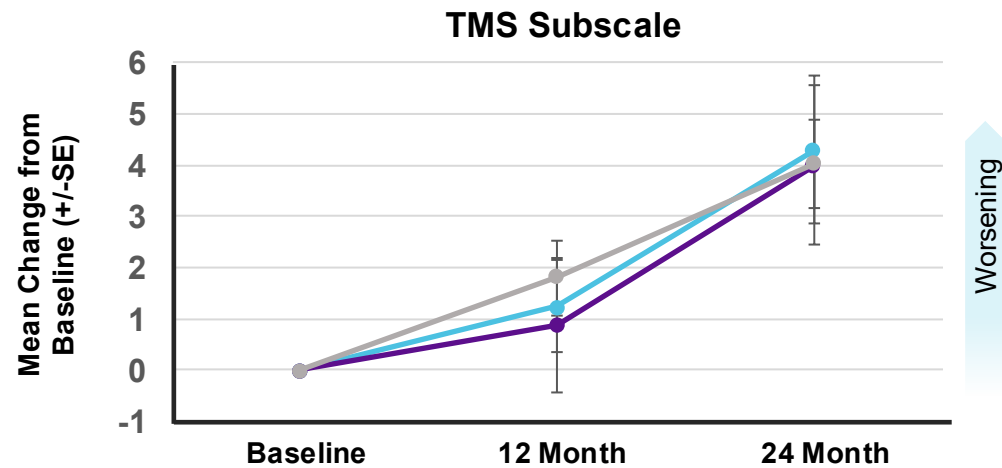
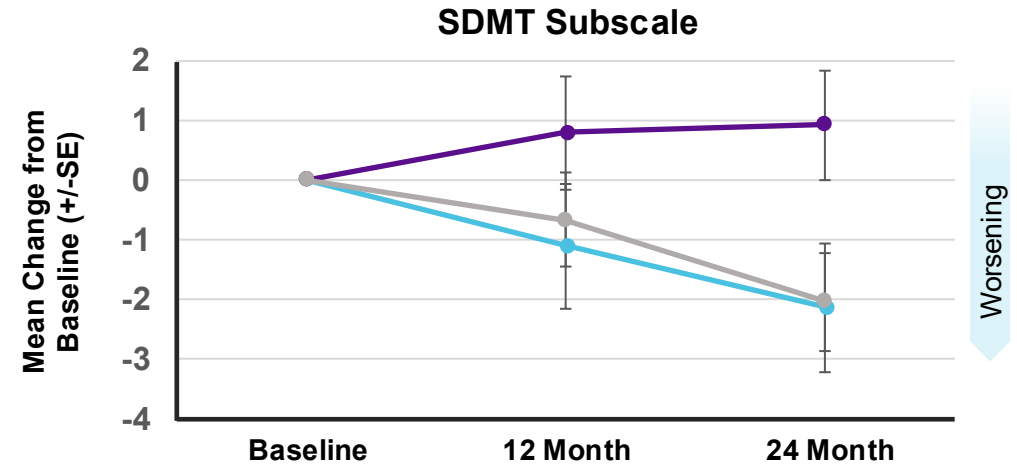
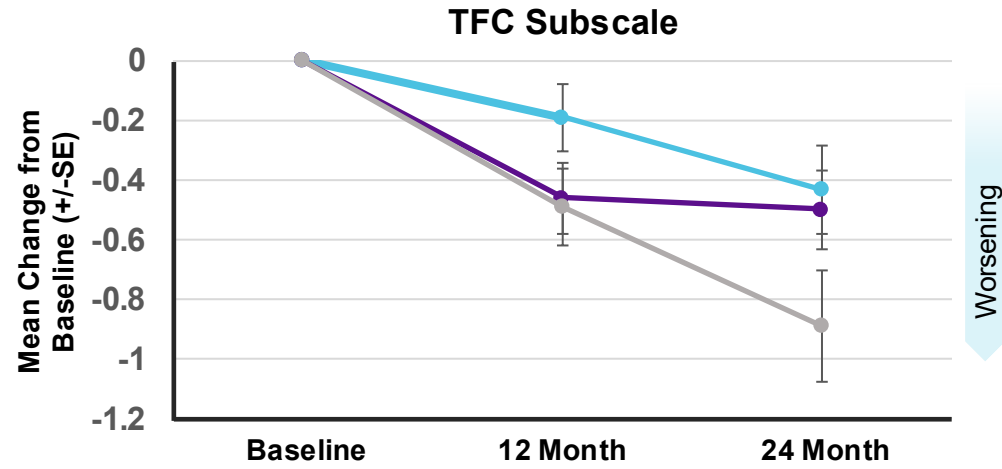


Mean difference in cUHDRS progression of 52% (10mg) and 28% (5mg) at Month 24

Baseline	12 Month	24 Month
Treatment Group	Mean (SE)	Mean (SE)
Natural History (N=73)	-0.58 (0.15)	-1.20 (0.20)
5 mg (N=21)	-0.42 (0.16)	-0.86 (0.24)
10 mg (N=24)	-0.34 (0.21)	-0.57 (0.24)

Results based on observed data

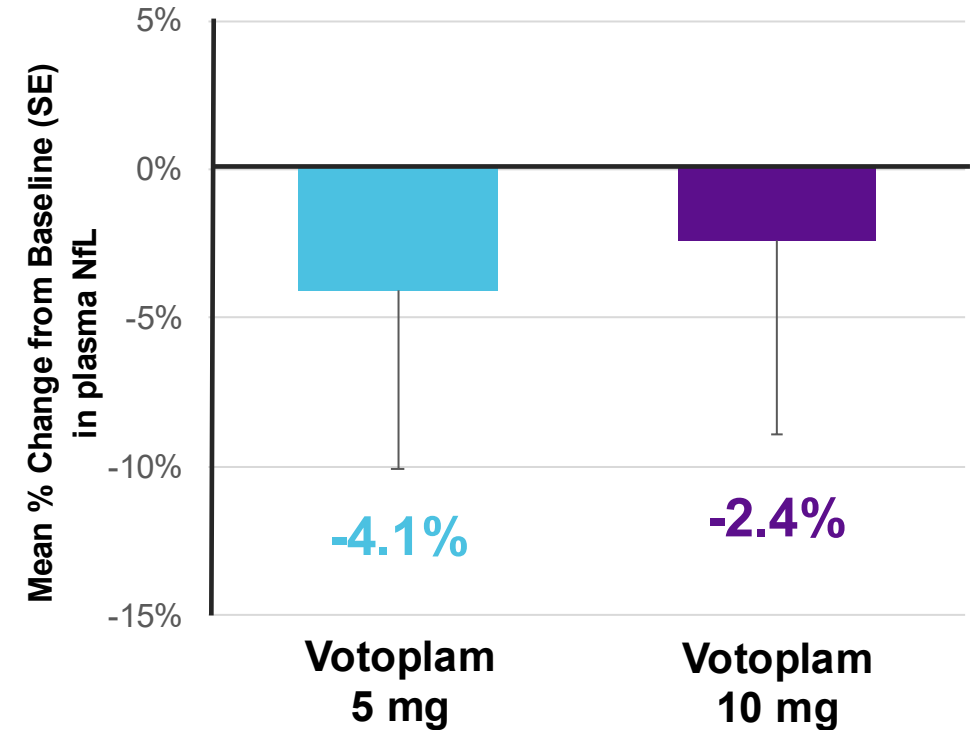
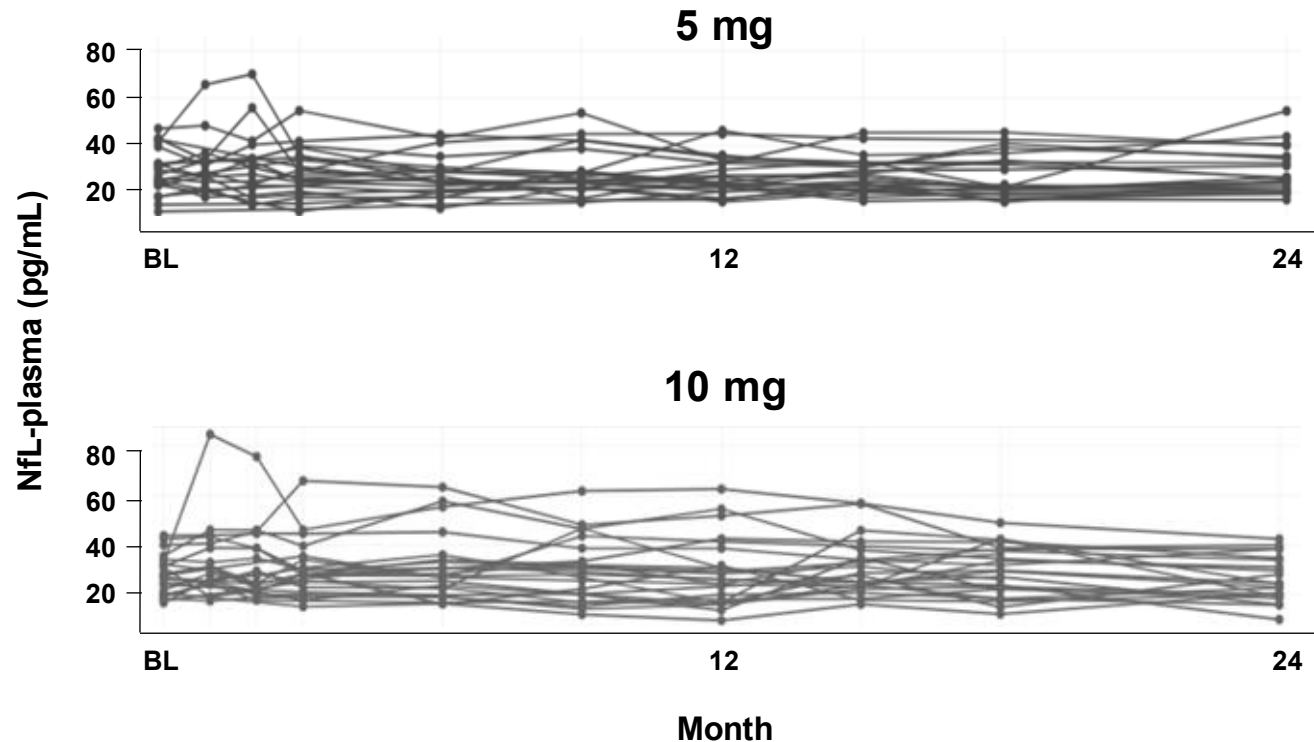
Evidence of Treatment Benefit Across cUHDRS Subscales for Stage 2 Participants



— NH Cohort — Votoplam 5 mg — Votoplam 10 mg

Results based on observed data

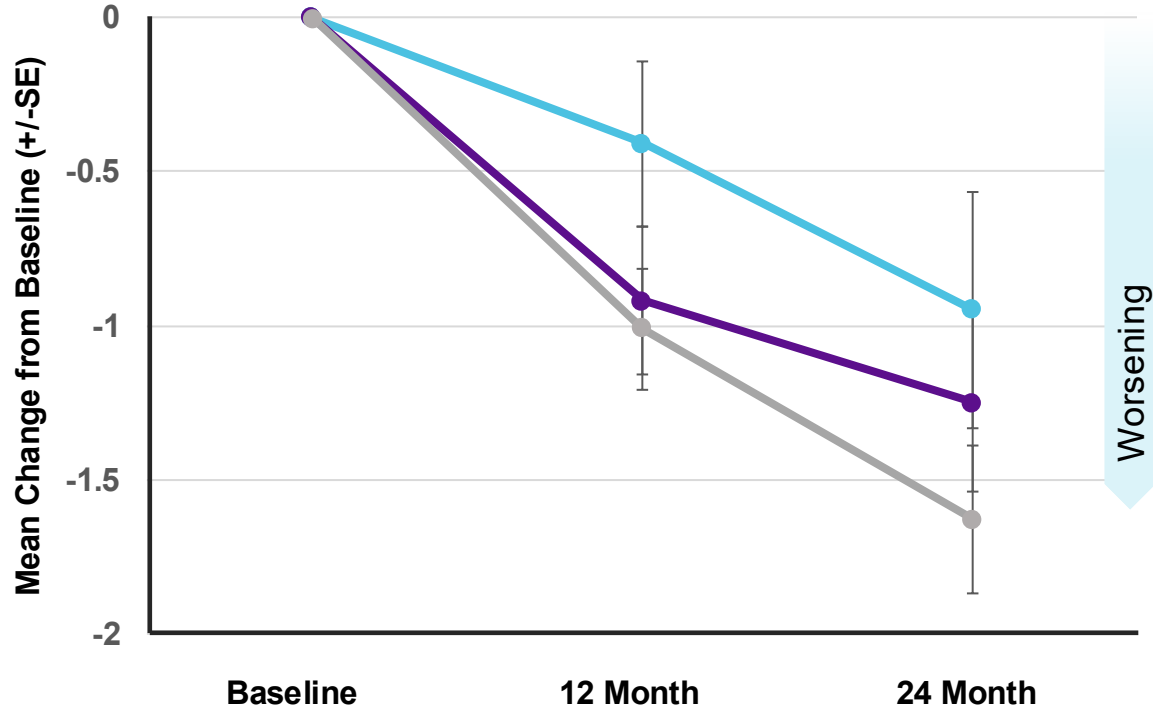
No Evidence of Treatment-related NfL Spikes at Month 24, with Mean Levels Below Baseline



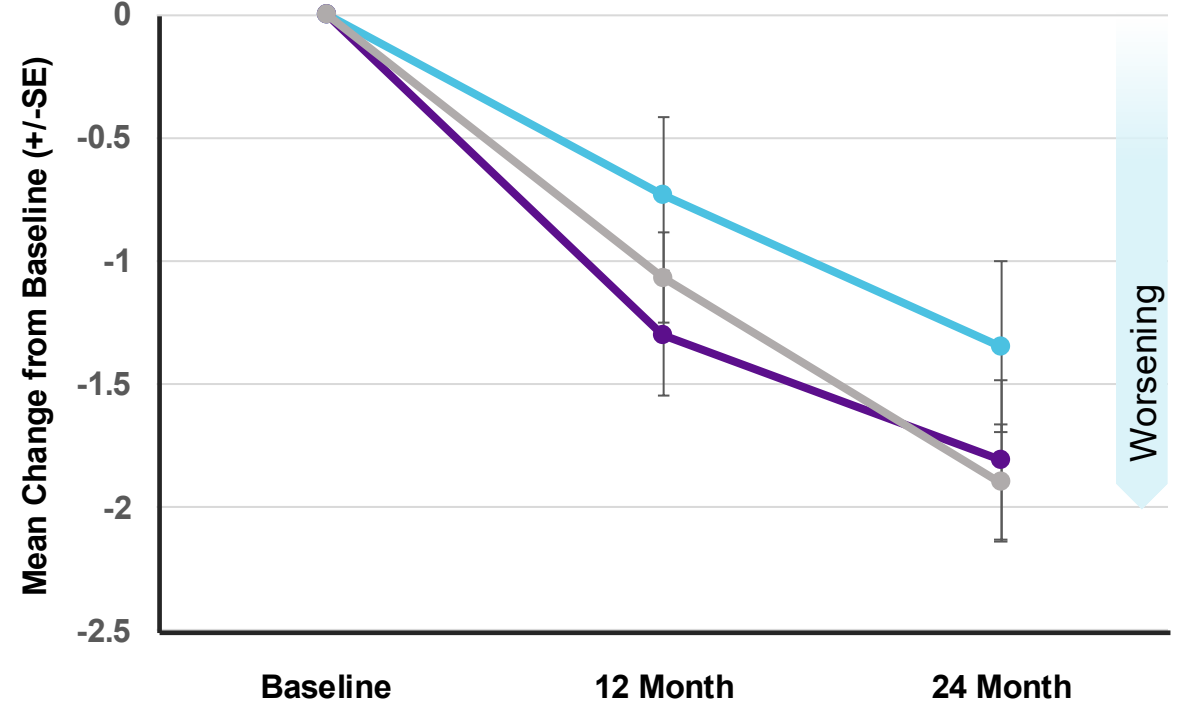
Plasma NfL reported to increase over time based on natural history*

Benefit Signals Observed at Month 24 in Stage 3 Participants

TFC Subscale



cUHDRS



Results based on observed data

— NH Cohort — Votoplam 5 mg — Votoplam 10 mg

Votoplam Treatment Continues to Show Favorable Safety Profile at Month 24 in Stage 2 and 3 Participants



Votoplam safety profile remains favorable after 24 months of treatment



No new AE signals identified at 24 months



Safety profile consistent for both dose levels and stages

Votoplam Treatment Showed Favorable Safety Profile at Month 24 in Stage 2 and 3 Participants

AE Category	PIVOT-HD		
	Placebo N (%)	Votoplam 5 mg N (%)	Votoplam 10 mg N (%)
Any TEAEs	46 (86.8)	43 (82.7)	49 (90.7)
Any TESAEs	4 (7.5)	1 (1.9)	2 (3.7)
Any TEAEs resulting in death	1 (1.9)	1 (1.9)	0
Any TEAEs leading to treatment discontinuation	0	1 (1.9)	2 (3.7)
TEAEs by maximum severity			
Grade 1	27 (50.9)	23 (44.2)	20 (37.0)
Grade 2	15 (28.3)	18 (34.6)	24 (44.4)
Grade 3	2 (3.8)	1 (1.9)	5 (9.3)
Grade 4	1 (1.9)	0	0
Grade 5	1 (1.9)	1 (1.9)	0

Long-Term Extension*	
Votoplam 5 mg N (%)	Votoplam 10 mg N (%)
38 (86.4)	45 (91.8)
3 (6.8)	3 (6.1)
0	0
0	0
20 (45.5)	23 (46.9)
16 (36.4)	18 (36.7)
2 (4.5)	3 (6.1)
0	1 (2.0)
0	0

*Grade 3 and 4 AEs not treatment related

INVEST-HD Global Phase 3 Trial Initiated by Novartis

INVEST-HD* Global Phase 3 Study Overview

- Individuals with early symptomatic disease
- 3:2 randomization of voptoplam 10mg: placebo
- Target enrollment: ~770 participants in >30 countries
- Primary endpoint: Change from baseline in cUHDRS
- Treatment period up to 36 months
- Interim analysis planned for efficacy and futility



*Study sponsored and funded by Novartis; NCT#: NCT07326709

Summary and Next Steps



Evidence of dose-dependent disease slowing on cUHDRS in Stage 2 participants



Continued evidence of favorable safety profile with no new AE signals identified



Align with partner Novartis on plans for potential regulatory interactions to discuss data

