

PIVOT-HD Topline Results

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The logo for PIVOT HD features the word "PIVOT" in a large, white, sans-serif font. A thick blue line starts at the bottom of the letter "V", curves downwards and then to the right, ending in an arrowhead that points to the letters "HD". The "HD" is in a smaller, white, sans-serif font.

Forward Looking Statements

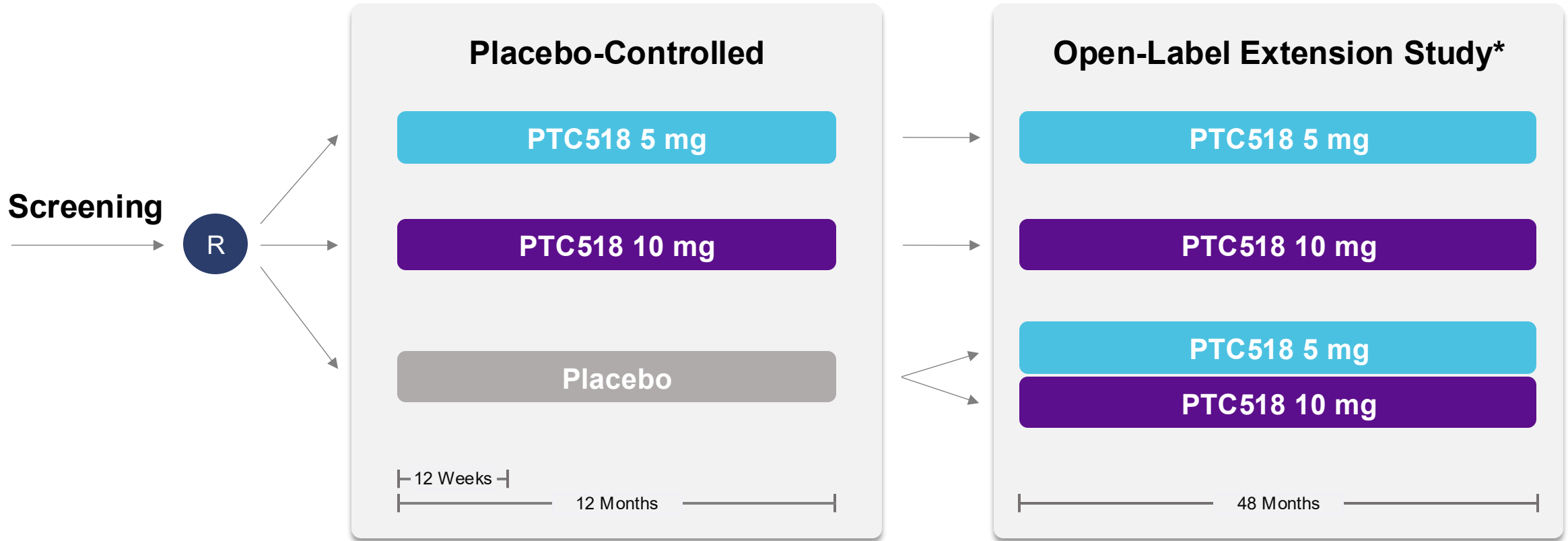
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PIVOT-HD Study Design



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

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

Dose-Dependent mHTT Lowering and Safety Confirmed with Signals of Longer-term Dose-Dependent Biomarker and Clinical Effect



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



Long-term positive clinical trends at Month 24 relative to natural history and dose-dependent NfL lowering



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



Continued favorable safety and tolerability profile with no treatment-related NfL spikes

12-Month Topline Results

PIVOT
HD

Baseline Characteristics of Enrolled Subjects



Baseline Characteristic	Stage 2			Stage 3		
	Placebo (N=29)	PTC518 5 mg (N=27)	PTC518 10 mg (N=25)	Placebo (N=24)	PTC518 5 mg (N=25)	PTC518 10 mg (N=29)*
Age (years) mean	45.4	45.5	46.8	52.4	53.1	48.7
Gender, n (%)						
Male	19 (65.5%)	12 (44.4%)	12 (48.0%)	14 (58.3%)	14 (56.0%)	17 (58.6%)
Female	10 (34.5%)	15 (55.6%)	13 (52.0%)	10 (41.7%)	11 (44.0%)	12 (41.4%)
CAG length						
Mean (SD)	44.3 (2.45)	44.1 (2.03)	43.7 (2.61)	43.2 (2.17)	43.1 (2.65)	44.1 (2.97)
Min – Max	41 – 49	41 – 49	41 – 50	40 – 48	40 – 50	40 – 50
TFC (Total Functional Capacity) Score Mean	13.0	13.0	13.0	11.6	11.6	11.9

PTC518 Treatment Resulted in Dose-Dependent Blood HTT Lowering

Stage 2

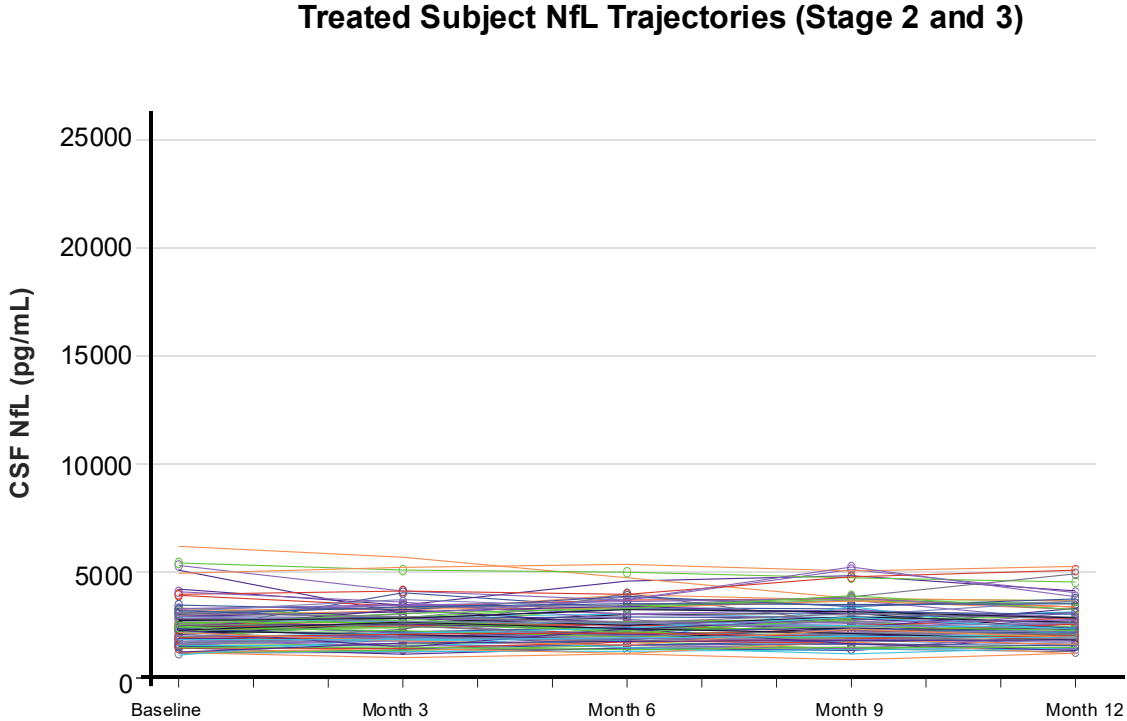
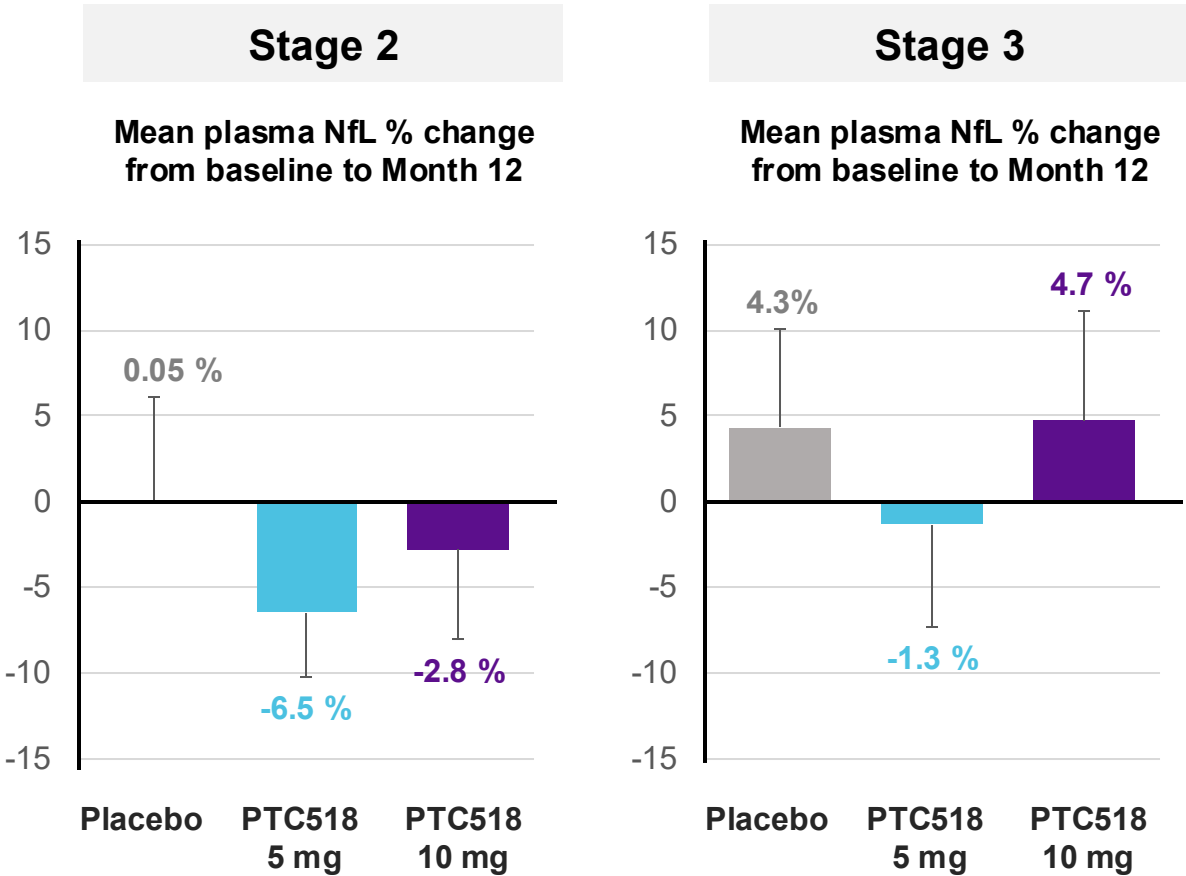
Biomarker	Month 12	
	Mean (SD) Treatment Effect	
	PTC518 5 mg	PTC518 10 mg
mHTT Blood (95% CI)	-23.4% (-34.4, -12.4)	-39.1% (-49.4, -28.7)
mHTT CSF (95% CI)	-23.2% (-51.4, 4.9)	-26.3% (-53.7, 1.1)

Stage 3

Biomarker	Month 12	
	Mean (SD) Treatment Effect	
	PTC518 5 mg	PTC518 10 mg
mHTT Blood (95% CI)	-23.3% (-33.4, -13.2)	-36.1% (-45.9, -26.4)
mHTT CSF (95% CI)	-20.8% (-47.4, 5.7)	-22.3% (-48.3, 3.6)

**Primary Endpoint of Blood HTT Lowering at Week 12
Achieved (p<0.0001) and Maintained at Month 12 (p<0.0001)**

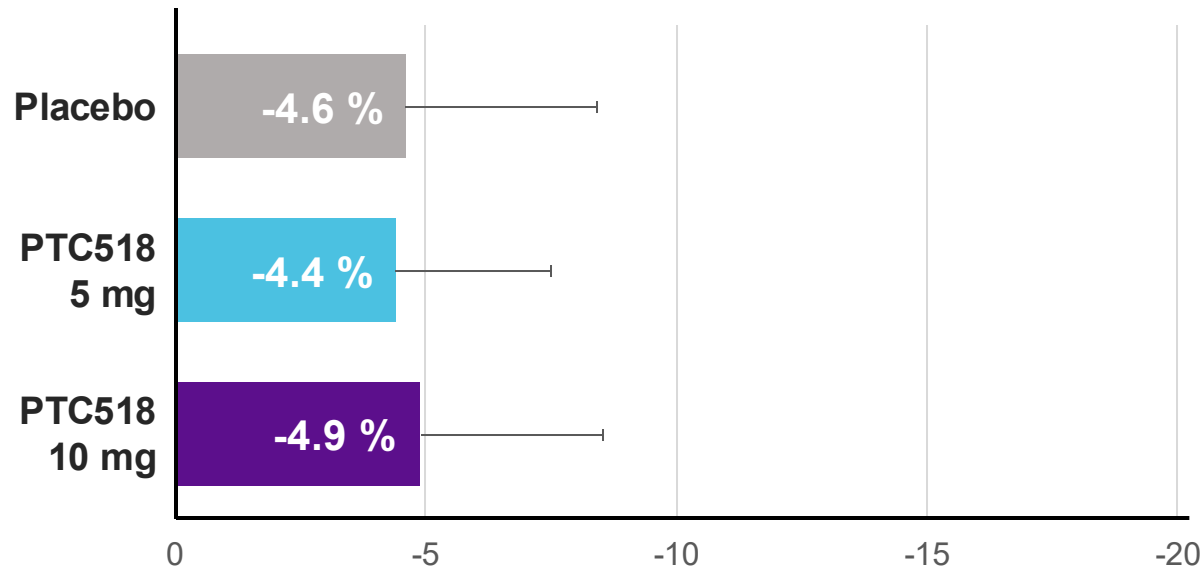
Favorable Trends of NfL Lowering in Stage 2 Subjects and no Treatment-Related Spikes



Caudate Brain Volume Changes Across Treatment Groups

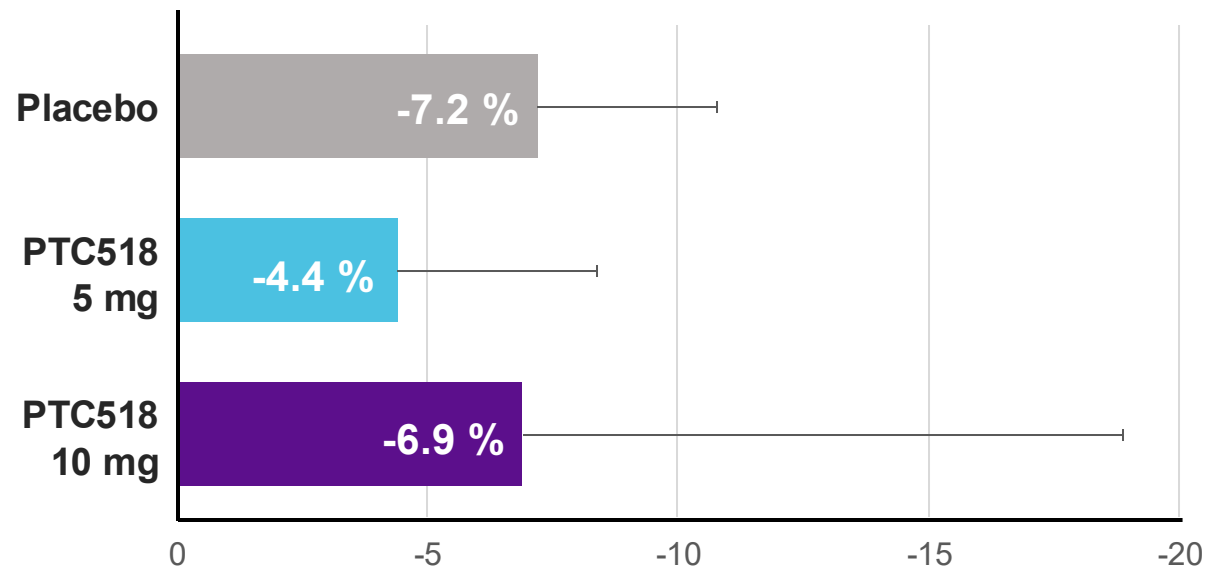
Stage 2

Mean (SD) % change from baseline to Month 12



Stage 3

Mean (SD) % change from baseline to Month 12



Early Signals of Favorable Effect on Clinical Scales in Stage 2 Subjects



Stage 2

Clinical Scale	Mean (SD) Change Baseline to Month 12		
	Placebo (N=29)	PTC518 5 mg (N=27)	PTC518 10 mg (N=25)
cUHDRS	-0.49 (1.25)	-0.41 (0.70)	-0.27 (0.99)
TFC	-0.3 (0.78)	-0.2 (0.49)	-0.5 (0.59)
TMS	3.3 (5.45)	1.5 (4.10)	0.7 (6.39)
SDMT	0.0 (5.39)	-1.1 (4.57)	1.1 (4.79)
SWR	-1.8 (13.16)	-2.4 (7.97)	-1.7 (8.76)

Stage 3

Clinical Scale	Mean (SD) Change Baseline to Month 12		
	Placebo (N=24)	PTC518 5 mg (N=25)	PTC518 10 mg (N=29)
cUHDRS	-0.82 (1.26)	-0.78 (1.40)	-1.43 (1.32)
TFC	-0.5 (0.95)	-0.4 (1.24)	-1.2 (1.56)
TMS	1.9 (7.01)	3.6 (5.90)	5.5 (7.27)
SDMT	-1.7 (5.99)	-0.7 (6.52)	-2.6 (3.75)
SWR	-5.3 (12.42)	-5.6 (10.20)	-3.8 (11.97)

Lower scores on cUHDRS, TFC, SDMT and SWR reflect worsening disease; higher scores on TMS reflect worsening disease

PTC518 Treatment Showed Favorable Safety and Tolerability Profile at Month 12



PTC518 was well tolerated with no treatment-related SAEs nor dose-limiting toxicities



Similar adverse event profile across all treatment groups and disease stages, including placebo



Most common adverse events were nasopharyngitis, influenza, headache and falls

PTC518 Treatment Showed Favorable Safety and Tolerability Profile at Month 12

AE Category	Stage 2			Stage 3		
	Placebo (N=29)	PTC518 5 mg (N=27)	PTC518 10 mg (N=25)	Placebo (N=24)	PTC518 5 mg (N=25)	PTC518 10 mg (N=29)
TEAEs, n (%)	26 (89.7)	22 (81.5)	22 (88.0)	20 (83.3)	21 (84.0)	27 (93.1)
TESAEs,* n (%)	3 (10.3)	1 (3.7)	1 (4.0)	1 (4.2)	0	1 (3.4)
TEAEs resulting in death, n (%)	0	1 (3.7)	0	1 (4.2)	0	0
TEAEs leading to treatment discontinuation, n (%)	0	0	0	0	1 (4.0)	2 (6.9)
TEAEs by maximum severity, n (%)						
Grade 1	15 (51.7)	10 (37.0)	8 (32.0)	12 (50.0)	13 (52.0)	12 (41.4)
Grade 2	8 (27.6)	10 (37.0)	12 (48.0)	7 (29.2)	8 (32.0)	12 (41.4)
Grade 3	2 (6.9)	1 (3.7)	2 (8.0)	0	0	3 (10.3)
Grade 4	1 (3.4)	0	0	0	0	0
Grade 5	0	1 (3.7)	0	1 (4.2)	0	0

Month 12 Results Confirm Dose-Dependent mHTT Reduction, Safety and Early Trends of Favorable Clinical Effect



Dose-dependent and durable lowering of HTT protein in blood



Early trends of favorable effect on clinical scales for Stage 2 subjects



Favorable safety profile with no treatment-related NfL spikes

24-Month Interim Results

Baseline Characteristics of Subjects Included in 24-Month Interim Results (Stage 2)

Baseline Characteristic	PTC518 5 mg (N=10)	PTC518 10 mg (N=11)
Age (years) Mean	44.7	46.8
Gender, n (%)		
Male	5 (50.0)	6 (54.5)
Female	5 (50.0)	5 (45.5)
CAG length		
Mean (SD)	44.5 (2.07)	43.7 (2.41)
Min – Max	42 – 49	42 – 50
TFC (Total Functional Capacity) Score		
Mean	13.0	13.0

Natural History Comparative Analysis Utilizing ENROLL-HD Disease Registry

ENROLL-HD matched to enrollment criteria of PIVOT-HD

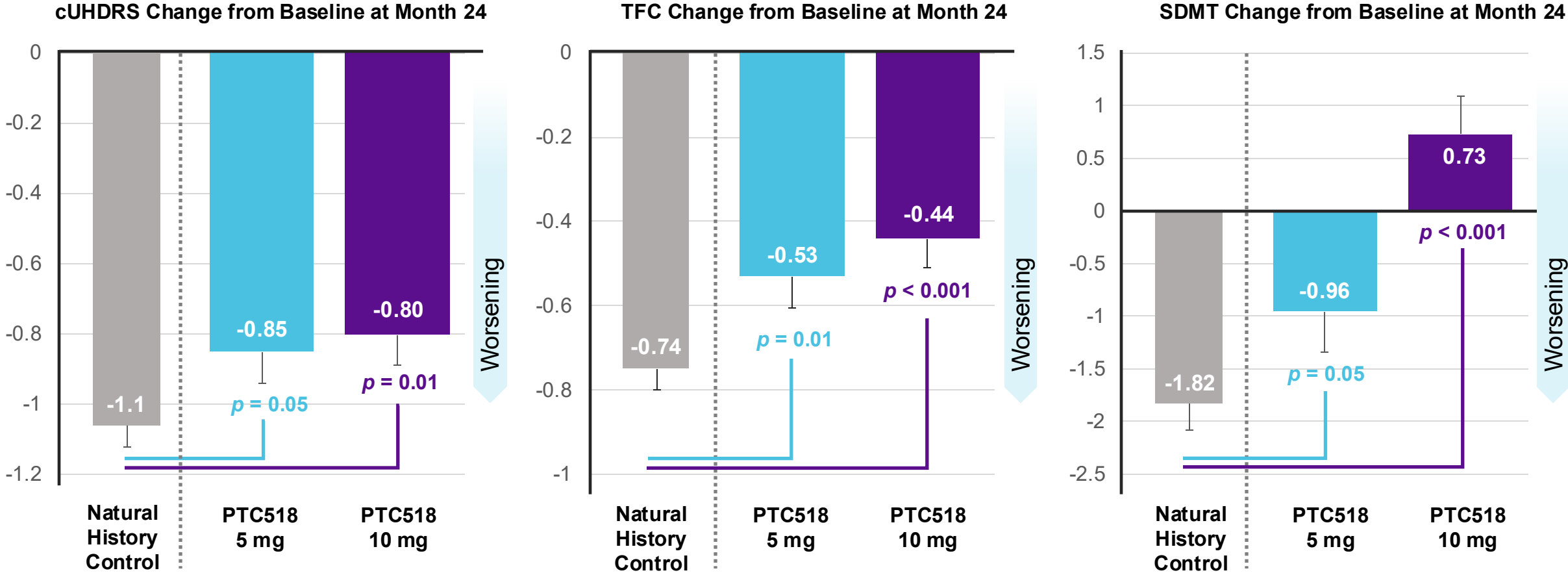
- Age \geq 25 years
- CAG between 40 and 50
- TFC score of 13
- IS score of 100
- PIN_{HD} score between 0.18 to 4.93

1,045 Subjects Identified



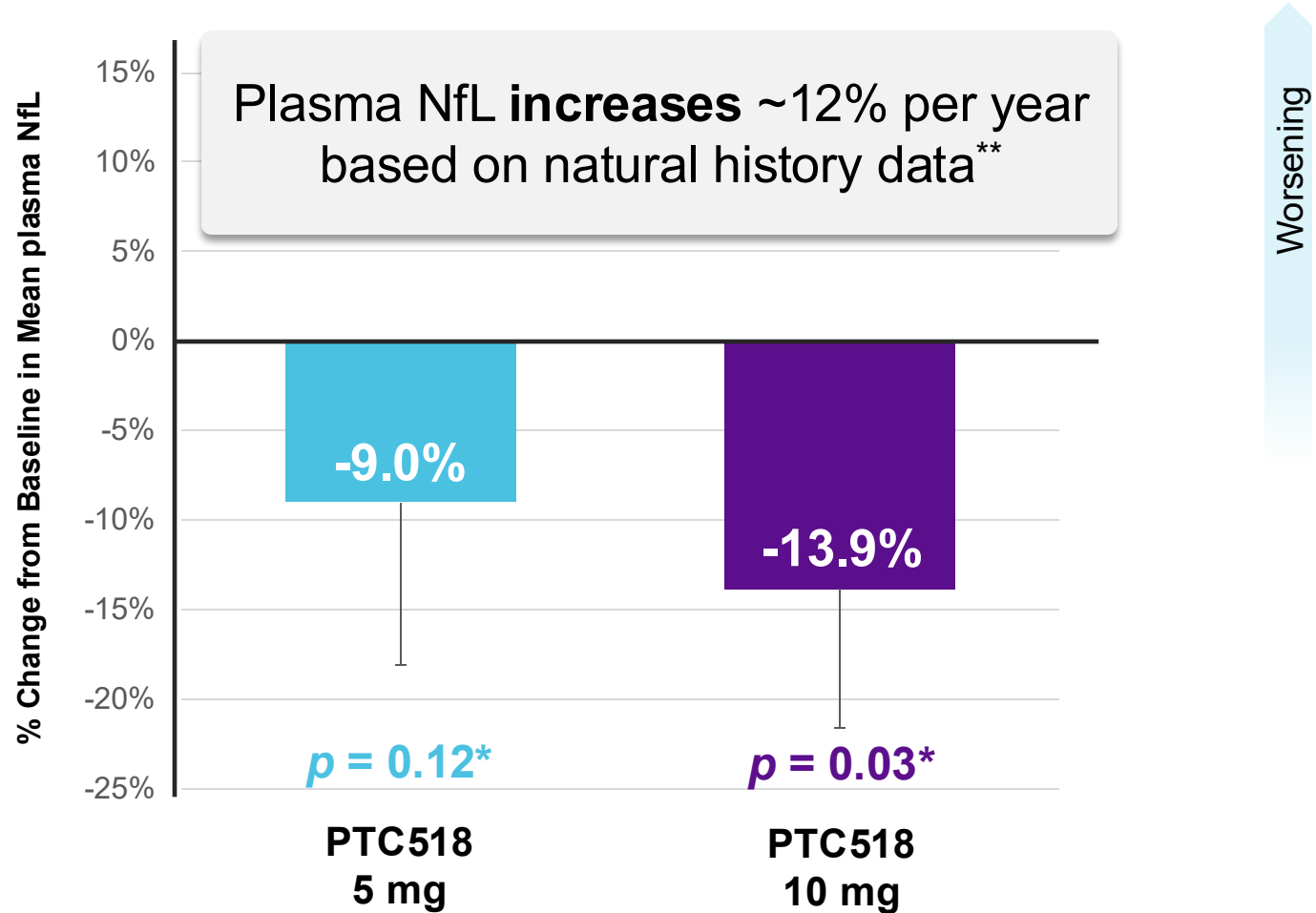
- Propensity score weighting analysis applied to compare **PTC518 treated subjects** to **Natural History** cohort
- Propensity scores calculated with seven prognostic factors

Favorable Effect on cUHDRS at Month 24 Relative to Propensity-Matched Natural History



TMS trend at Month 12 not maintained at Month 24

Dose-Dependent NfL Lowering From Baseline At Month 24



PTC518 Treatment Continues to Show Favorable Safety and Tolerability Profile at Month 24



PTC518 was well tolerated, with no dose-limiting toxicities



Adverse event profile remains consistent through Month 24



No reported treatment-related SAEs nor NfL spikes at Month 24

Favorable Trends of Slowing of Progression and NfL Lowering at Month 24



Dose-dependent clinical trends of disease slowing relative to matched natural history at Month 24



Dose-dependent NfL lowering at Month 24

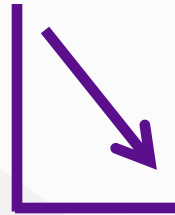


Continued favorable safety and tolerability profile

Summary and Next Steps



Primary endpoint reached with durable mHTT lowering, safety and signals of clinical effect in Stage 2 patients



Dose-dependent trends on clinical scales and NfL lowering at Month 24



Complete data analyses and plan for development and regulatory discussions

