PIVOT-HD Interim Data Update

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Patient Living with HD

PIVOT HD

PTC THERAPEUTICS 25 YEARS

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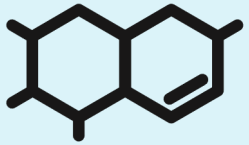
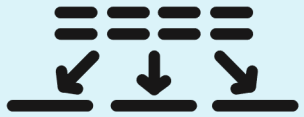
PTC518 Program Leveraged Learnings from Successful Development of Evrysdi

PTC518 developed from PTC's validated splicing platform

Databases of Splicing Targets



Novel Chemical Library



HTSpliceseq

Expert Team

Key learnings from successful development of Evrysdi

- Importance of molecule selectivity and specificity
- CNS bioavailability with broad brain biodistribution
- Leverage systemic exposure to confirm target engagement and splicing activity and inform dose selection

Evrysdi™ risdiplam 60 mg powder for oral solution

Key Objectives for 12-Week Interim Data Readout

- Determine HTT protein lowering after 12 weeks of treatment with PTC518 at 5mg and 10mg
- Define CSF/plasma drug exposure in Huntington's disease patients
- Confirm the relationship of HTT mRNA to protein lowering at steady state
- Evaluate PTC518 safety and tolerability

12-Week Interim Data Met Key Objectives

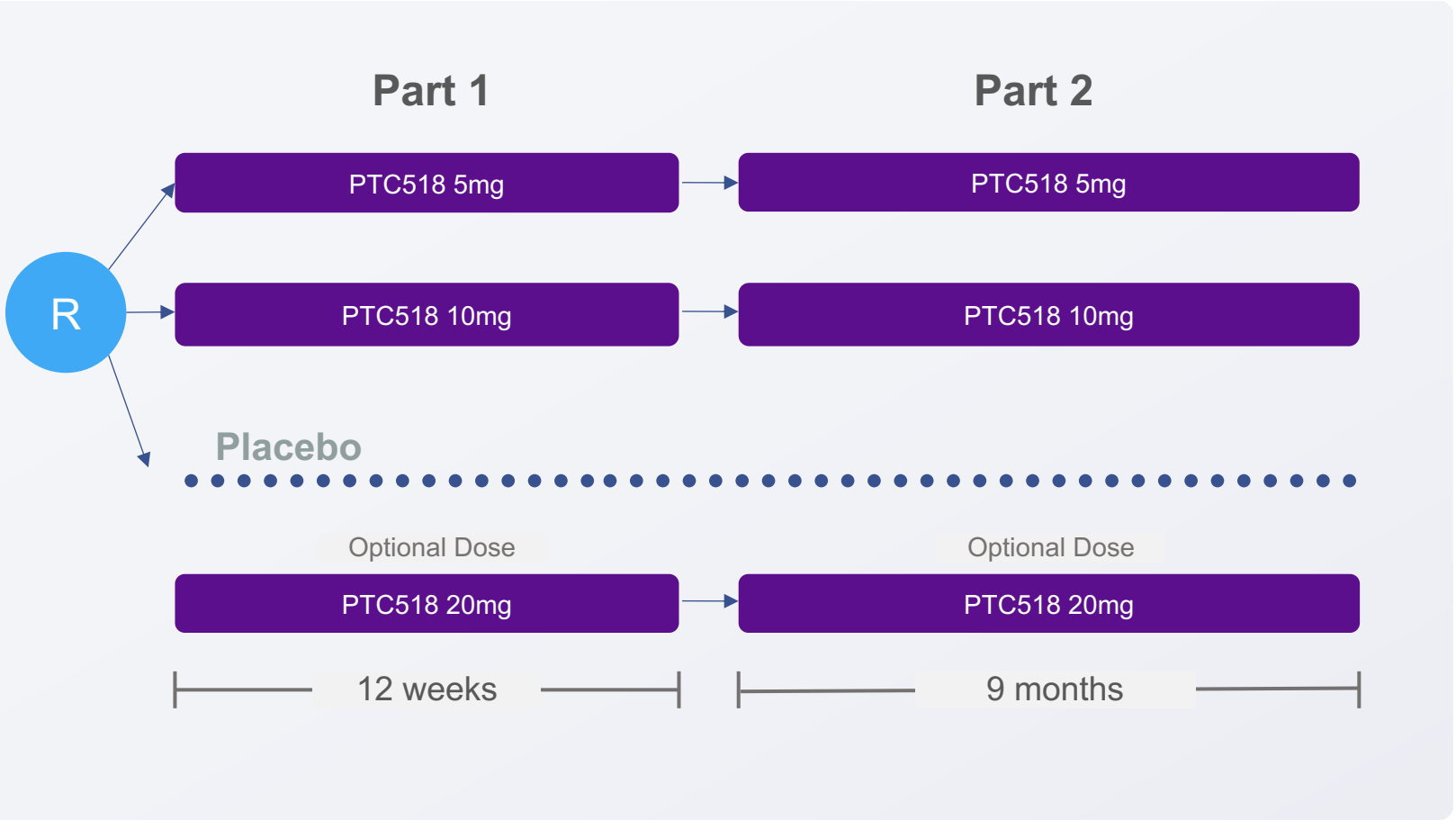
PTC518 treatment resulted in dose-dependent lowering of HTT mRNA and protein levels in blood cells

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

PIVOT-HD Study Design



Primary Endpoints

- Safety and tolerability of PTC518
- Percent reduction in HTT mRNA and protein in blood

Secondary Endpoints

- Percent reduction in mHTT protein in CSF
- Changes in neurofilament light chain (NfL) in plasma and CSF
- Change in brain volume on volumetric MRI imaging

PIVOT-HD Trial Populations

Inclusion Criteria
Stage 2

- Ambulatory Huntington's patients age 25 and older
- CAG repeats 40-50 inclusive
- Motor and Cognitive Function:
  - UHDRS-IS score of **100**
  - UHDRS TFC score of **13**
- PIN_{HD} score of **0.18 - 4.93**
  - Multivariate calculation including SDMT, TMS, age, CAG

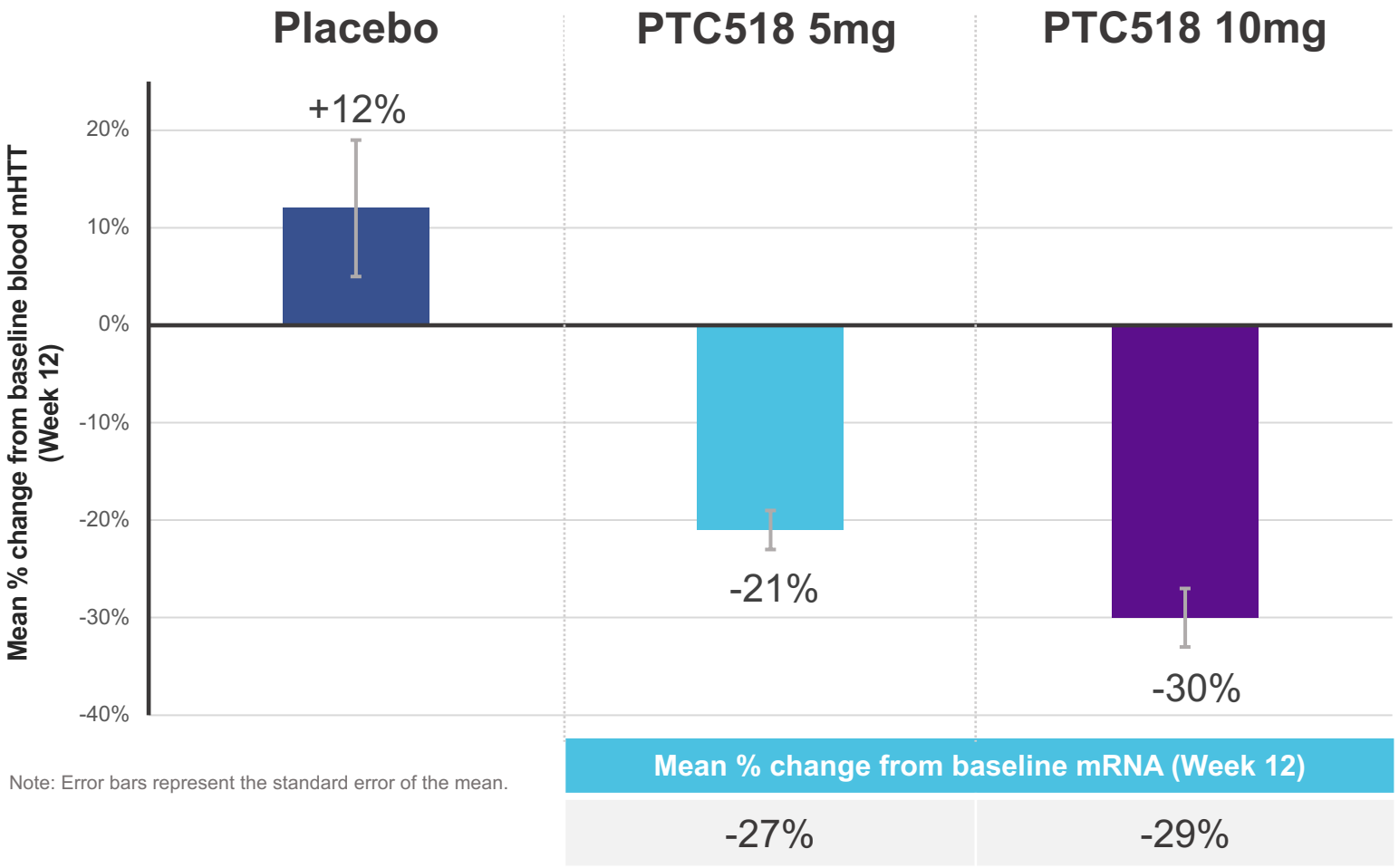
Inclusion Criteria
Early Stage 3

- Ambulatory Huntington's patients age 25 and older
- CAG repeats 40-50 inclusive
- Motor and Cognitive Function:
  - UHDRS-IS score of **less than 100 and/or**
  - UHDRS TFC score of **11 or 12**

PIVOT-HD Interim Analysis Patient Characteristics

Category	PTC518 5mg (N=13)	PTC518 10mg (N=11)	Placebo (N=9)	Overall (N=33)
Age (years) mean	46.2	47.4	46.9	46.8
Gender, n (%)				
Male	5 (38.5%)	6 (54.5%)	6 (66.7%)	17 (51.5%)
Female	8 (61.5%)	5 (45.5%)	3 (33.3%)	16 (48.5%)
CAG length				
Mean (SD)	44.08 (1.9)	43.73 (2.4)	44.11 (2.0)	43.97 (2.1)
Min – Max	42 - 49	42 - 50	42 - 47	42 – 50
TFC (Total Functional Capacity) Score				
Mean	13	13	13	13

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



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

Dose-dependent lowering of HTT protein

mRNA and protein lowering **~1:1**

PTC518 CSF Drug Levels Confirm Targeted CNS Exposure at Week 12

Treatment Group	Mean CSF Concentration (ng/mL)	Mean Free Plasma Concentration (ng/mL)
5mg	0.923	0.917
10mg	2.037	1.402

Ratio of CSF to Free Plasma Concentration

5mg **1.1 to 1**

10mg **1.5 to 1**

PTC518 Treatment Demonstrated to Be Well Tolerated

PTC518 was well tolerated, with no treatment-related serious adverse events and no adverse events leading to discontinuation

Similar adverse event profile across treatment groups, including placebo group

Most common adverse events were upper respiratory tract infection and headache

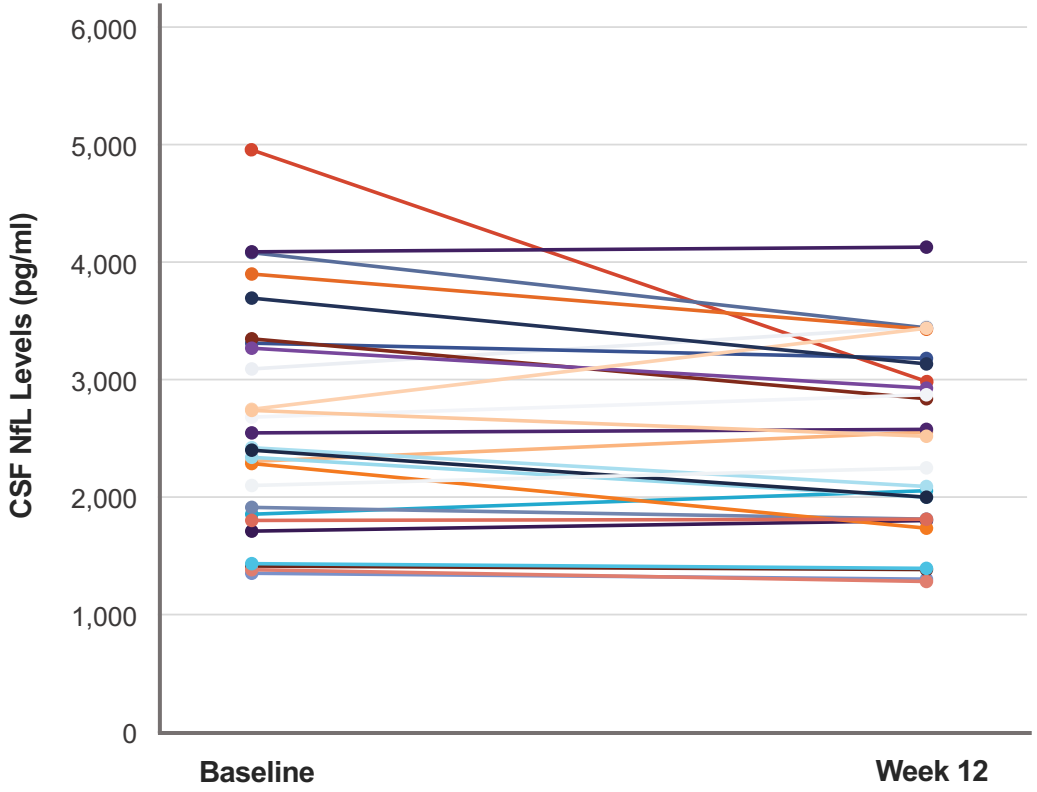
PTC518 Treatment Demonstrated to Be Well Tolerated

Category	PTC518 5mg (N = 13)	PTC518 10mg (N=11)	Placebo (N=9)	Overall (N=33)
Subjects with at least one TEAE	9 (69.2)	7 (63.6)	6 (66.7)	22 (66.7)
Subjects with at least one serious TEAE	0	0	0	0
Subjects with at least one TEAEs leading to study treatment discontinuation	0	0	0	0
Subjects with at least one TEAE leading to death	0	0	0	0
Subjects with at least one treatment related AE#	3 (23.1)	4 (36.4)	1 (11.1)	8 (24.2)
Subjects with at least one TEAEs by maximum severity N (%)	9 (69.2)	7 (63.6)	6 (66.7)	22 (66.7)
Grade 1	4	2	5	11
Grade 2	4	5	1	10
Grade 3	1*	0	0	1
Grade 4/5	0	0	0	0

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

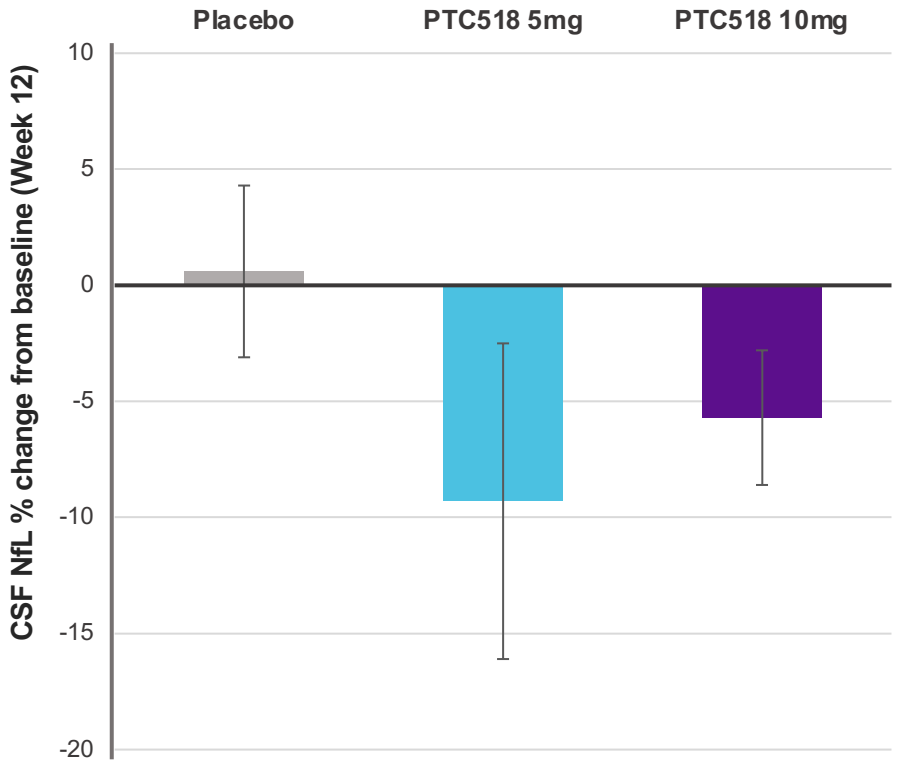
CSF NfL Levels Trended Lower in Subjects Treated with PTC518

Individual Subject CSF NfL Trajectories



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

Mean Change in CSF NfL Levels from Baseline to Week 12

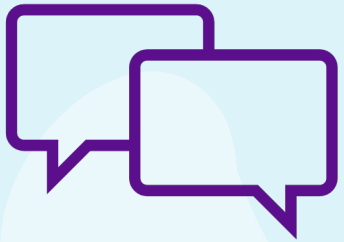


Note: Error bars represent the standard error of the mean.

Summary and Next Steps

Dose-dependent lowering of HTT protein levels, safety, and CNS biodistribution objectives achieved

Continue enrollment in Stage 2 and early Stage 3 patient cohorts



Share safety data with FDA to support US enrollment in PIVOT-HD