PIVOT-HD Interim Results

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PTC THERAPEUTICS™

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Week 12 Interim Readout Met Key Objectives

PTC518 treatment resulted in dose-dependent lowering of HTT mRNA and protein levels in blood cells

PTC518 demonstrated desired CSF exposure with higher concentrations of free drug in the CSF than plasma

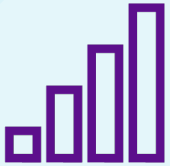
PTC518 was well tolerated with no treatment-related serious adverse events and no reports of peripheral neuropathy

CSF NfL levels remained stable after 12 weeks of treatment with no treatment-related spikes

Key Objectives for Month 12 Interim Results

Demonstrate durability of HTT protein lowering with PTC518 in blood cells

Demonstrate evidence of activity on disease biomarkers



Demonstrate evidence of CNS activity on functional clinical scales

Demonstrate continued safety and tolerability of PTC518 over 12 months

Evidence of Durability of Effect, Safety and Dose-Dependent Benefit on Clinical Measures

PIVOT HD

Dose-dependent and durable lowering of HTT protein in blood at 12 months

Dose-dependent lowering of CSF mHTT levels

Dose-dependent trends of improvement on key clinical measures including TMS and cUHDRS

PTC518 was well tolerated with no evidence of treatment-related NfL spikes at 12 months

FDA Partial Clinical Hold Lifted

Note: Results based on interim readout

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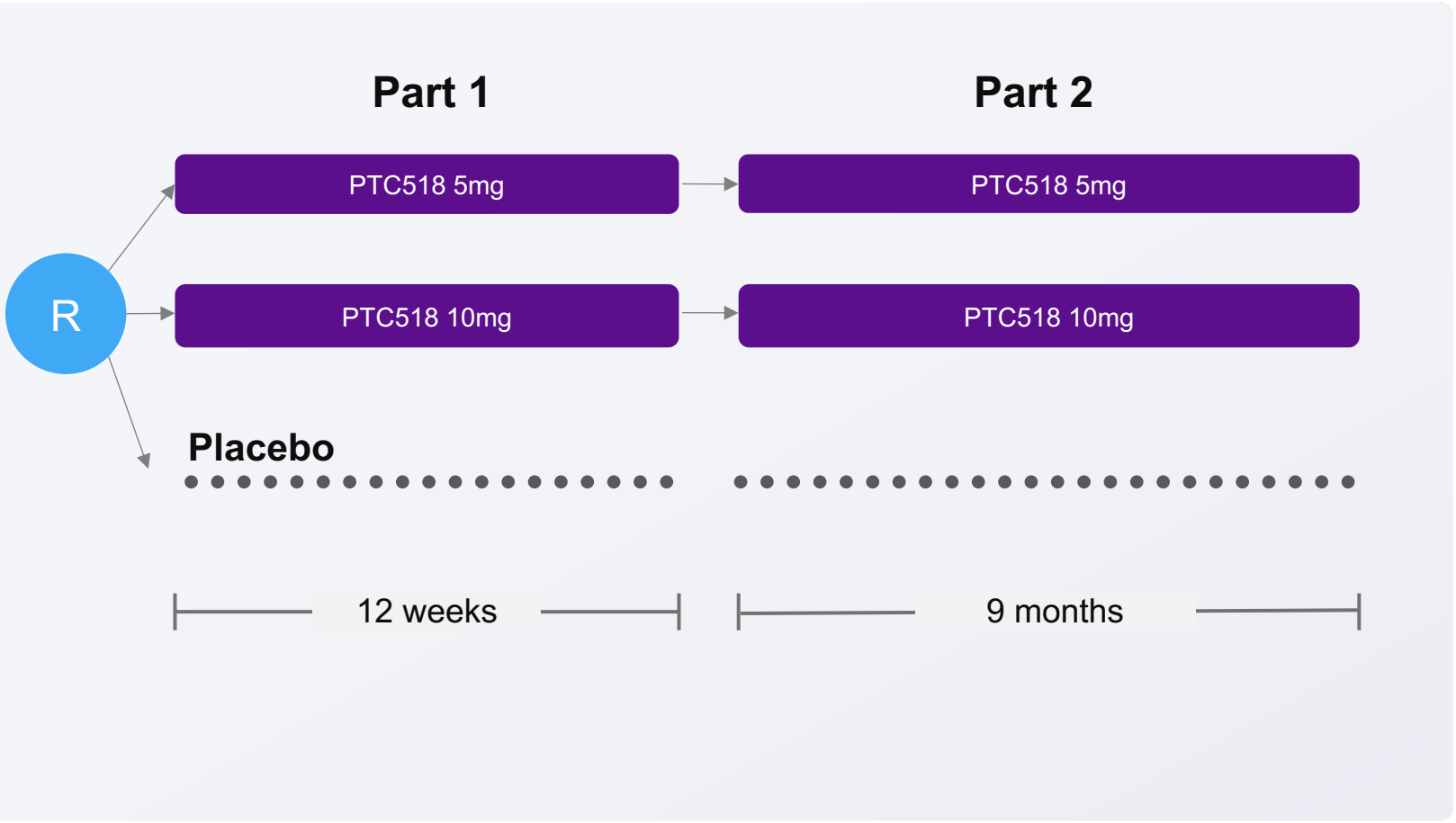
PIVOT-HD Study Design



Week 12 Endpoints

- Safety and tolerability
- Blood HTT mRNA and protein lowering
- CNS exposure

Month 12 Endpoints

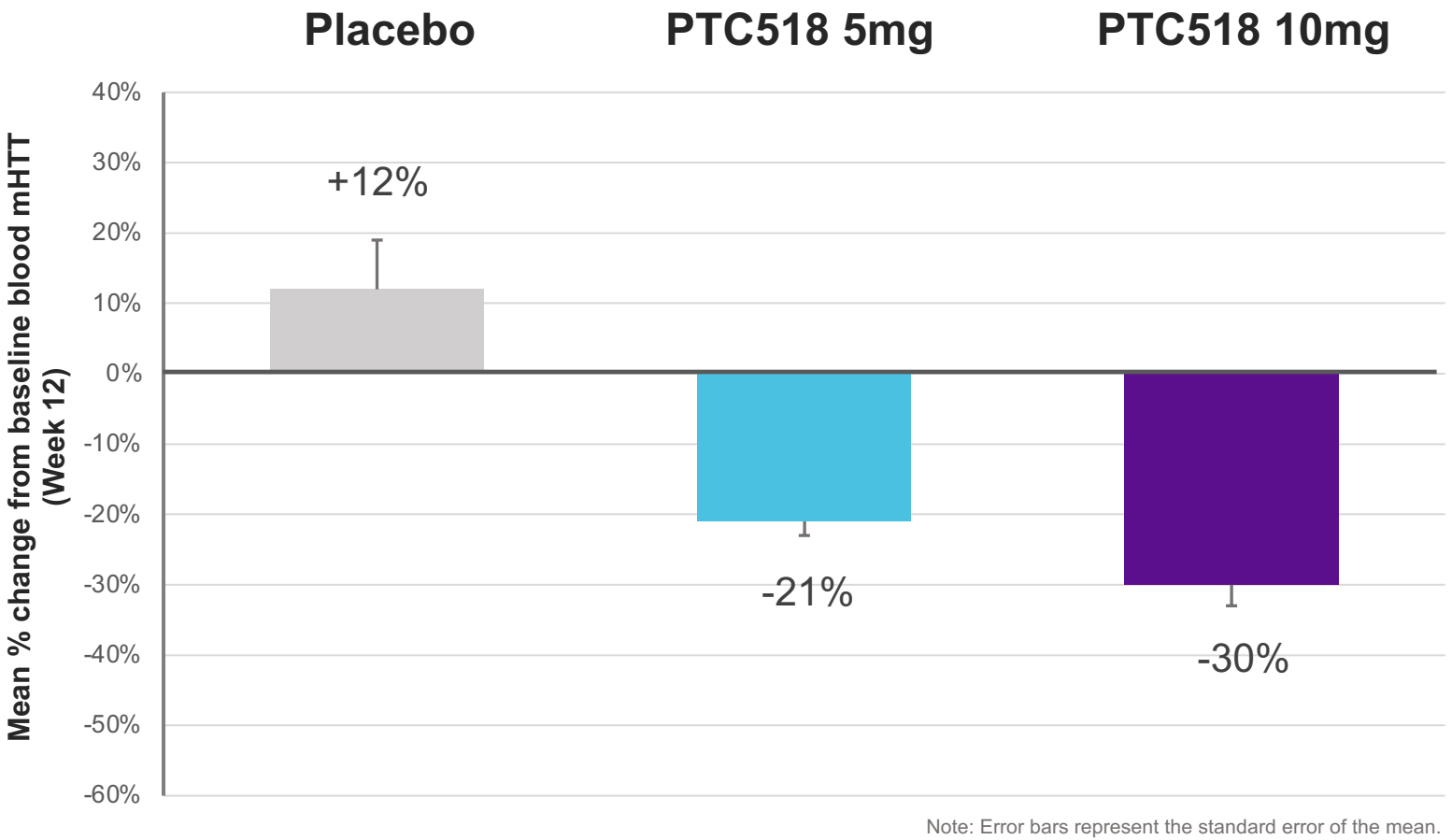
- CSF HTT protein lowering
- CNS biomarkers
- HD clinical scales

Cohort of Month 12 Patient Characteristics

Category	Placebo (N=10)	PTC518 5mg (N=10)	PTC518 10mg (N=12)	Overall (N=32)
Age (years) mean	47.4	45.3	46.9	46.6
Gender, n (%)				
Male	7 (70.0%)	4 (40.0%)	7 (58.3%)	18 (56.3%)
Female	3 (30.0%)	6 (60.0%)	5 (41.7%)	14 (43.8%)
CAG length				
Mean (SD)	44.3 (2.00)	44.1 (2.13)	43.7 (2.31)	44.0 (2.11)
Min – Max	42 – 47	42 – 49	42 – 50	42 – 50
TFC (Total Functional Capacity) Score				
Mean	13	13	13	13

Blood HTT Protein Lowering Results

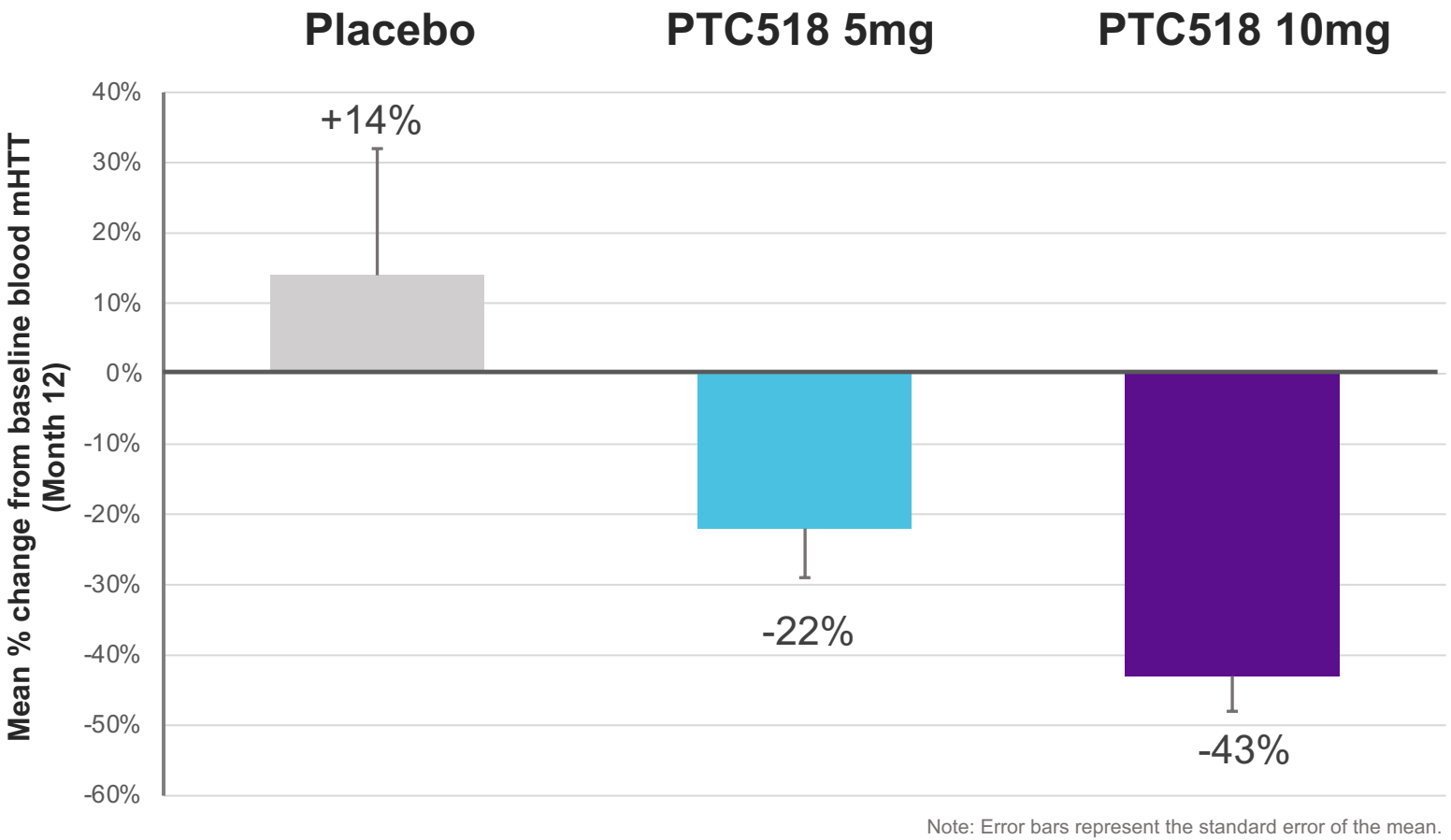
PTC518 Treatment Resulted in Dose-Dependent Blood mHTT Protein Lowering at Week 12 (June 2023)



Note: Error bars represent the standard error of the mean.

Dose-dependent lowering of HTT protein

PTC518 Treatment Results in Durable, Dose-Dependent Blood mHTT Protein Lowering at Month 12



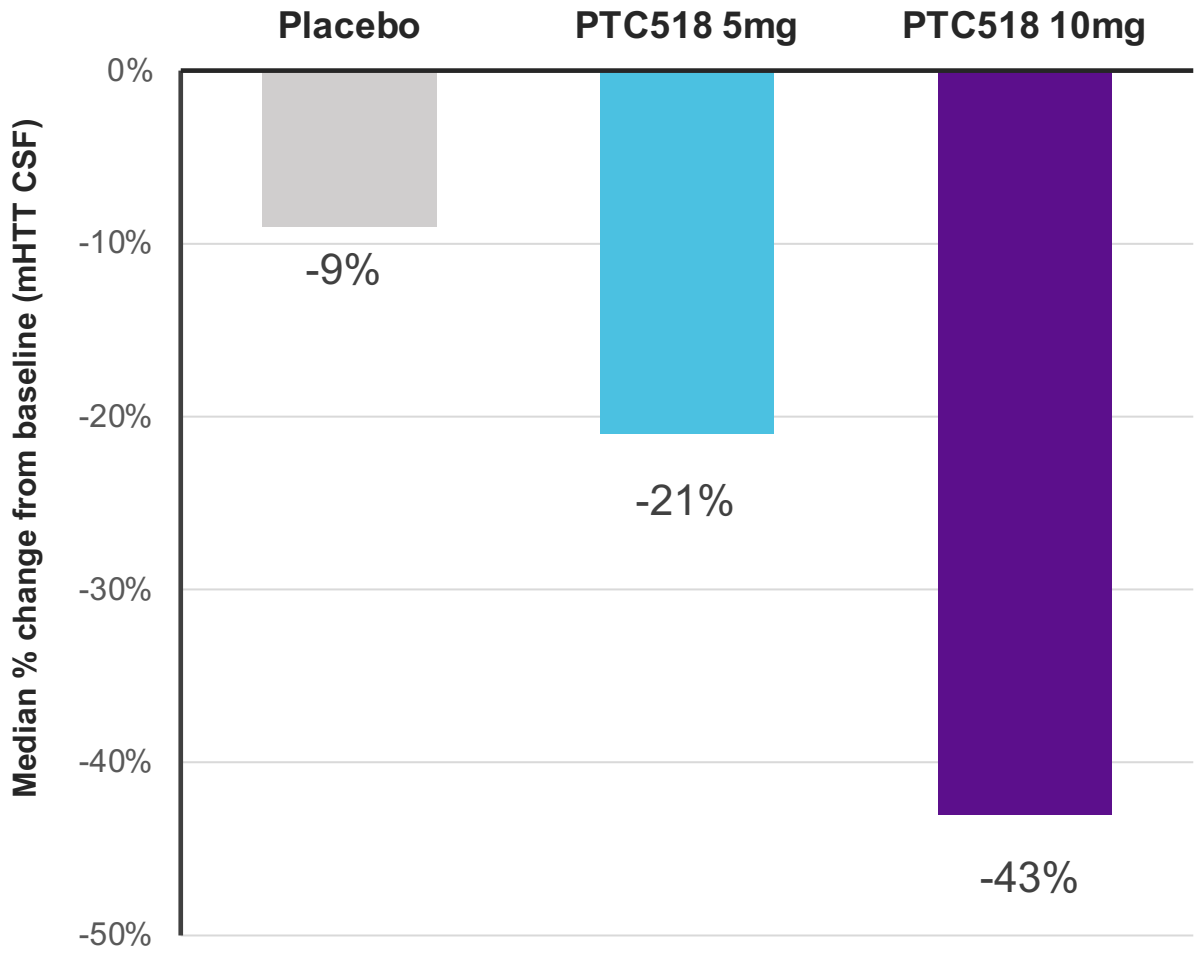
Note: Error bars represent the standard error of the mean.

Dose-dependent lowering of HTT protein with steady state reached at 6-9 months

Note: For each subject the mean values of pre- and post-treatments are used

Biomarker and Clinical Scale Results

PTC518 Treatment Results in Dose-Dependent CSF mHTT Protein Lowering at Month 12



CSF protein lowering consistent with protein lowering in blood

NfL Levels Consistent Across Treatment Groups With No Evidence of Treatment-Related Spikes

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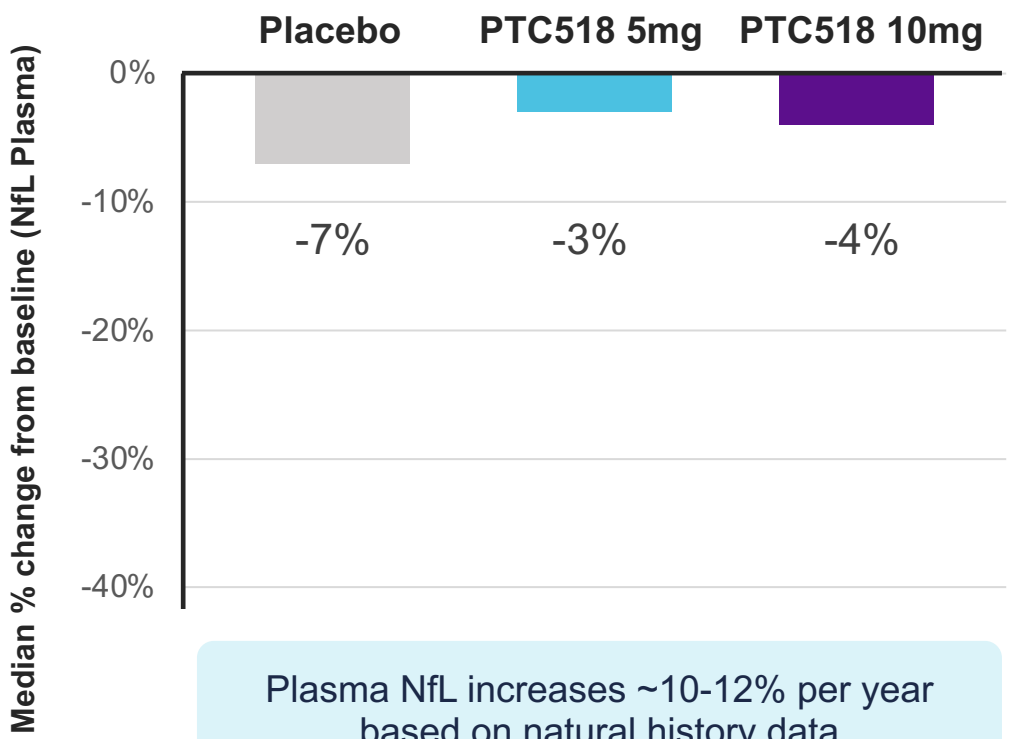
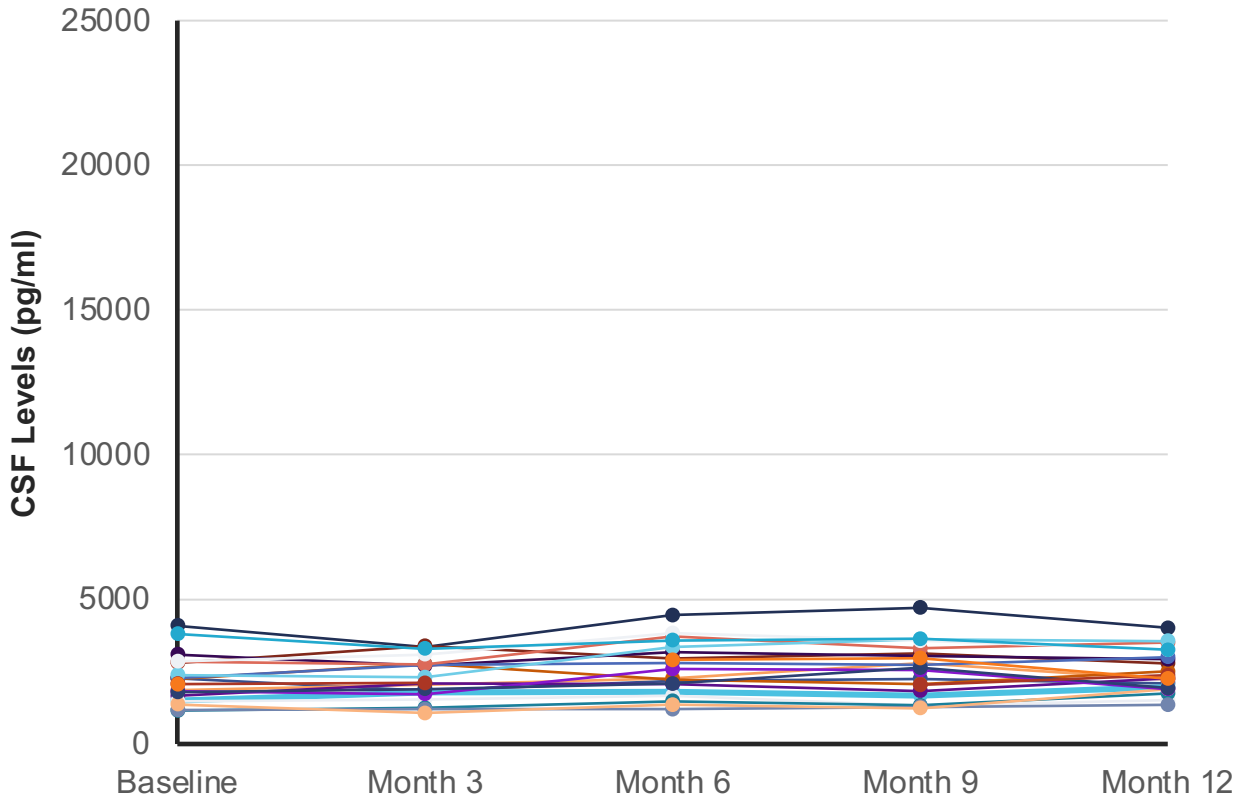
Change in Plasma NfL Levels from Baseline to Month 12



Plasma NfL increases ~10-12% per year based on natural history data

Individual Subject CSF NfL Trajectories



Note: One patient excluded due to non-treatment related viral syndrome

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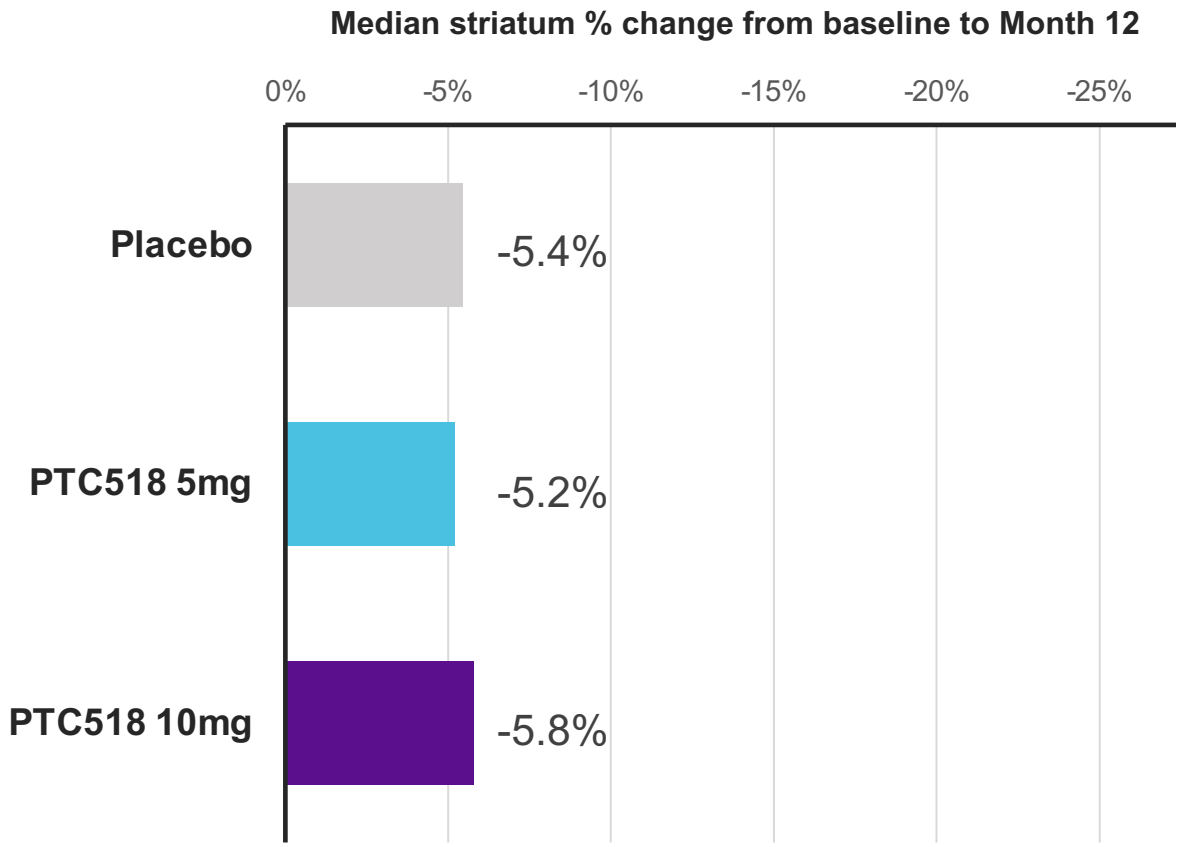
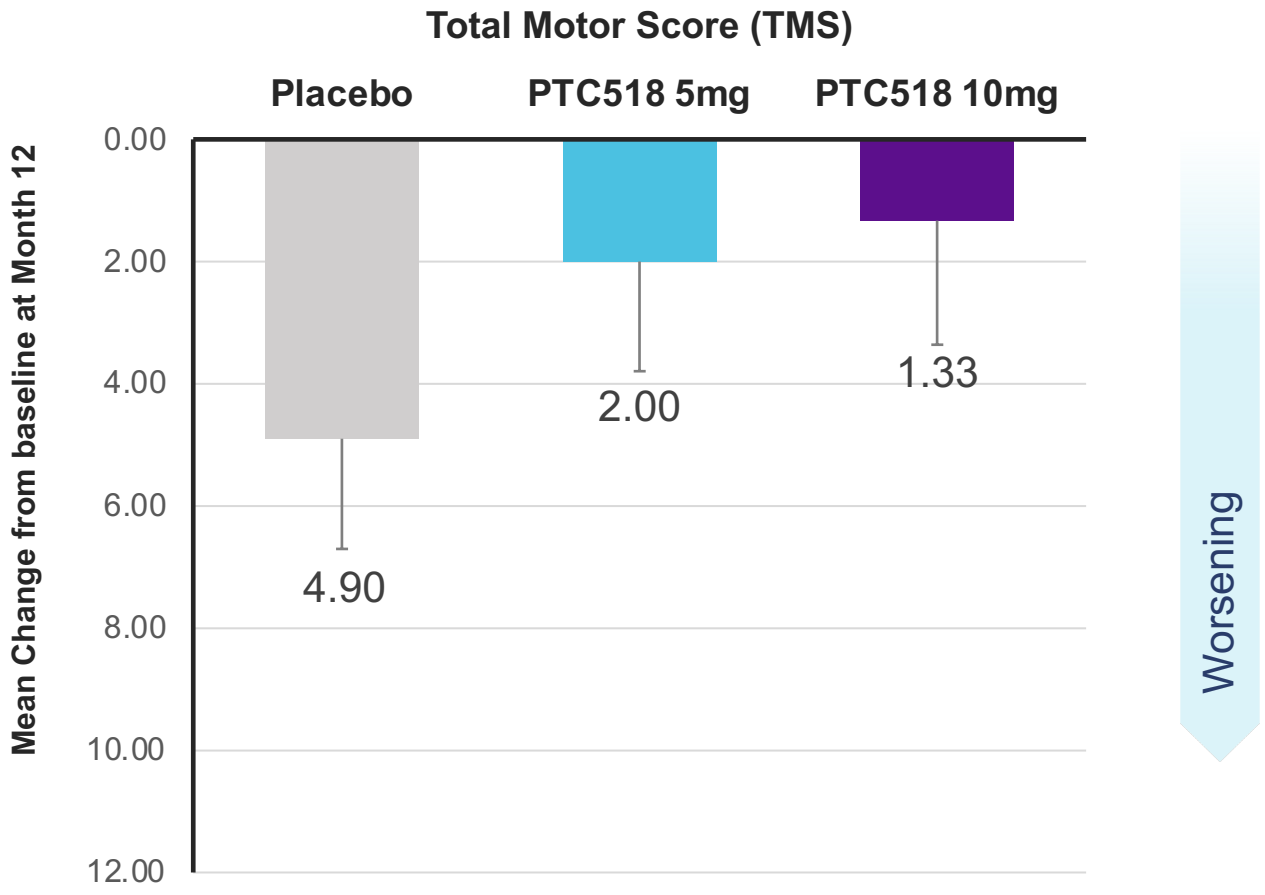
Change in Striatum Brain Volume Consistent Across Treatment Groups

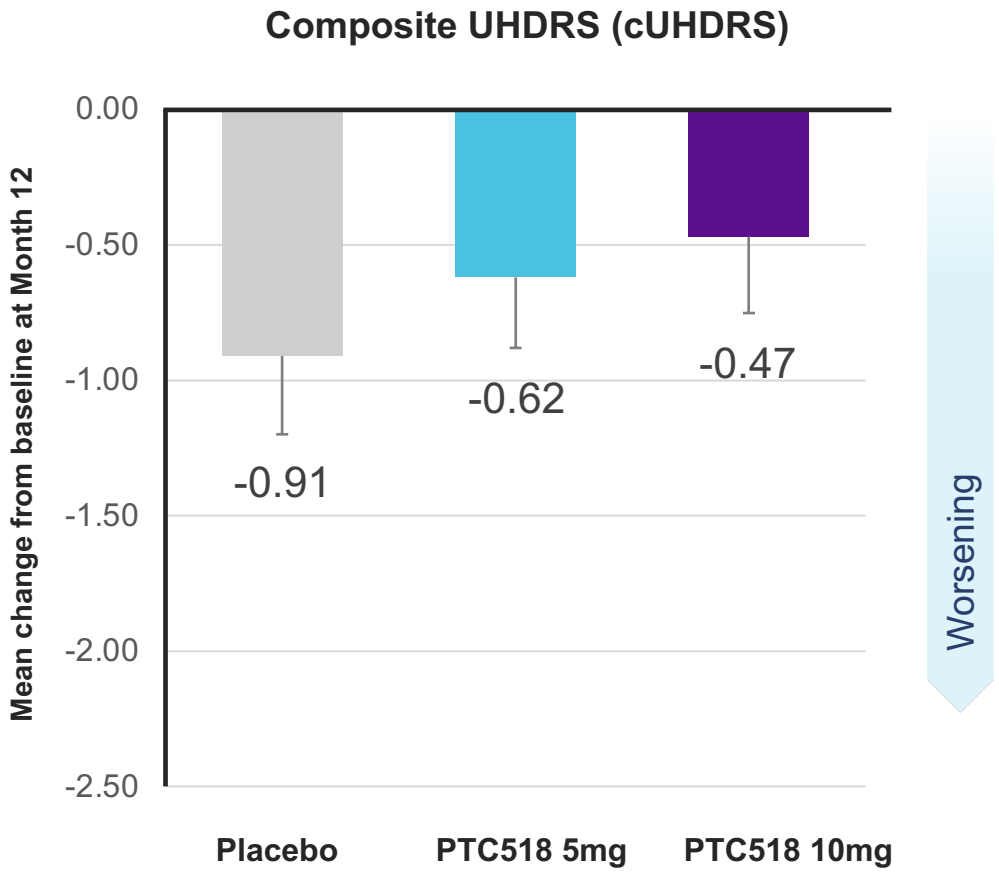


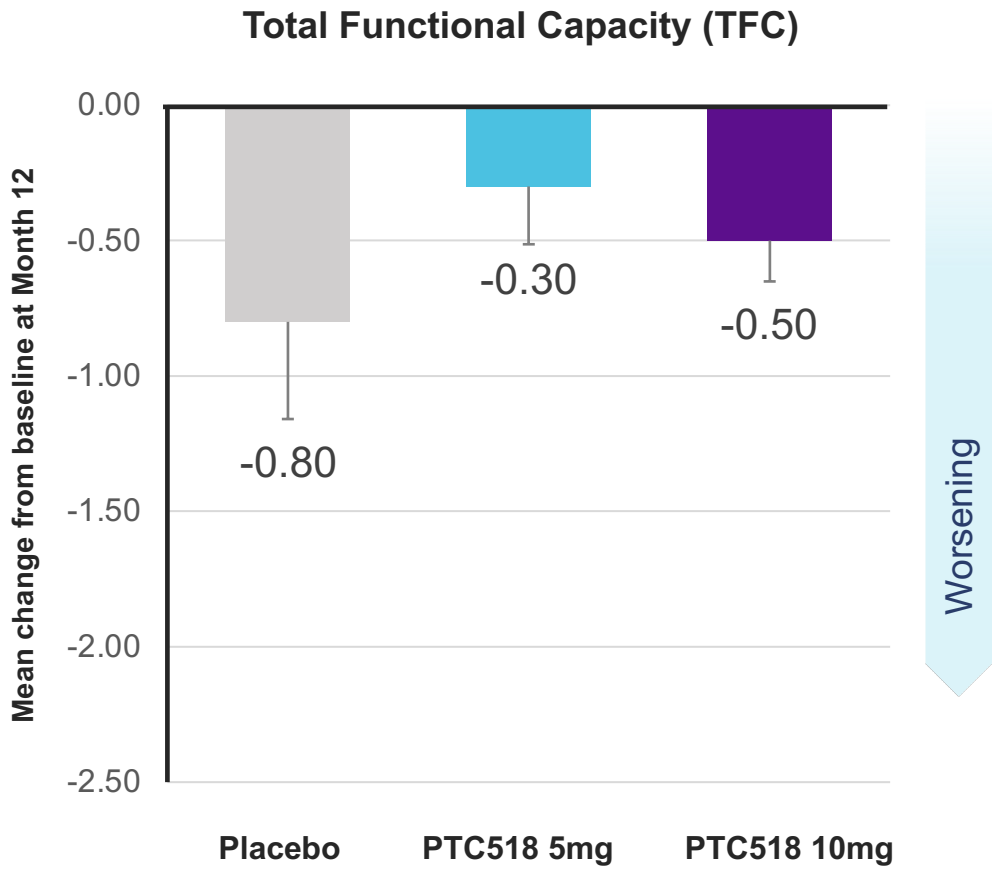
PTC518 Treatment Demonstrated Trend of Dose-Dependent Improvement of Total Motor Score



Note: Error bars represent the standard error of the mean.

PTC518 Treatment Demonstrated Trends of Improvement on Other Key Clinical Measures





Note: Error bars represent the standard error of the mean.

Safety

PTC518 Treatment Continues to be Well Tolerated At Month 12

PIVOT HD

PTC518 was well tolerated, with no dose-limiting toxicities

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

Similar adverse event profile across all treatment groups, including placebo

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PTC518 Treatment Continues to be Well Tolerated at Month 12

Category	Placebo (N=10)	PTC518 5mg (N=12)	PTC518 10mg (N=10)
Subjects with at least one TEAE	8 (80.0)	9 (90.0)	11 (91.7)
Subjects with at least one serious TEAE	2 (20.0)	0	1 (8.3)
Subjects with at least one TEAEs leading to study treatment discontinuation	0	0	0
Subjects with at least one TEAE leading to death	0	0	0
Subjects with at least one treatment related AE#	1 (10.0)	5 (50.0)	6 (50.0)
Subjects with at least one TEAEs by maximum severity N (%)	8 (80.0)	9 (90.0)	11 (91.7)
Grade 1	5 (50.0)	4 (40.0)	3 (25.0)
Grade 2	1 (10.0)	4 (40.0)	7 (58.3)
Grade 3	2 (20.0)	1 (10.0)	1 (8.3)
Grade 4/5	0	0	0

* Unrelated to drug
# Judged by the investigator to be probably or possibly related to treatment

Evidence of Durability of Effect, Safety and Dose-Dependent Benefit on Clinical Measures

Dose-dependent and durable lowering of HTT protein in blood at 12 months

Dose-dependent lowering of CSF mHTT levels

Dose-dependent trends of improvement on key clinical measures including TMS and cUHDRS

PTC518 was well tolerated with no evidence of treatment-related NfL spikes at 12 months

FDA Partial Clinical Hold Lifted

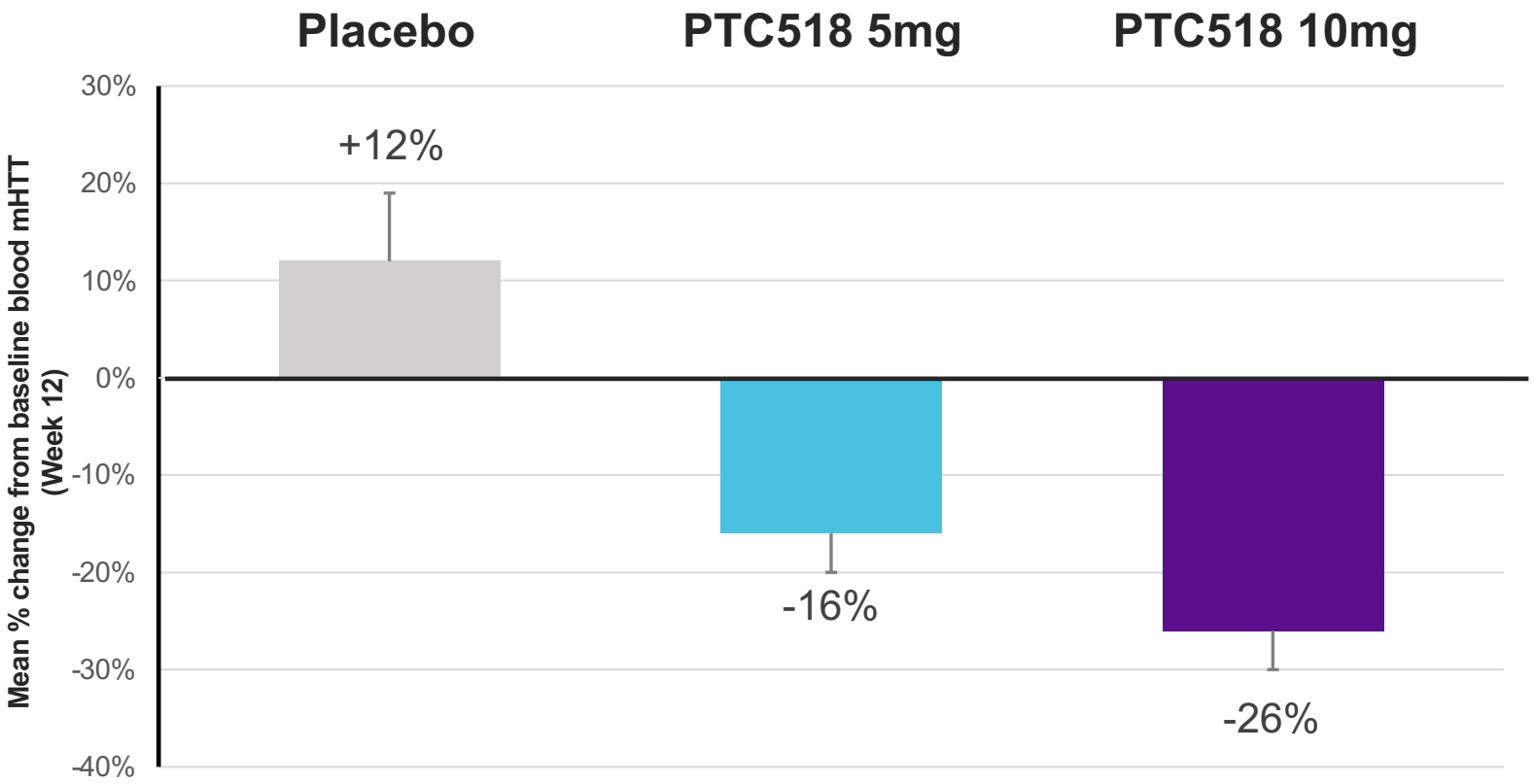
Note: Results based on interim readout

Additional Week 12 Data

Patient Characteristics of Additional Week 12 Subjects

Category	Placebo (Stage 2 N=18) (Stage 3 N=11)	PTC518 5mg (Stage 2 N=13) (Stage 3 N=13)	PTC518 10mg (Stage 2 N=14) (Stage 3 N=12)	Overall (Stage 2 N=45) (Stage 3 N=36)
Age (years) mean	48.6	48.7	47.0	48.1
Gender, n (%)				
Male	20 (69.0%)	12 (46.2%)	14 (53.8%)	46 (56.8%)
Female	9 (31.0%)	14 (53.8%)	12 (46.2%)	35 (43.2%)
CAG length				
Mean (SD)	43.7 (2.46)	43.9 (2.76)	44.4 (2.80)	44.0 (2.65)
Min – Max	40 - 49	40 – 50	41 – 50	40 – 50
TFC (Total Functional Capacity) Score				
Mean	12.5	12.4	12.4	12.4

PTC518 Treatment Resulted in Dose-Dependent Blood mHTT Protein Lowering at Week 12



Note: Error bars represent the standard error of the mean.

Dose-dependent lowering of HTT protein

Note: Results include all subjects for whom biomarker data are available

PTC518 Safety Profile Consistent for Additional Week 12 Subjects

PTC518 was well tolerated, with no dose-limiting toxicities

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

Similar adverse event profile across all treatment groups, including placebo

Summary and Next Steps

Evidence of favorable CNS activity with trends of improvement on key clinical measures and continued safety

Continue PIVOT-HD and PIVOT-HD Open Label Extension studies

Begin preparations for Phase 3 clinical trial