PTC518 Huntington's Disease Program Update

September 23, 2021

Forward Looking Statements:

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. All statements contained in this release, other than statements of historic fact, are forward-looking statements, including statements regarding: the future expectations, plans and prospects for PTC, including with respect to the expected timing of clinical trials and studies, availability of data and other matters; PTC's strategy, future operations, future financial position, future revenues, projected costs; and the objectives of management. Other forward-looking statements may be identified by the words "guidance", "plan," "anticipate," "believe," "estimate," "expect," "intend," "may," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions.

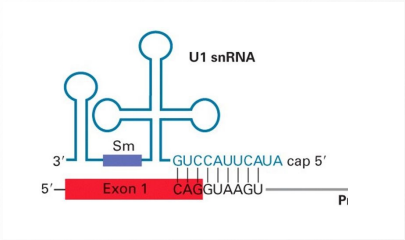
PTC's actual results, performance or achievements could differ materially from those expressed or implied by forward-looking statements it makes as a result of a variety of risks and uncertainties, including those related to: the outcome of pricing, coverage and reimbursement negotiations with third party payors for PTC's products or product candidates that PTC commercializes or may commercialize in the future; the enrollment, conduct, and results of PTC518 clinical studies for HD; significant business effects, including the effects of industry, market, economic, political or regulatory conditions; changes in tax and other laws, regulations, rates and policies; the eligible patient base and commercial potential of PTC's products and product candidates; PTC's scientific approach and general development progress; and the factors discussed in the "Risk Factors" section of PTC's most recent Annual Report on Form 10-K, as well as any updates to these risk factors filed from time to time in PTC's other filings with the SEC. You are urged to carefully consider all such factors.

As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. There are no guarantees that any product will receive or maintain regulatory approval in any territory, or prove to be commercially successful.

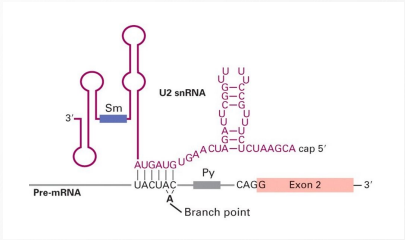
The forward-looking statements contained herein represent PTC's views only as of the date of this presentation and PTC does not undertake or plan to update or revise any such forward-looking statements to reflect actual results or changes in plans, prospects, assumptions, estimates or projections, or other circumstances occurring after the date of this presentation except as required by law.

Small Molecule Splicing Modulation Platform

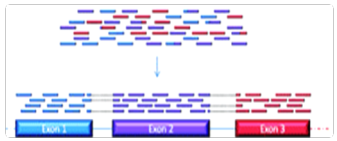
Identify Splice Site targets → **Identification of splicing compound** → **Preclinical Pipeline** → **Clinical Target Pipeline** → **Approved Drug**



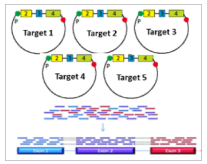
5’ Splice Site



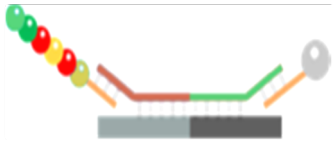
3’ Splice Site



HTrnaSeq



HTSpliceoseq



Nanostring Plex Screen

Spinal Muscular Atrophy - *SMN*

Evrysdi® risdiplam 60 mg powder for oral solution

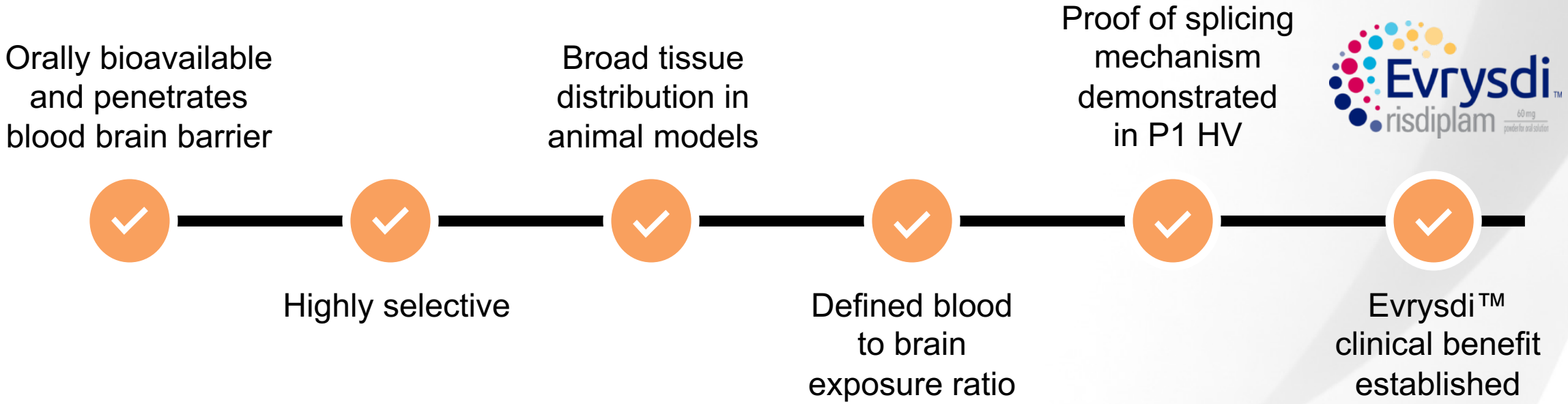
Huntington’s Disease
HTT

Familial Dysautonomia
IKBKAP

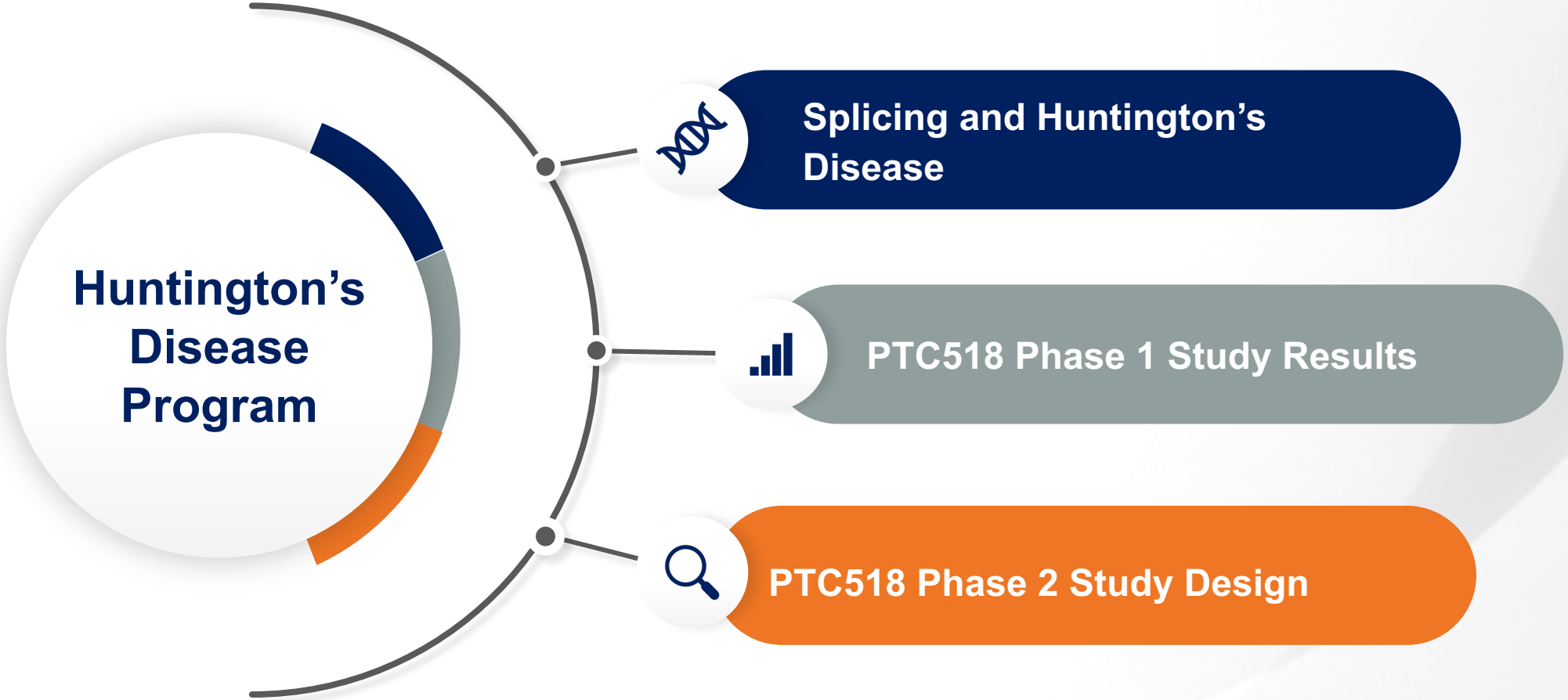
MAPT-Tauopathies
ATXN3-SCA3
Undisclosed target 1
Undisclosed target 2
Undisclosed target 3
Undisclosed target 4
Undisclosed target 5

PTC THERAPEUTICS

Evrysdi™ (risdiplam) Roadmap to Success



PTC518 Huntington's Disease Program Update Agenda



Huntington's Disease Is a Debilitating Neurodegenerative Disorder with No Available Disease Modifying Treatments

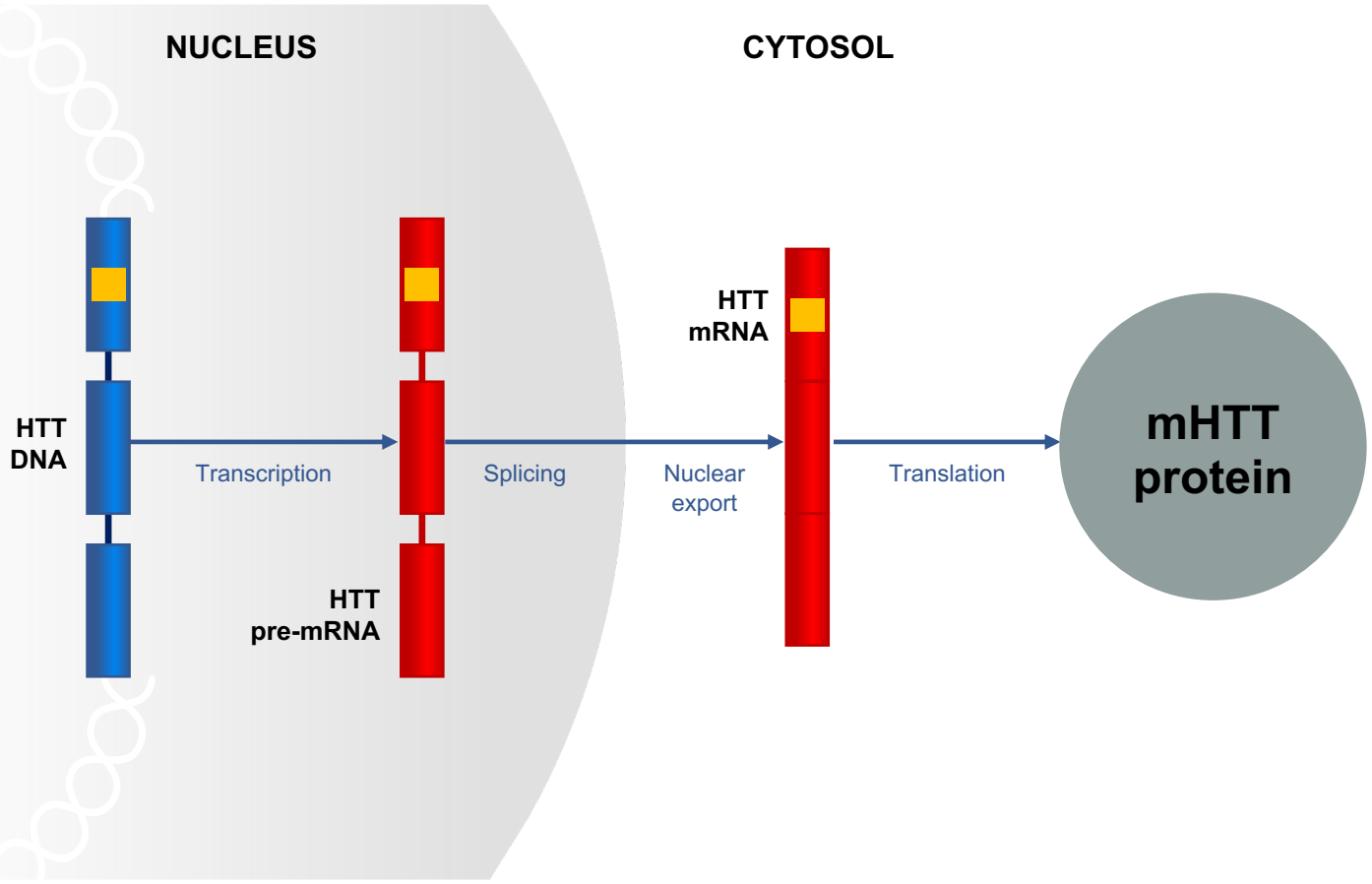
Huntington's Disease

- Caused by a monogenic defect; autosomal dominant inheritance
- Leads to movement, psychiatric and cognitive disorders
- 135,000 patients worldwide

Current Treatments

- No approved disease modifying therapies

HD Is a Monogenic Gain of Function Disorder and Lowering HTT Targets The Root Cause of Pathogenesis



Toxic gain of function mutation
Expansion of CAG repeat in huntingtin (HTT) gene

Huntington's disease
Whole brain atrophy
HTT protein aggregates

Therapeutic approach:
Make less HTT

 Modified from Tabrizi,S. *Cell*.2019.

HD Is a Monogenic Gain of Function Disorder and Lowering HTT Targets The Root Cause of Pathogenesis

Toxic gain of function mutation
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Therapeutic approach:
Make less HTT

Multiple models demonstrate partial reduction of wild type HTT is well tolerated

HTT reduction correlates with clinical benefit

 Modified from Tabrizi,S. *Cell*.2019.

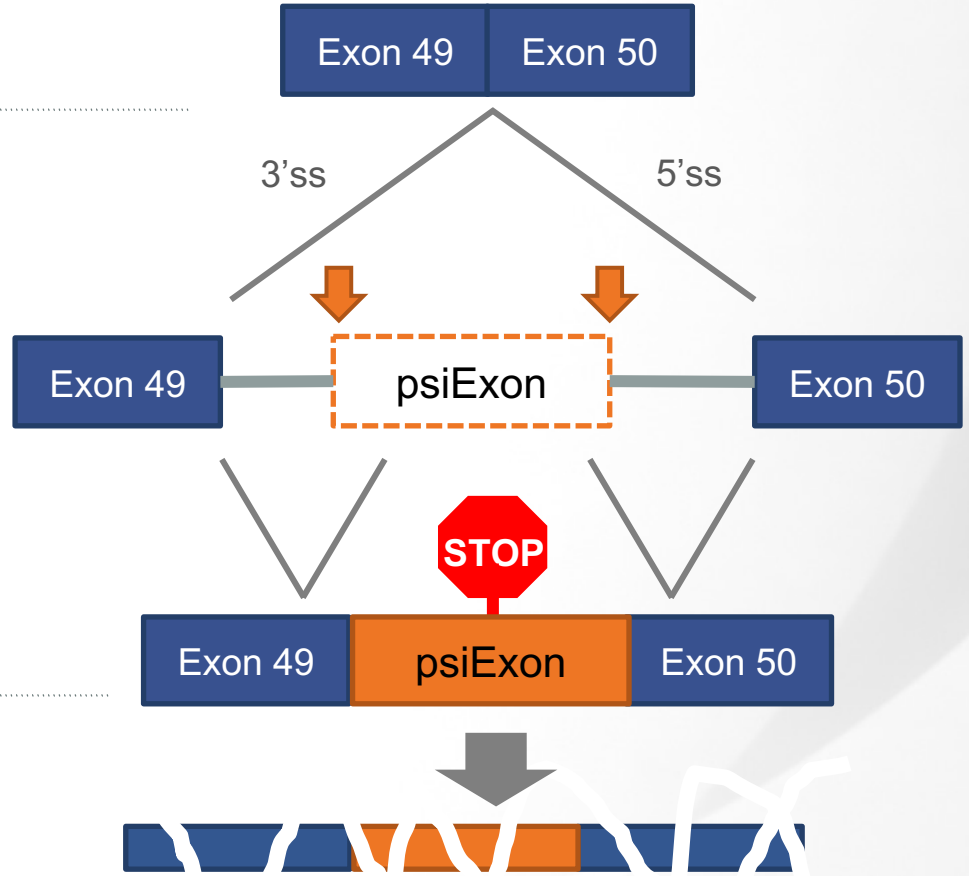
Identification of a Novel Splicing Mechanism that Leads to Degradation of Mutant HTT mRNA

No compound

Pseudoexon is not spliced in;
full length HTT protein is produced

With PTC518

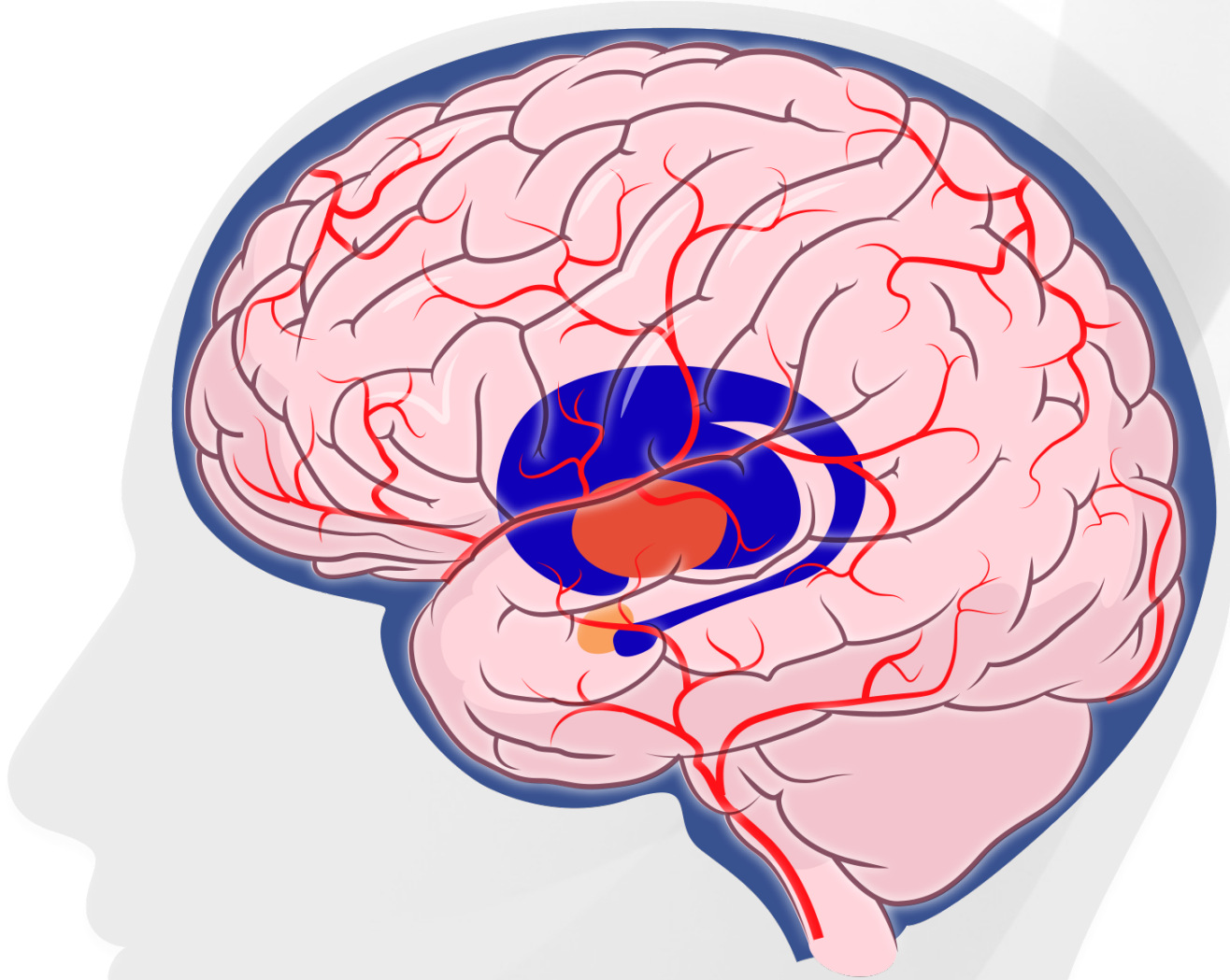
Pseudoexon is spliced in;
Nonsense mutation leads
to mRNA degradation

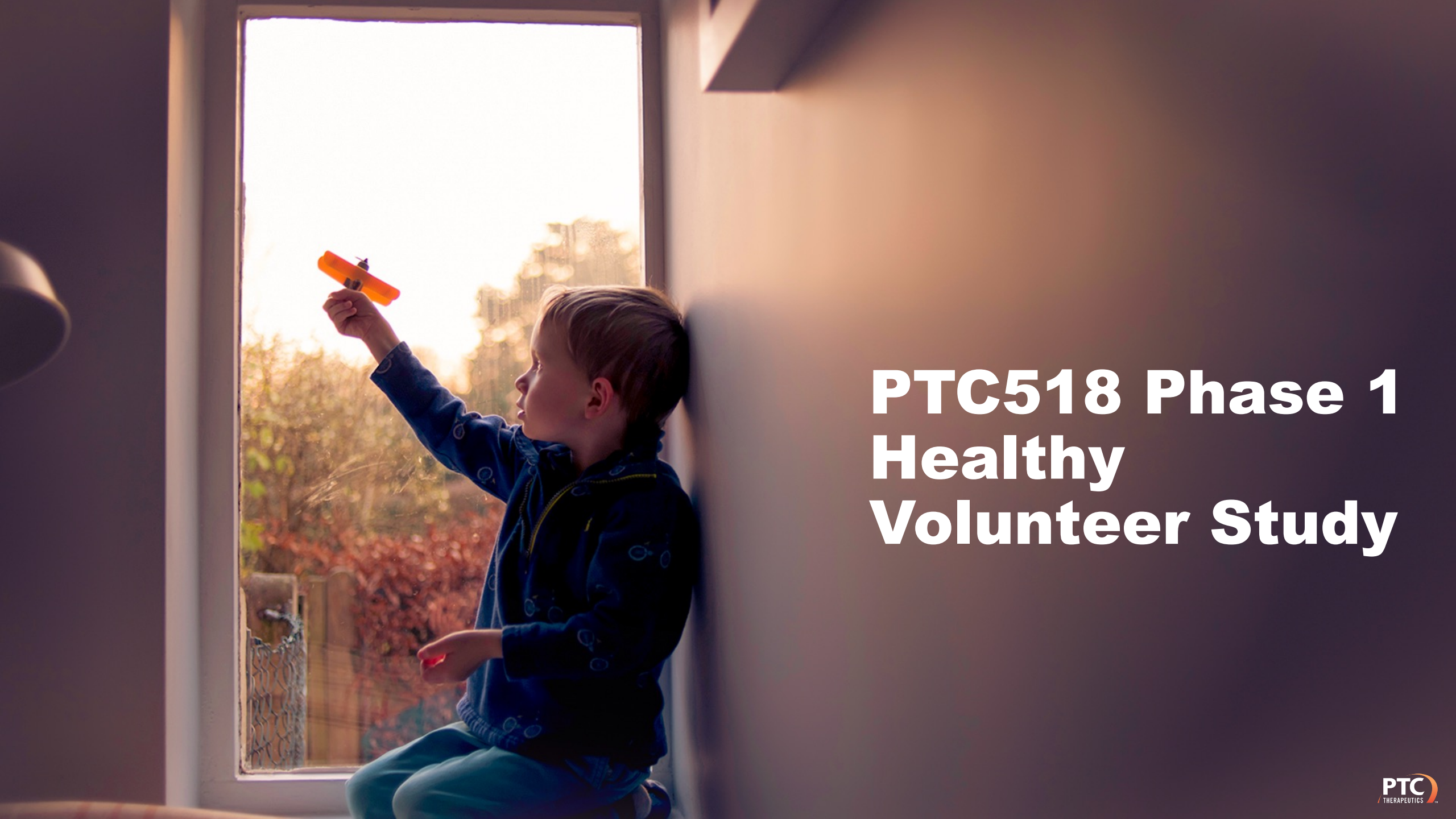


Nonsense-mediated *HTT* mRNA decay

Characteristics of PTC518 Were Demonstrated in Preclinical Studies

- Orally bioavailable and penetrates blood brain barrier
- Reduces HTT mRNA and protein in the CNS and periphery
- Reversible and titratable
- Uniform lowering in key regions of the brain
- Not effluxed
- Highly selective





PTC518 Phase 1 Healthy Volunteer Study

The PTC518 Phase 1 Trial Was a 4-Part Study

Phase 1 trial in healthy volunteers

Preliminary Results:
Single and multiple ascending dose:
Evaluate safety & tolerability; HTT mRNA splicing

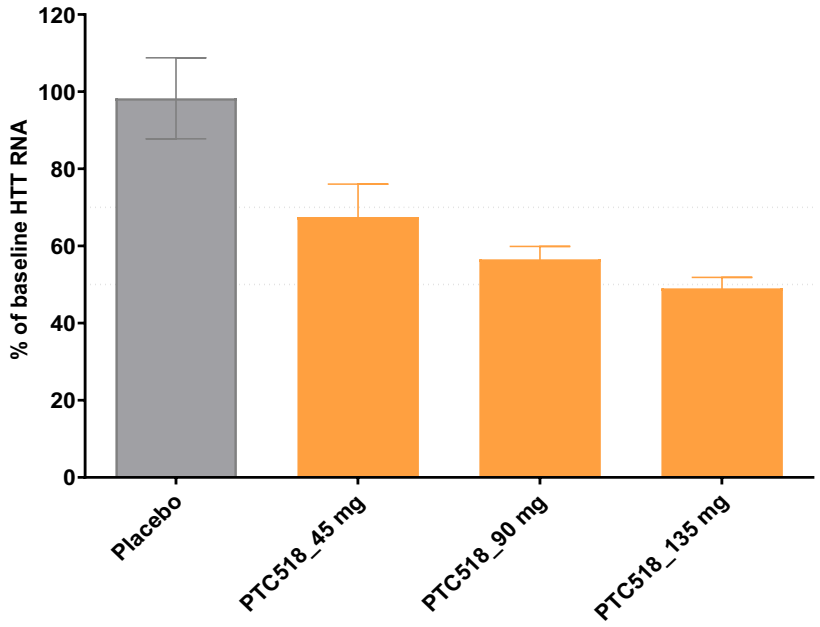
Multiple ascending dose longer duration:
HTT mRNA splicing & protein lowering

CSF sampling:
Evaluate pharmacokinetics of PTC518 in the CSF
Compare drug levels in CSF with plasma compartment

Food effect:
Evaluate the effects of food on PTC518 pharmacokinetics

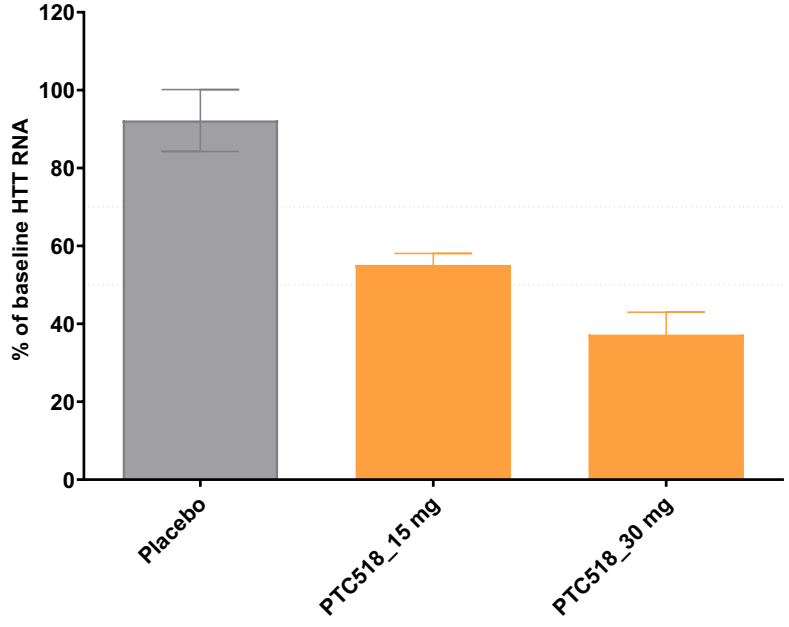
Proof of Mechanism of PTC518 Was Confirmed By Dose-Dependent *HTT* mRNA Splicing in Healthy Volunteers

SAD Study



- Whole blood *HTT* splicing in humans
  - Doses evaluated = 5mg, 15mg, 45 mg, 90 mg, and 135 mg
  - Time – one day; single dose; splicing evaluated 24h post dose

MAD Study



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

Phase 1 SAD & MAD Interim Results Showed That PTC518 Reduced HTT mRNA in a Dose-Dependent Manner

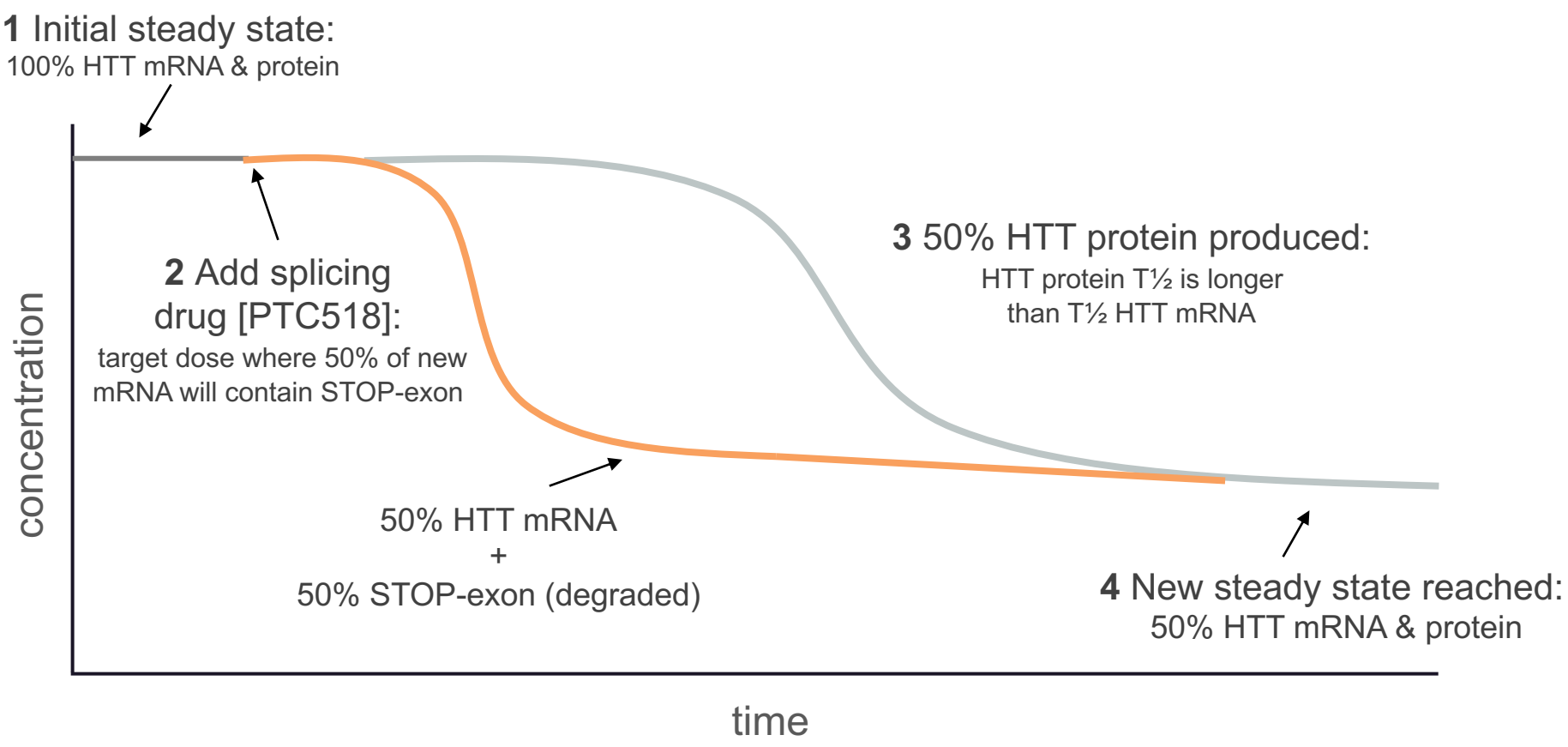
Well tolerated

Predictable pharmacology

Dose-dependent splicing of HTT mRNA

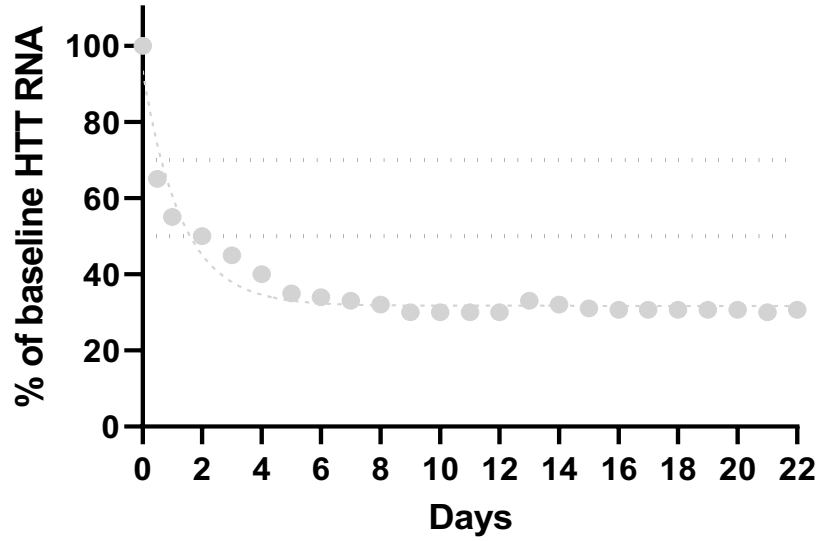
MAD showed long drug half-life with maintenance of splicing up to 72 hours following last dose

Decay Rates Can Be Modeled To Predict Drug-Dependent Decrease in mRNA and Protein Concentration Over Time

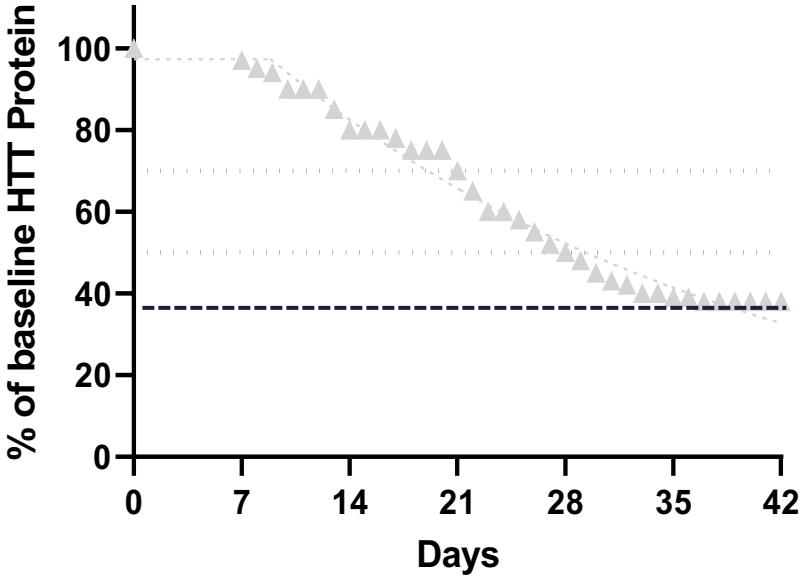


PTC518 Is Predicted to Achieve Equivalent HTT mRNA and Protein Reduction at Steady-State

HTT mRNA abundance
Steady state lowering should reach within 1 week



HTT protein abundance
Steady state lowering should take ≥6 weeks



 Data on file

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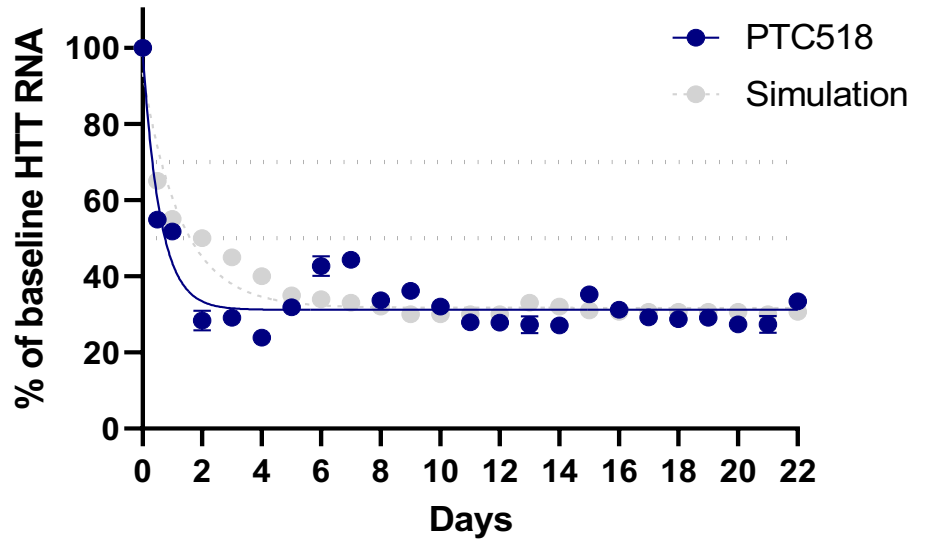

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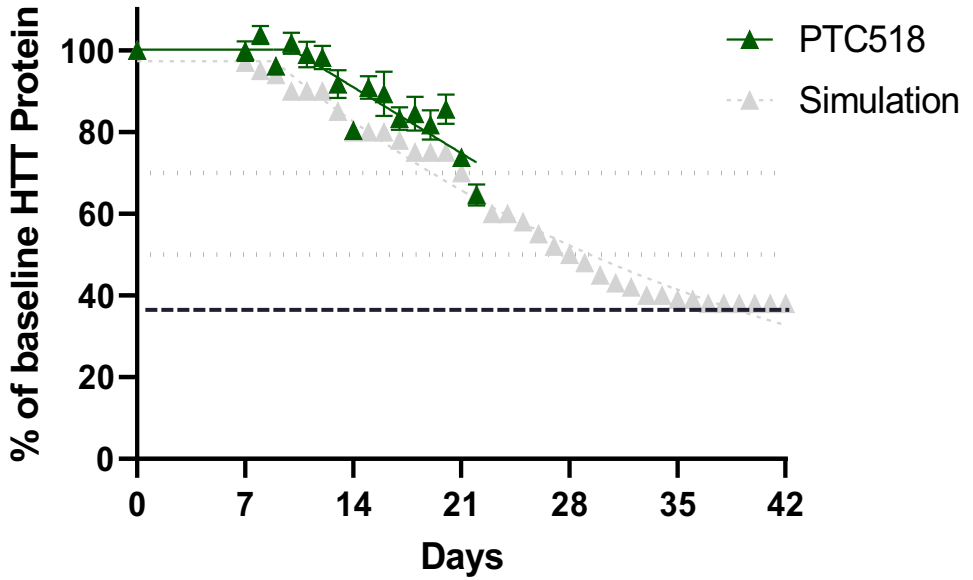

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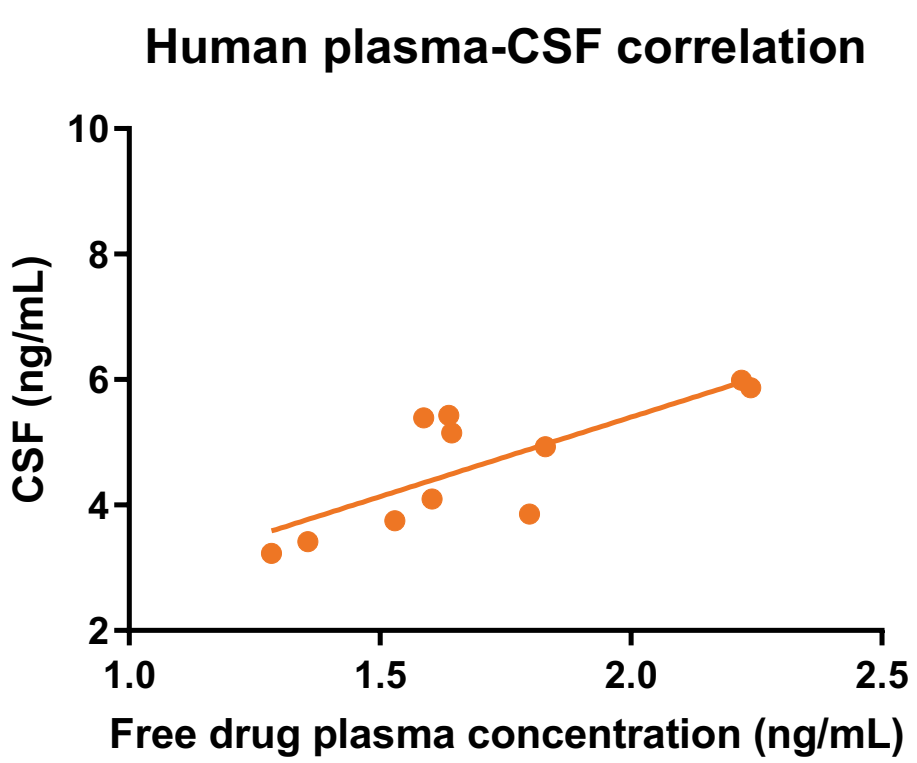
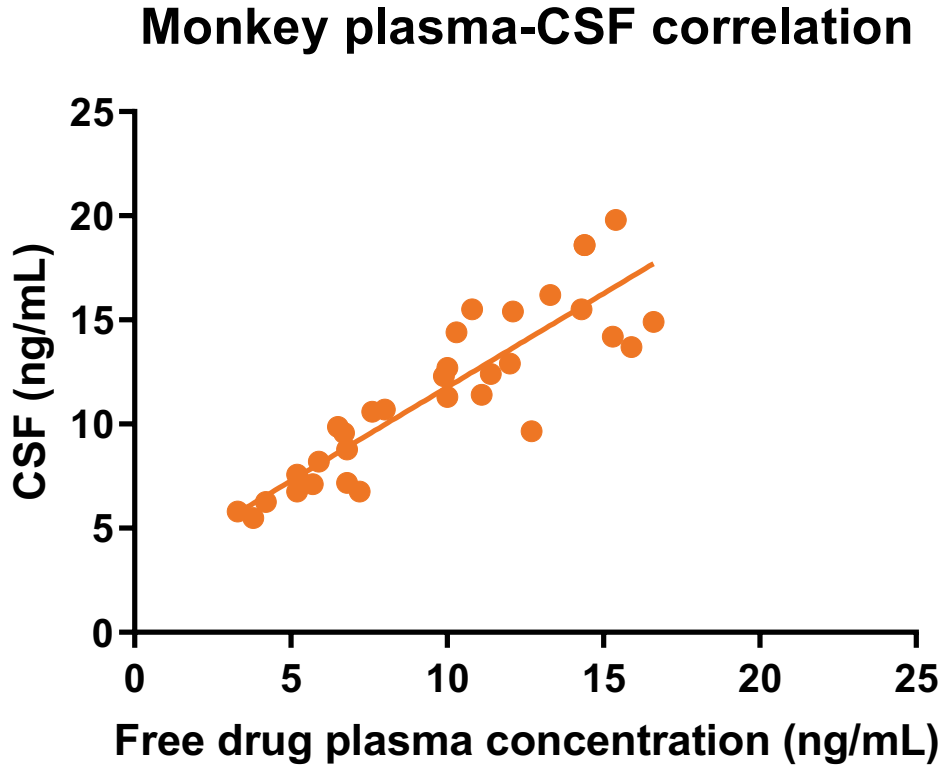
PTC518 Crosses the Blood Brain Barrier in Non-Human Primates and Humans





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Phase 1 Results Showed That PTC518 Reduced HTT mRNA and Protein in a Dose-Dependent Manner and Passed the Blood Brain Barrier

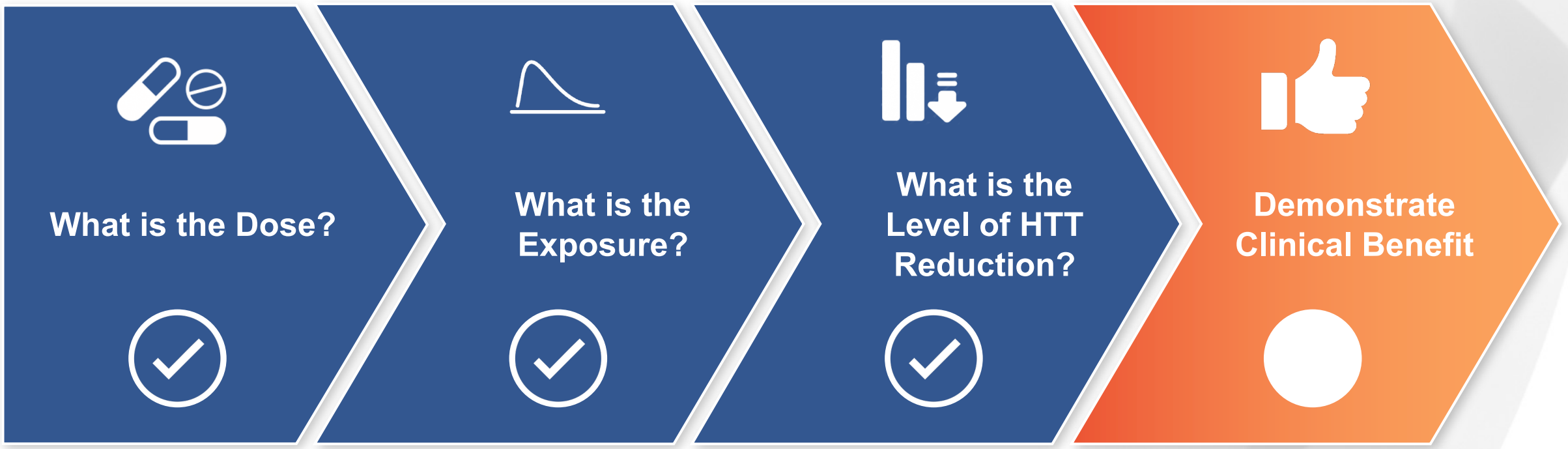
Well tolerated

Predictable pharmacology

Dose-dependent reduction of HTT mRNA and Protein

PTC518 levels in the CSF are equal to or greater than levels observed in blood

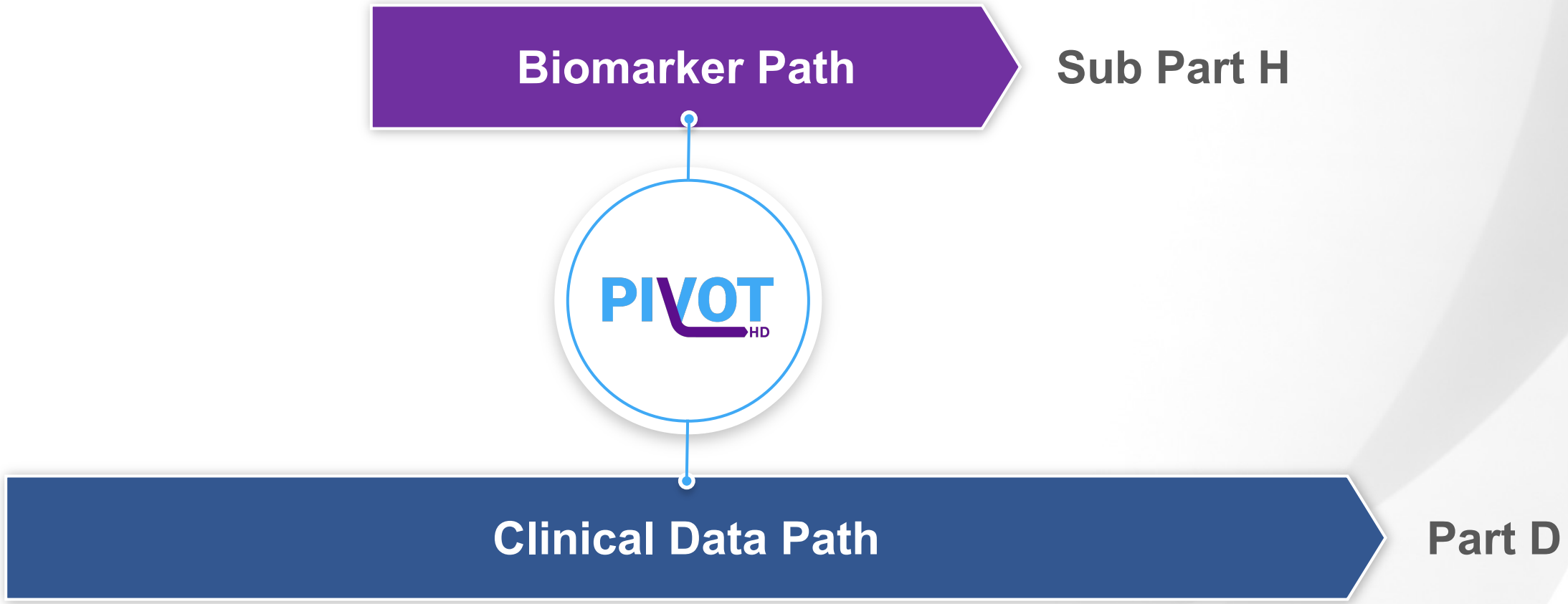
Results Confirm Exposure of PTC518 Can Lead to Clinically Meaningful HTT Reduction mRNA and Protein



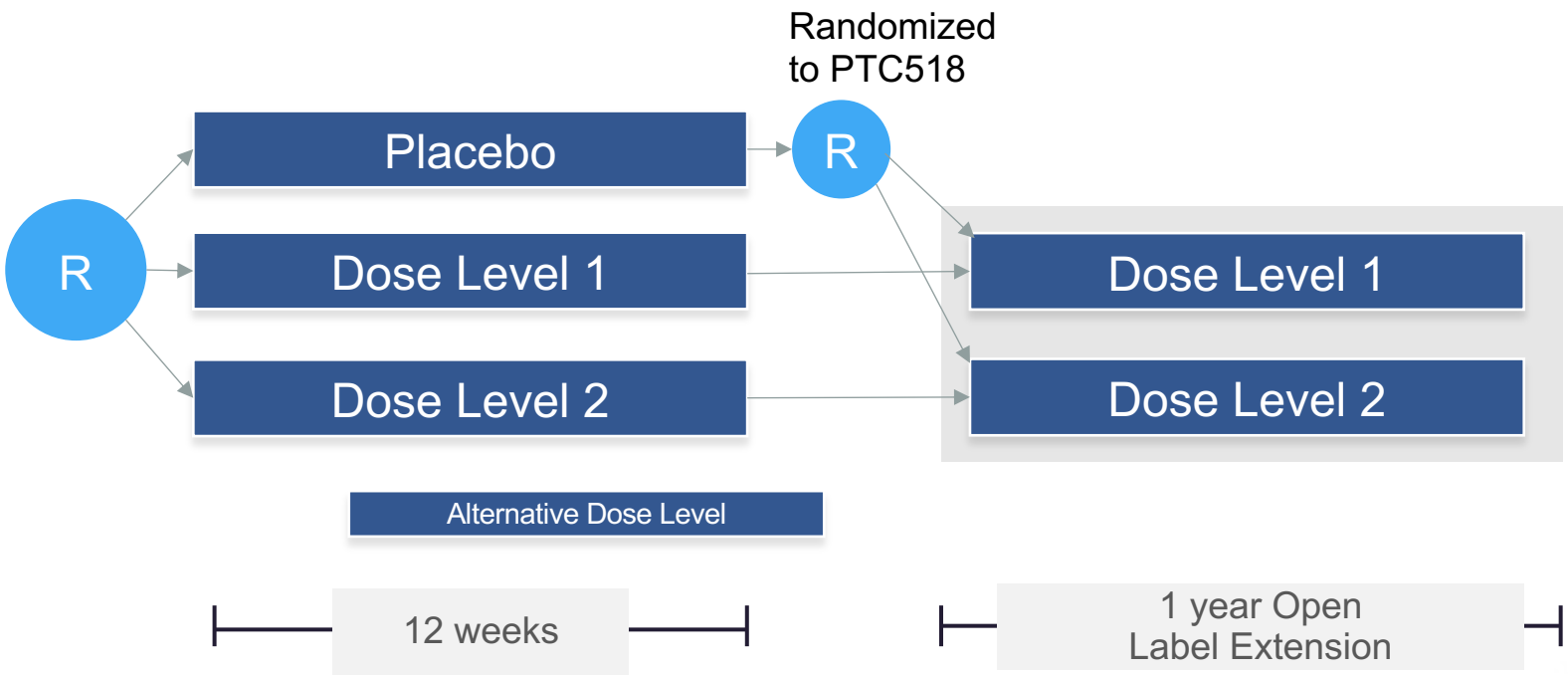
PTC518 Phase 2 Study Design

Phase 2 study objectives

Strategies For Potential FDA Approval



PTC518 Phase 2 Study – PIVOT HD Planned Study Design



- Double blind, multiple dose, 12-week placebo-controlled study with a long-term open label extension
- Global clinical trial
- N~100-150 patients
- Trial to initiate by YE2021

PIVOT HD Endpoint Strategy

Primary endpoints

- Safety and tolerability of PTC518 in Huntington's disease patients
- Percent reduction in HTT mRNA and protein in blood

Biomarker endpoints

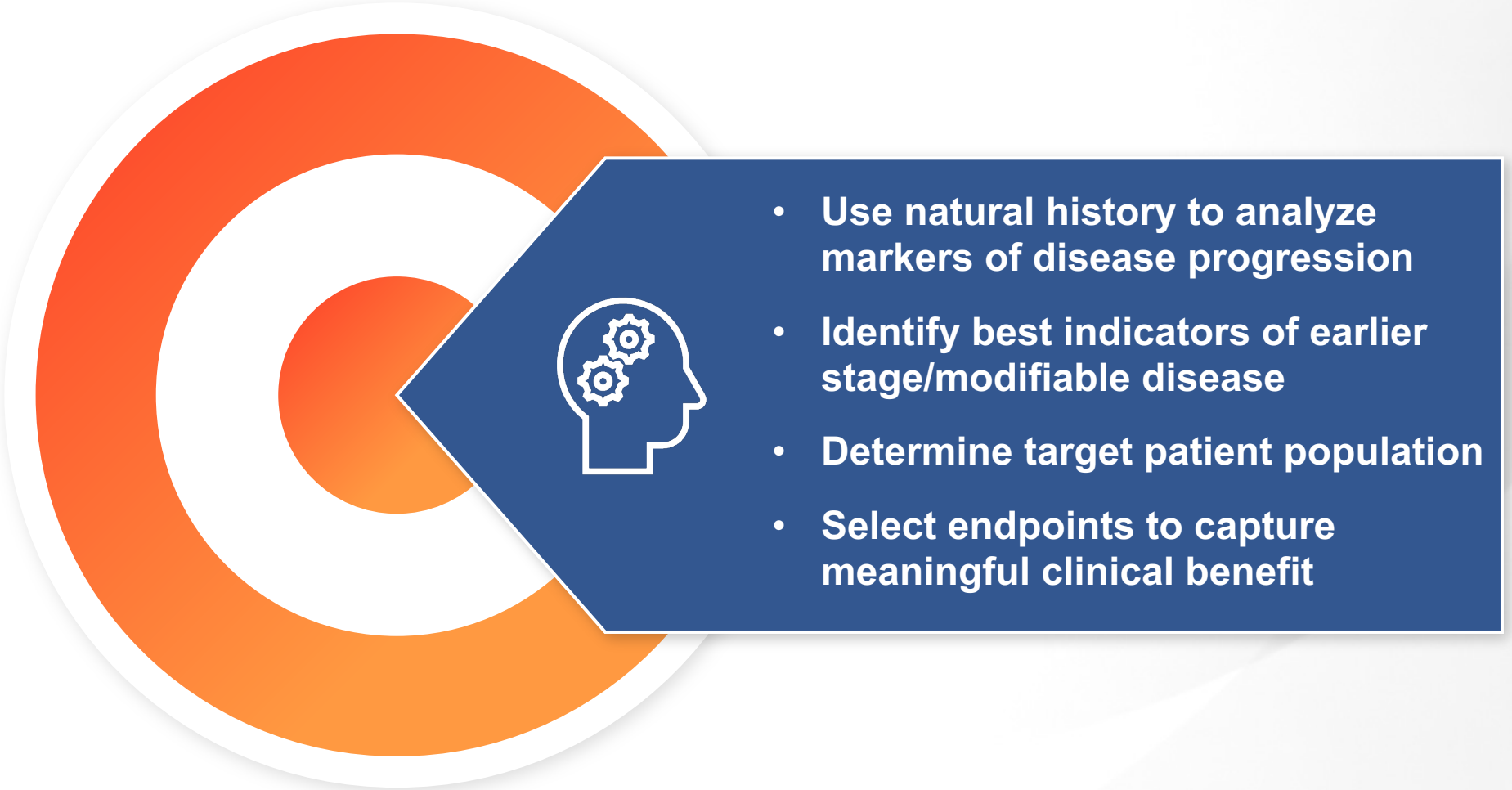
- Percent reduction in HTT protein in CSF
- Changes in neurofilament light chain (NfL) in plasma and CSF
- Change in caudate, putamenal, ventricular volume on volumetric MRI imaging

Clinical endpoints

- Changes in clinical scales of motor and cognitive function

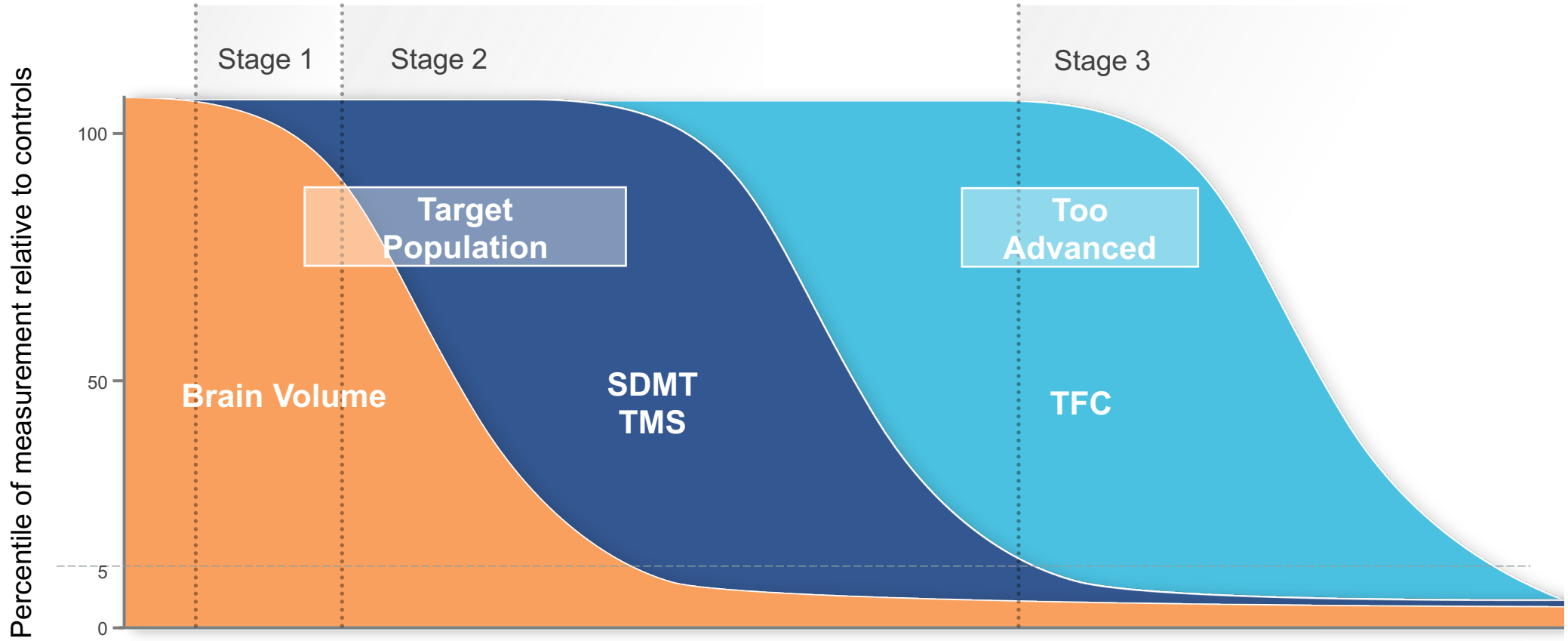
Identifying Optimal Clinical Trial Population

Finding the Goldilocks Population



- Use natural history to analyze markers of disease progression
- Identify best indicators of earlier stage/modifiable disease
- Determine target patient population
- Select endpoints to capture meaningful clinical benefit

Optimal Endpoints Vary by Disease Stage



 Schematic adapted from Natural History Analyses

PIVOT HD Inclusion Criteria

- Age 25 years and older
- Ambulatory
- CAG repeat 42-50 inclusive
- Specific clinical and radiographic parameters
  - Brain volumetric MRI values
  - Total motor score (TMS)
  - Cognitive score
  - Prognostic index of Huntington's disease (PIN_{HD})

Summary

Phase 1 completed with achievement of all study objectives including protein reduction and projected CSF exposure

Phase 2 trial to be initiated by YE 2021

- Multiple dose placebo-controlled trial of PTC518 in HD patients
- Study designed to capture biomarker effects that could potentially support accelerated approval
- Inclusion criteria optimized based on extensive natural history data analyses

Questions