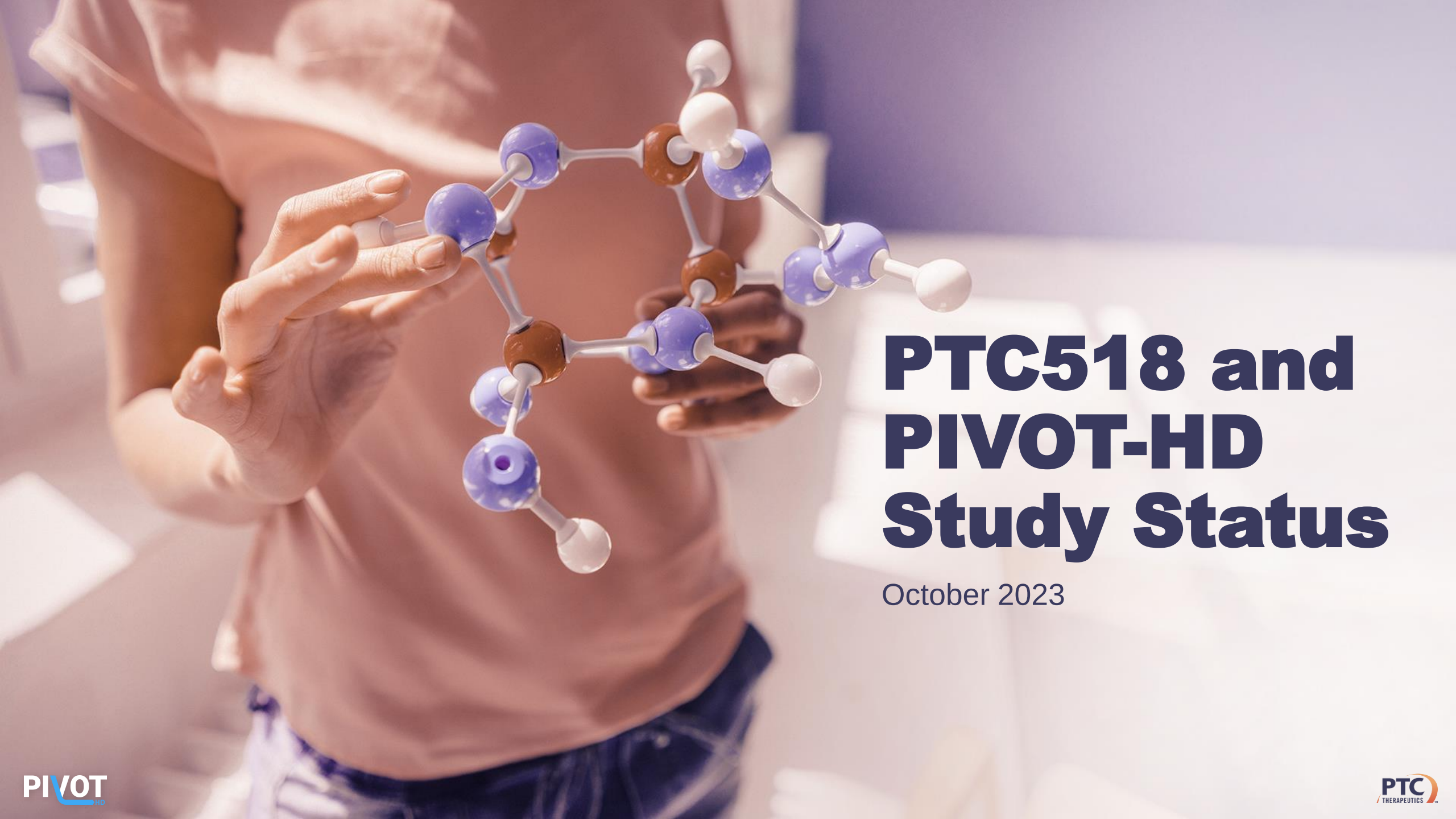
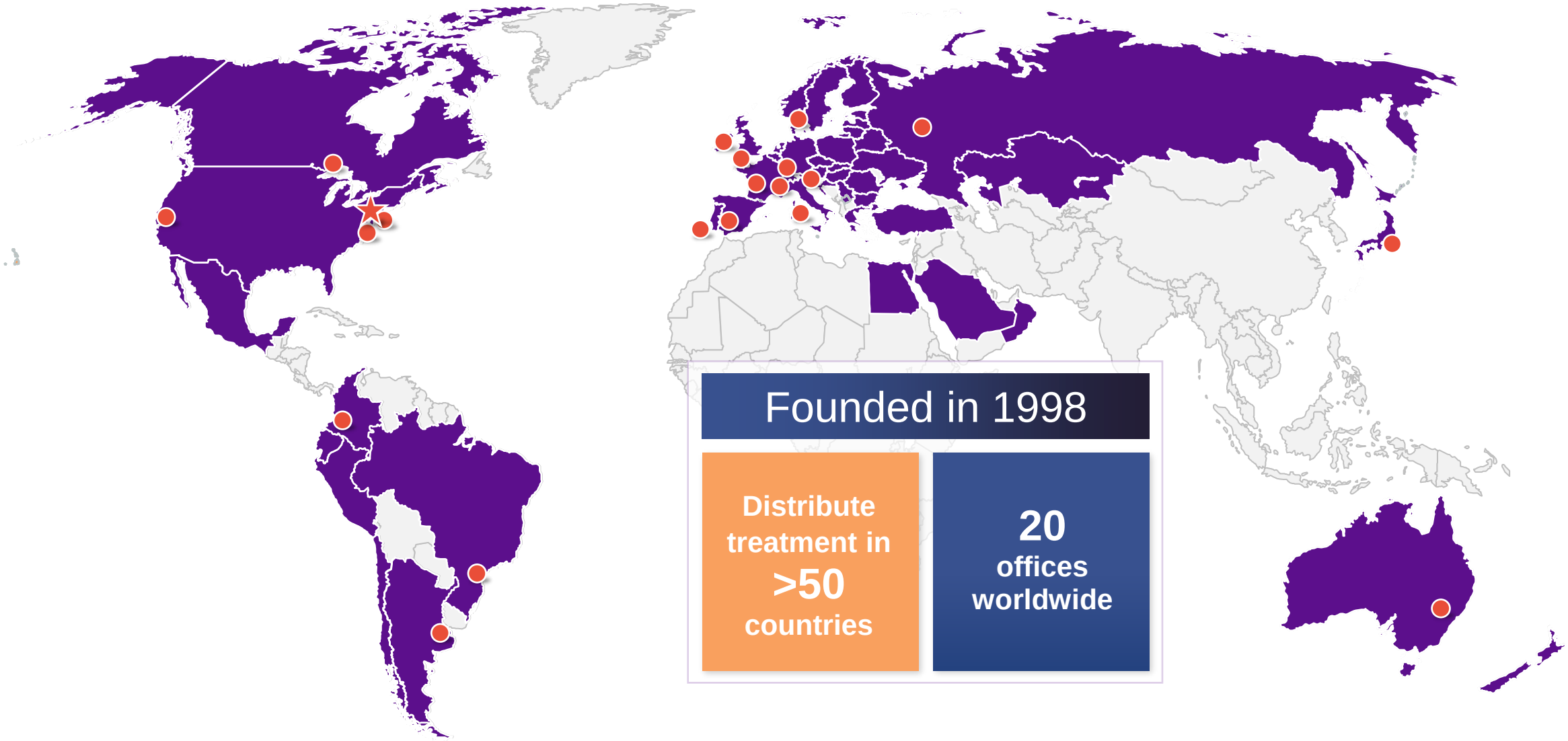


PTC518 and PIVOT-HD Study Status

October 2023

A Focus on Global Reach and Access for Patients



Founded in 1998

Distribute treatment in >50 countries

20 offices worldwide

Our Robust and Diverse Pipeline is Driven By Our Unique Science

Commercial

translarna™ ataluren

Emflaza® (deflazacort)
6 mg | 18 mg | 30 mg | 36 mg tablets
22.75 mg/mL oral suspension

Evrysdi® risdiplam

*PTC receives royalties for Evrysdi

Upstaza™ (eladocagene exuparvovec)

Tegsedi® (inotersen) injection 284 mg/1.5 mL

waylivra® (volanesorsen) injection 285 mg/1.5 mL

Neurology

Metabolism

Oncology

Research

- MAP-Tau
- SCA-3
- 10 Undisclosed
- 2 Undisclosed
- 3 Undisclosed

Development

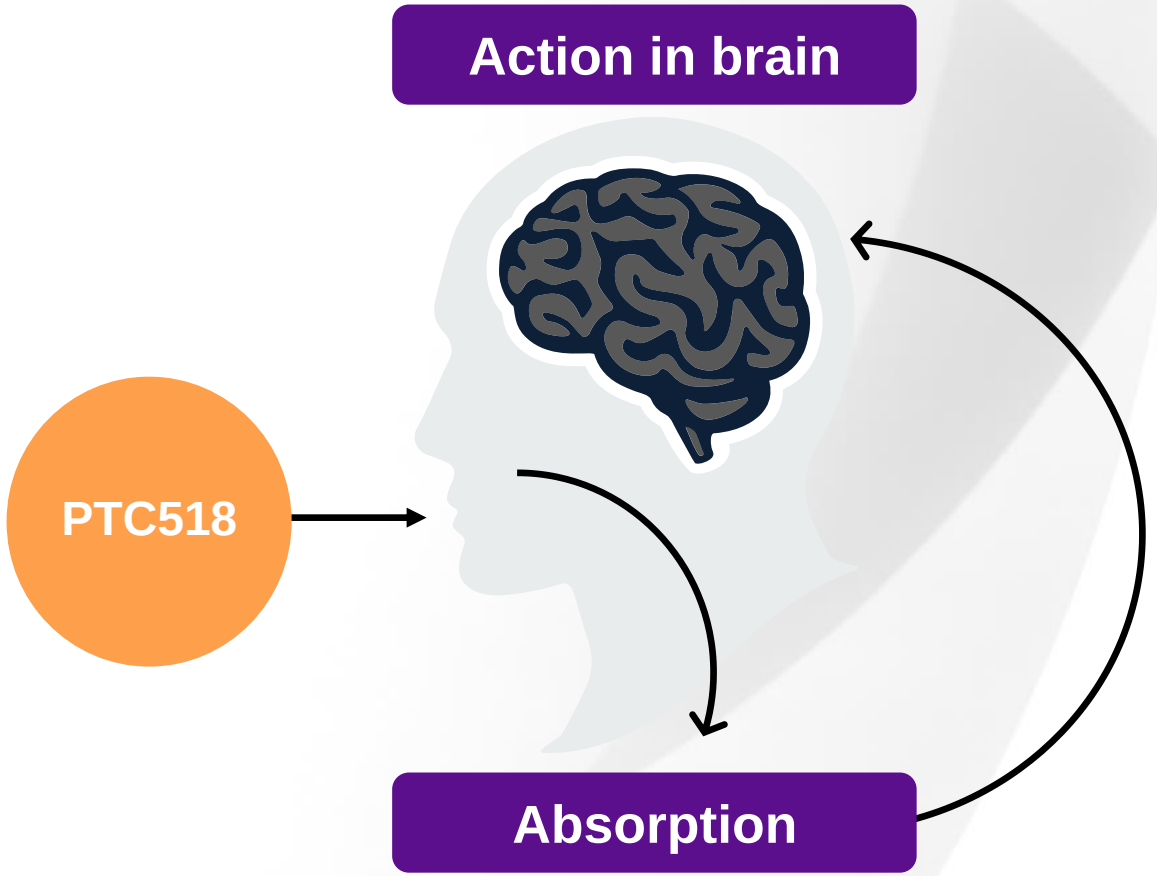
- PTC518 HD
- Vatiquinone FA
- Utreloxastat ALS
- Sepiapterin PKU
- Unesbulin LMS
- Unesbulin DIPG

PTC THERAPEUTICS 25 YEARS

PTC is Applying Splicing Technology to Treat HD by Targeting its Root Genetic Cause

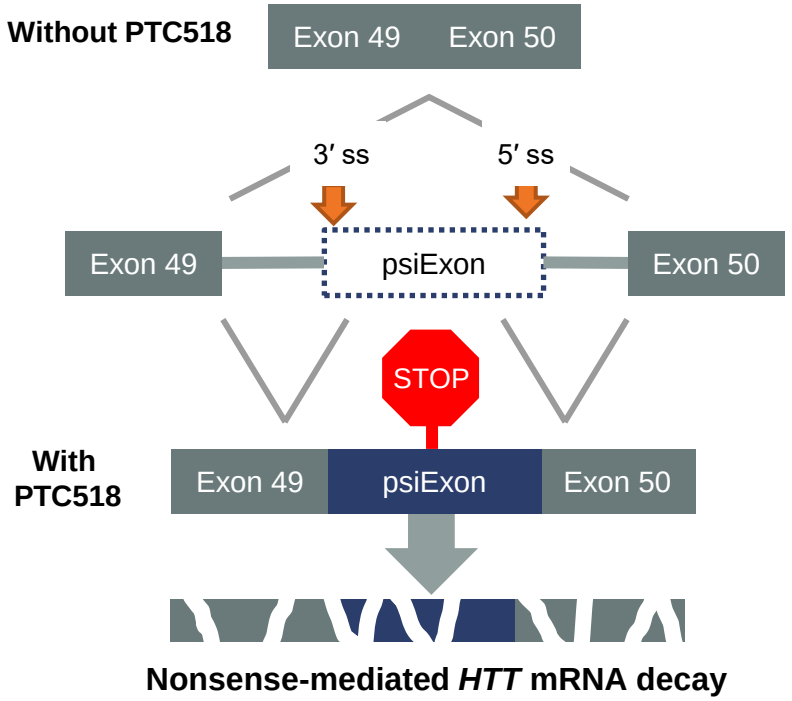
PTC518 is orally bioavailable penetrates the blood-brain barrier, and is not effluxed, providing:

- Titratable dosing and reversible effects
- Broad tissue distribution
- Treatment of HD everywhere in the body (brain, muscle, immune system, others)
- Huntingtin (HTT) lowering in the whole brain

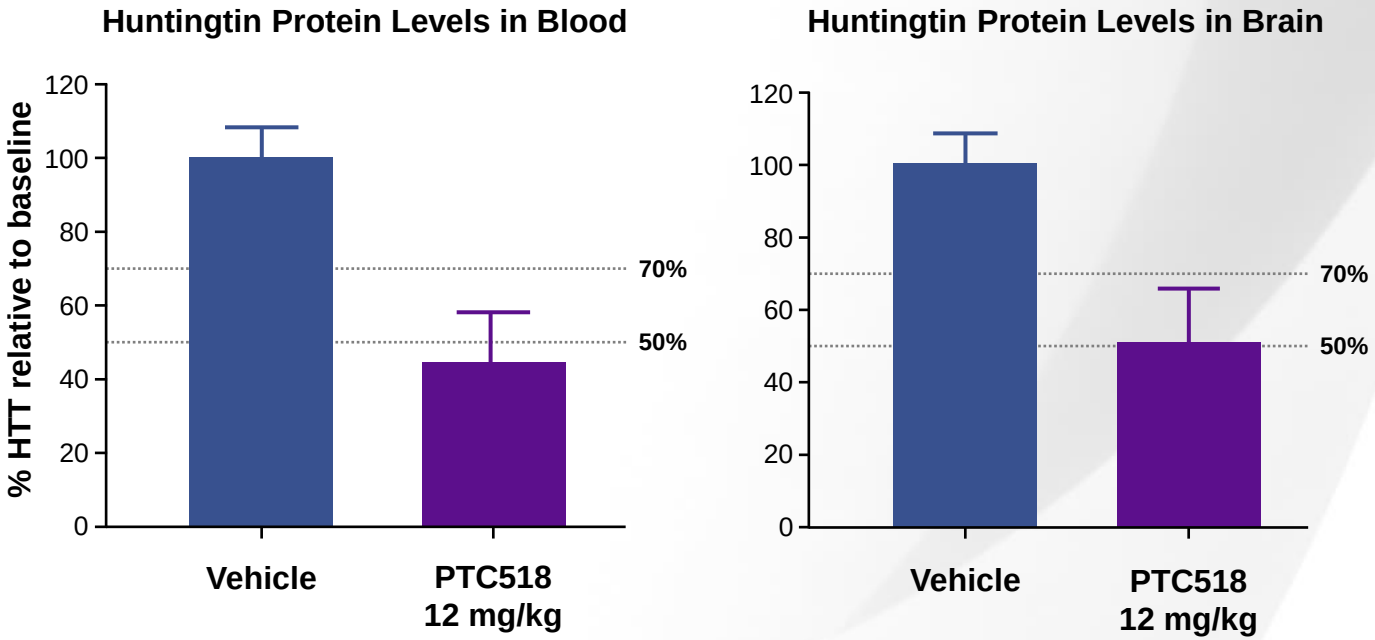


PTC518 is a Splicing Modifier Which Lowers Huntingtin in the Blood and Brain of HD Mice

With PTC518, an Inducible Pseudoexon (psiExon) is Included in the *HTT* Pre-mRNA



PTC518: Even Huntingtin Lowering in Blood and Brain of BACHD Mice



- BACHD, bacterial artificial chromosome-mediated transgenic mouse model of Huntington's disease; HD, Huntington's disease; HTT/*HTT*, huntingtin; mRNA, messenger ribonucleic acid; ss, splice site.
- PTC Therapeutics, data on file.

PTC518 was Investigated in a Four-Part Phase 1 Trial

Phase 1 Trial of PTC518 in Healthy Volunteers

1 Single Ascending Dose

- Each subject took a single dose of PTC518 or placebo
- Five groups of eight healthy volunteers
- Measured safety and tolerability; *HTT* mRNA splicing

2 Multiple Ascending Dose

- Each subject took multiple doses of PTC518 or placebo
- Three groups of eight healthy volunteers
- Measured safety and tolerability; *HTT* mRNA splicing and protein lowering

3 Food Effect

- Measured the effects of food on PTC518 pharmacokinetics

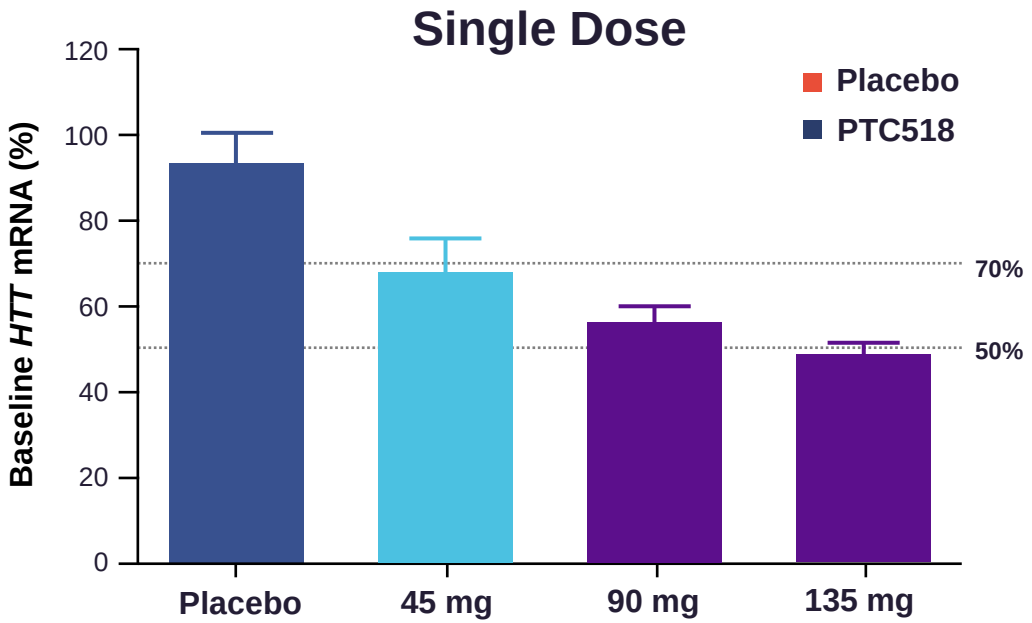
4 CSF Sampling

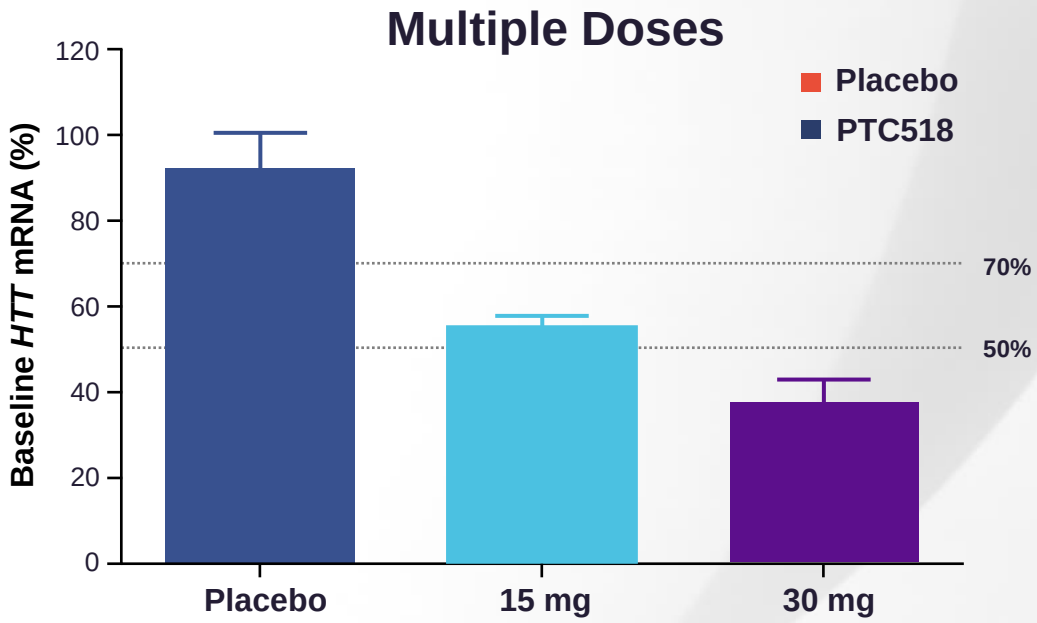
- Measured pharmacokinetics of PTC518 in the cerebrospinal fluid (CSF)
- Compared drug levels in CSF with plasma

CSF, cerebrospinal fluid; HTT, huntingtin; mRNA, messenger ribonucleic acid.

- PTC Therapeutics, data on file.

Single and Multiple Ascending Dose Studies: Proof of Mechanism Demonstrated by Dose-Dependent *HTT* Splicing





Whole blood *HTT* splicing in humans
- Doses evaluated = 45, 90, 135 mg
- Time – Day 1; single dose; splicing evaluated 24 hours post dose

Whole blood *HTT* splicing in humans
- Doses evaluated = 15, 30 mg
- Time – Day 14; multiple doses; splicing evaluated 6 hours post dose on Day 14

- *HTT*, huntingtin; mRNA, messenger ribonucleic acid.
- PTC Therapeutics, data on file.

Phase II Clinical Trial in HD Patients

The PIVOT-HD Trial Will Measure Safety and Effectiveness of PTC518

Primary Endpoints

Safety and tolerability of PTC518

Lowering of HTT protein in blood

Biomarker Endpoints

Lowering of HTT protein in CSF

Blood markers of safety

Brain imaging (MRI)

Clinical Endpoints

UHDRS

PBA-s

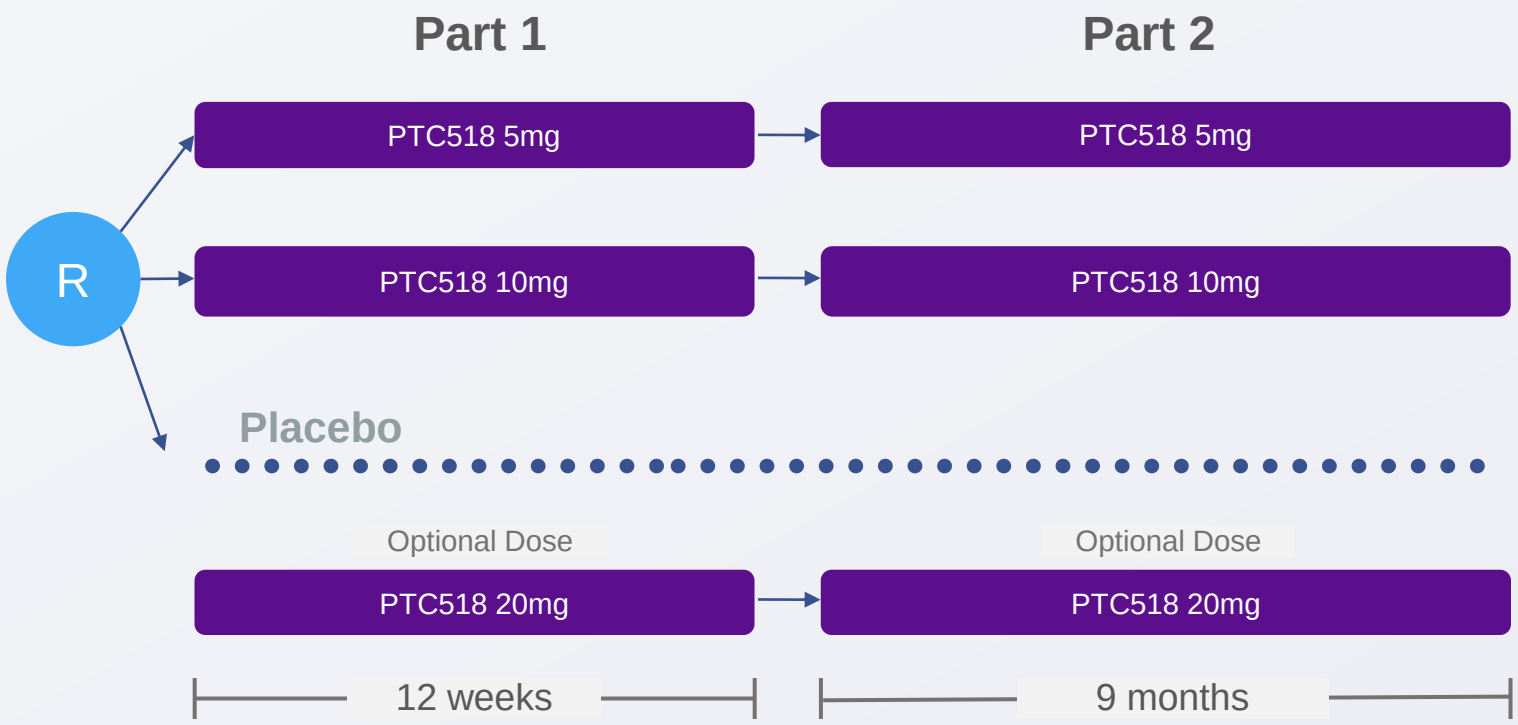
Wearable assessments

FuRST 2.0

FuRST, Functional HD, Huntington's disease rating Scale; HTT, huntingtin; MRI, magnetic resonance imaging; PBA-s, Problem Behaviors Assessment; UHDRS, Unified Huntington's Disease Rating Scale.

PTC Therapeutics, data on file.

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 TFC score of 13

  or

  - UHDRS TFC score of **11 or 12**

PIVOT HD: Site Locations

Original Sites

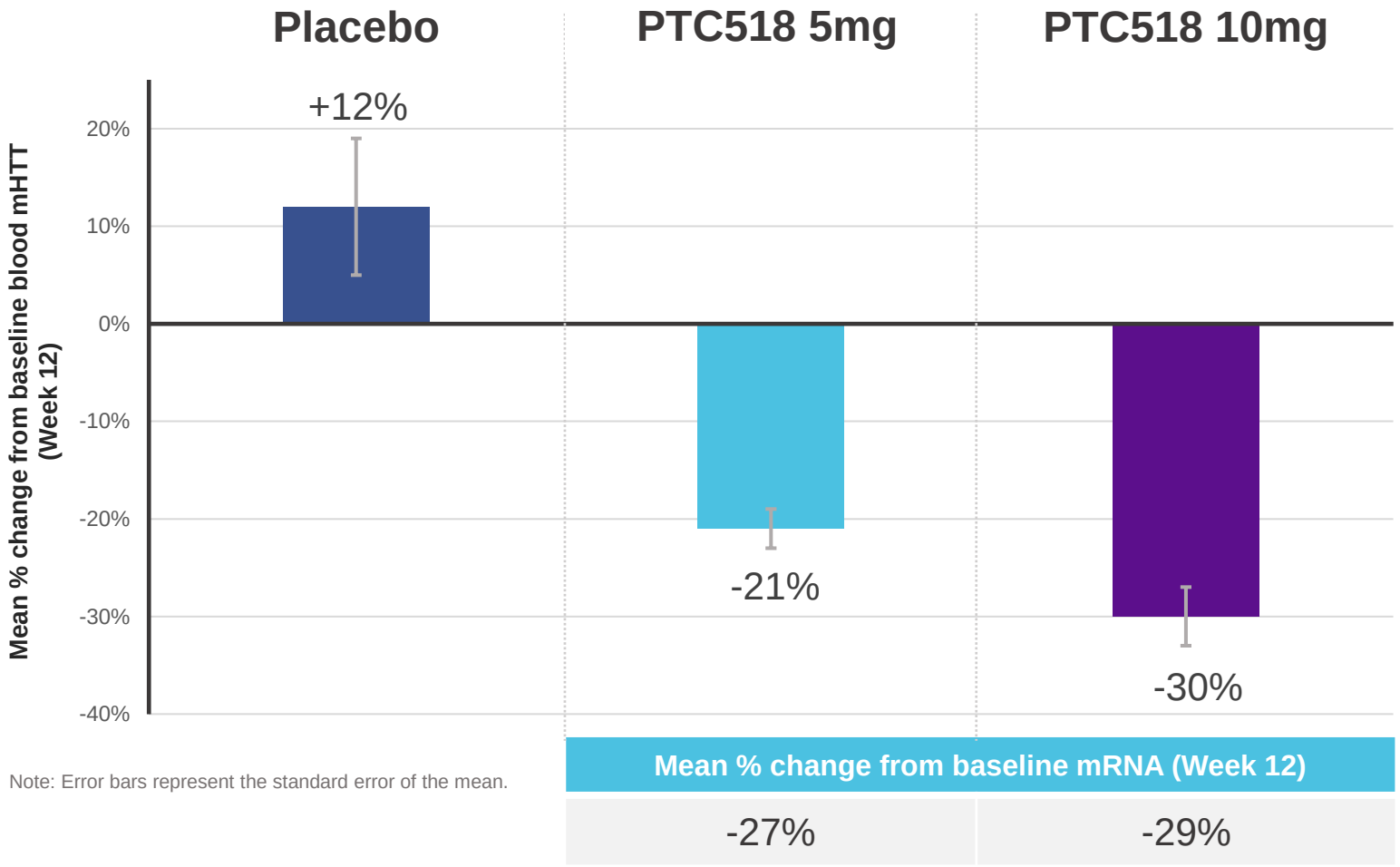
Recently Added

PIVOT-HD Interim Data Update

From June 2023

Patient Living with HD

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 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

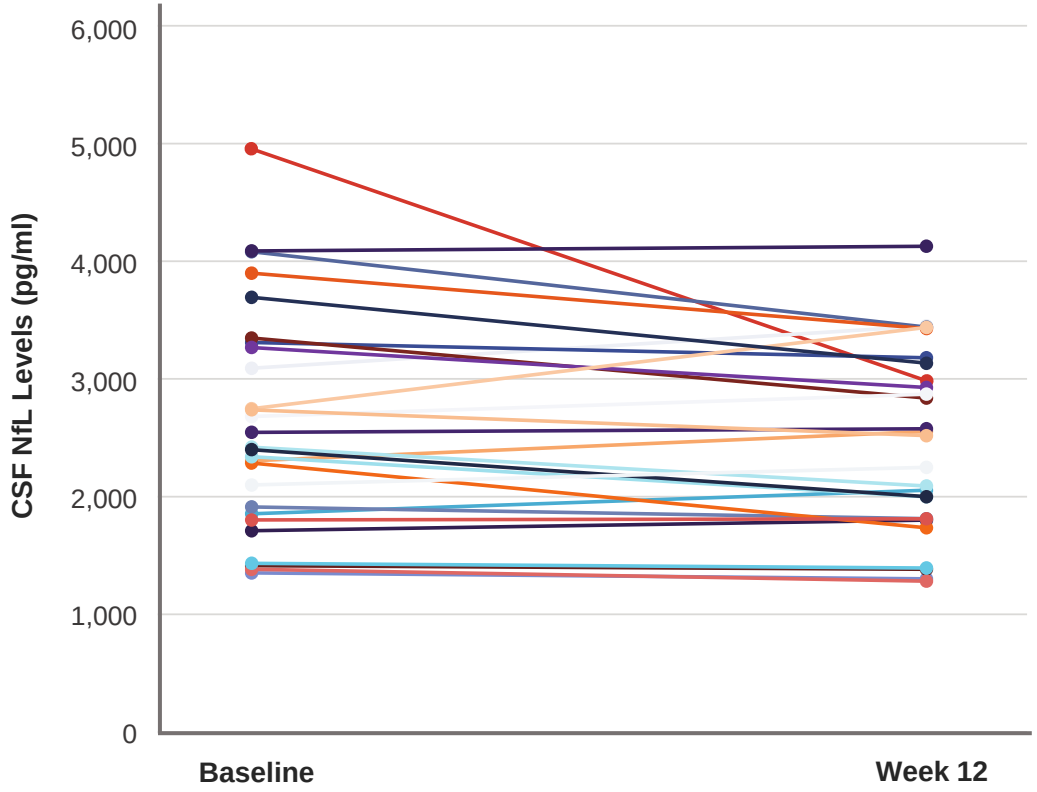
PTC518 Treatment Demonstrated to Be Well Tolerated

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

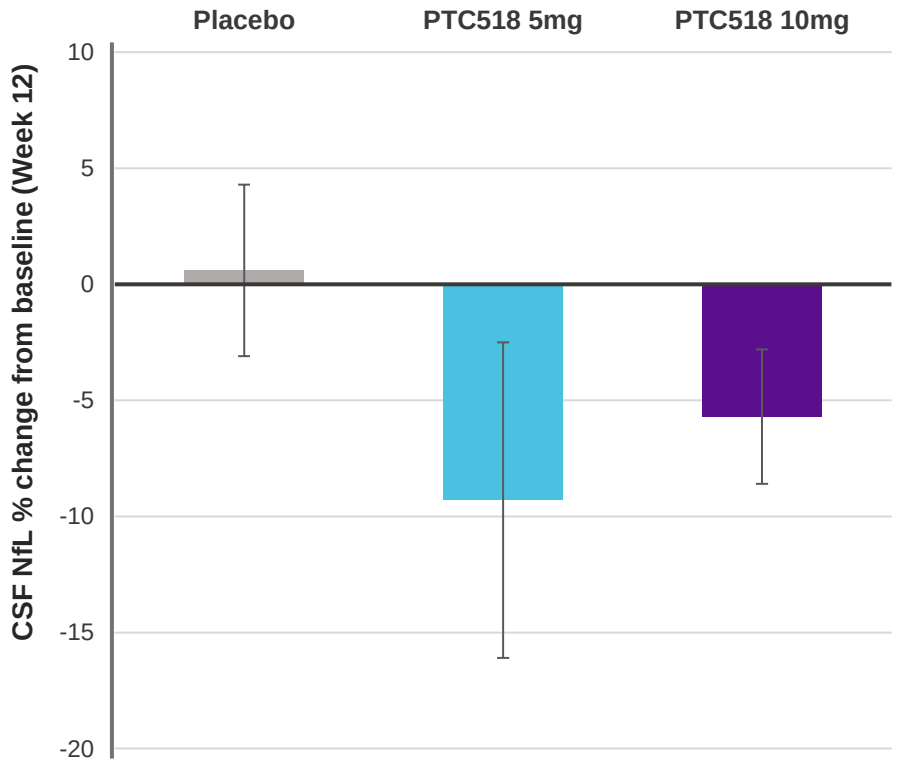
CSF NfL Levels Trended Lower in Subjects Treated with PTC518

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

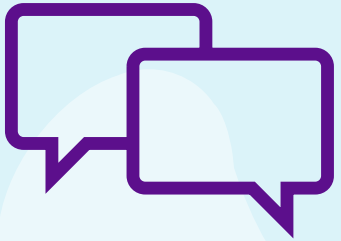


Note: Error bars represent the standard error of the mean.

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

Summary: The PIVOT-HD Trial is Up and Running!

- PTC518 is a new splicing modifier drug which is orally available
- PTC518 crosses the blood–brain barrier and lowers huntingtin in the brain and body
- PIVOT-HD, the Phase 2 study of PTC518, started in the first quarter of 2022
- Check ClinicalTrialsRegister.eu or the ClinicalTrials.gov website for regular updates on the trial (search “PTC518” or use trial identifier NCT05358717)

Thank you to all Patients and Families for getting us this far!