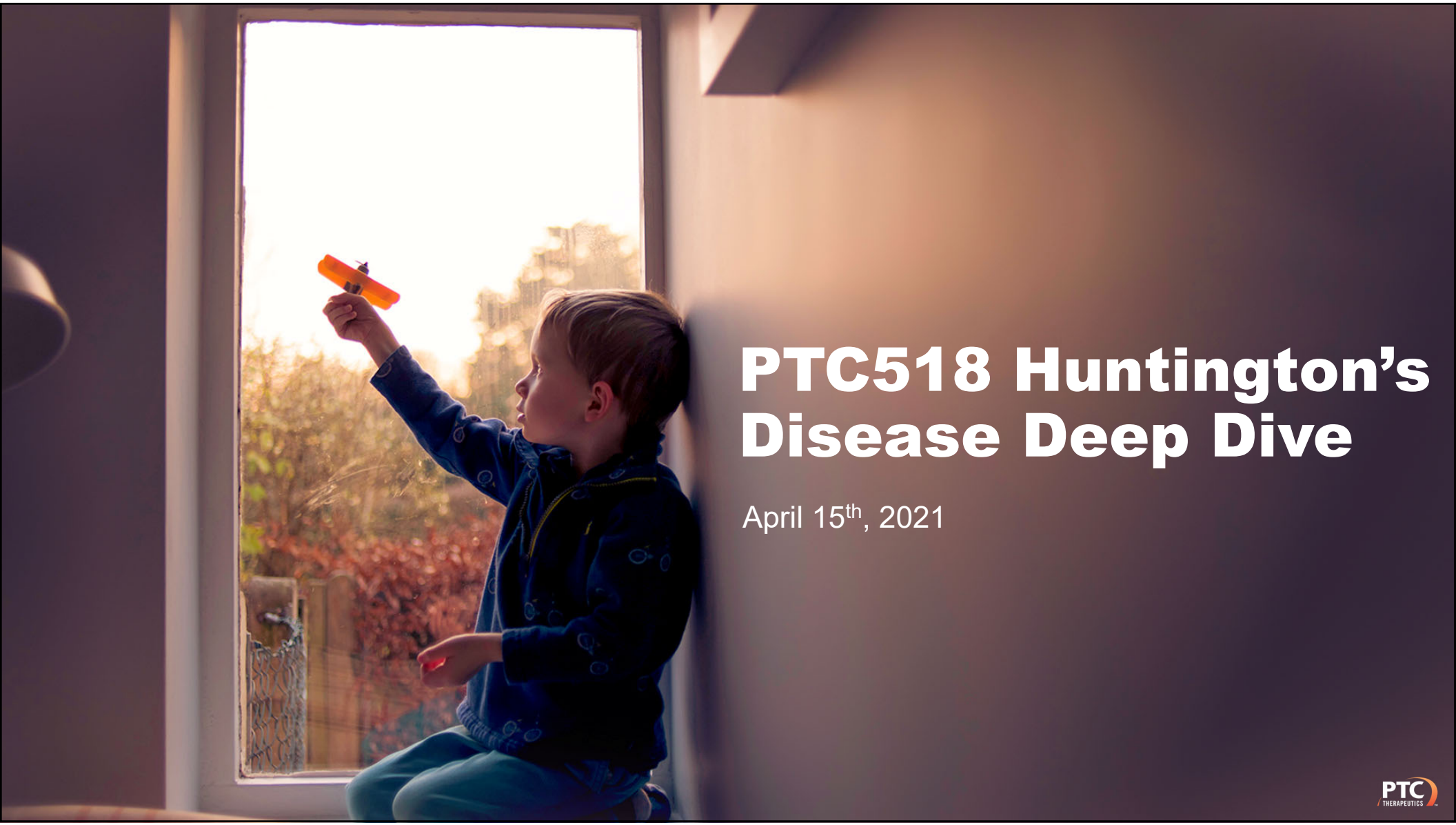


PTC518 Huntington's Disease Deep Dive

April 15th, 2021

Forward Looking Statements:

This presentation 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 with respect to the future expectations, plans and prospects for PTC, PTC's strategy, including with respect to the expected timing of clinical trials and studies, availability of data, regulatory submissions and responses and other matters, 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 ongoing studies under the SMA collaboration and events during, or as a result of, the studies that could delay or prevent further development under the program, including any regulatory submissions and commercialization with respect to Evrysdi; 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.

Diversified Platform Drives Strong Portfolio

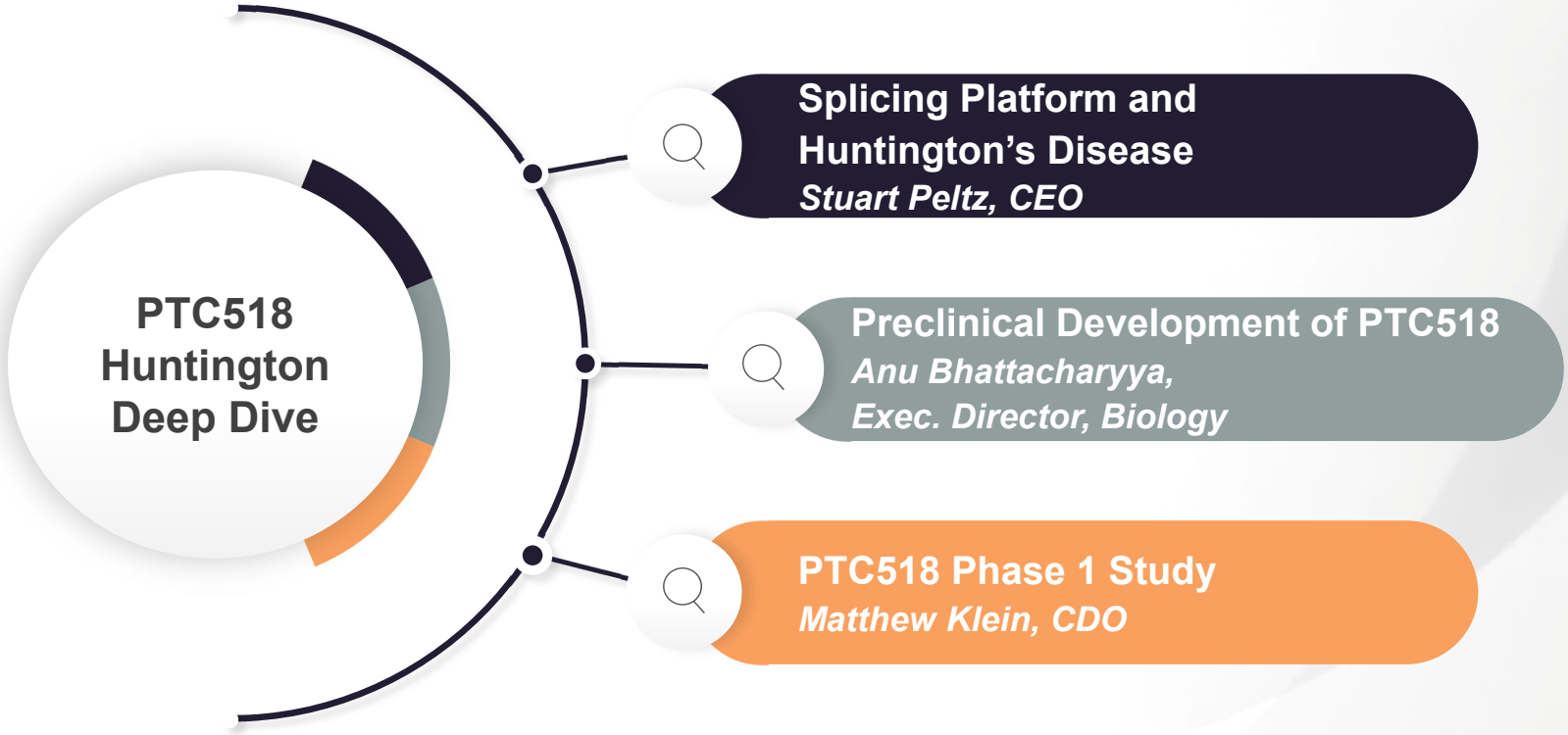
SCIENTIFIC PLATFORMS and RESEARCH

	Deflazacort	LatAm Commercial	Nonsense Mutation	Splicing	Gene Therapy	Bio-e	Metabolic	Oncology	Virology
Commercial	Emflaza® (deflazacort) 6 mg | 18 mg | 30 mg | 36 mg tablets 22.75 mg/mL oral suspension	Tegsedi™ (inotersen) injection 284 mg/1.5 mL; waylivra™ (volanesorsen sodium) injection 300 mg in 1.5 mL	translarna™ ataluren	Evrysdi® risdiplam 0.75 mg/mL powder for oral solution	PTC-AADC				
Clinical			US Dystrophin	PTC518 HD		Vatiquinone ME Vatiquinone FA PTC857 GBA-PD	PTC923 PKU	PTC596 DIPG PTC596 LMS PTC299 AML	PTC299 COVID-19
Research				SCA-3 MAP-Tau	FA Angelman IRDs Cog Disorders	Undisclosed			

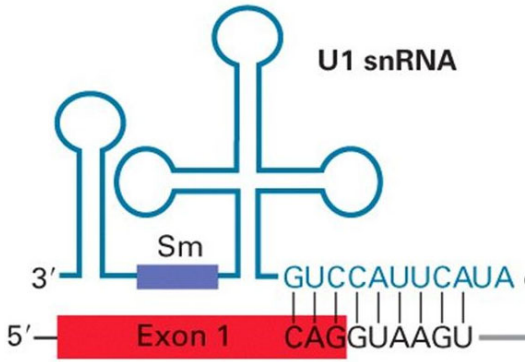
Potential registrational studies

- AADC, aromatic L-amino acid decarboxylase deficiency; AML; acute myeloid leukemia; COVID-19, coronavirus disease 2019; DIPG, diffuse intrinsic pontine glioma; FA, Friedreich's ataxia; GBA, glucocerebrosidase; HD, Huntington's disease; IRD, inherited retinal dystrophy; LMS, leiomyosarcoma; ME, Mitochondrial Epilepsy; PD, Parkinson's disease; PKU, phenylketonuria; SCA-3, spinocerebellar ataxia type 3.

PTC518 Huntington's Disease Deep Dive Agenda

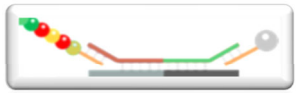


PTC is the Leader in Splicing With 20 Years of Expertise and Proven Track Record

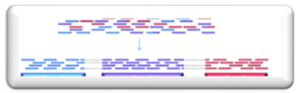


Exploiting splicing

Databases of Splicing Targets



Isoform plex



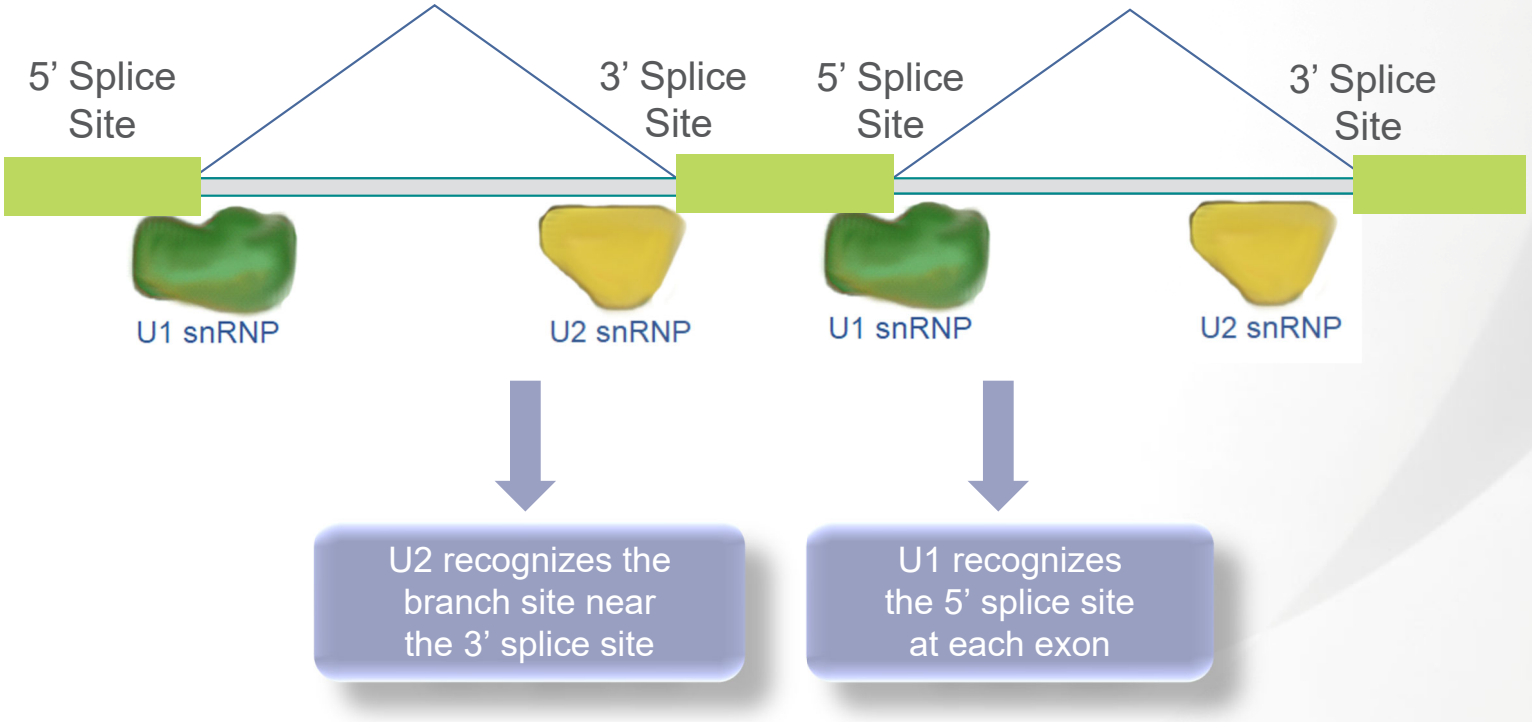
HTSpliceseq

Proprietary systems and specialty libraries

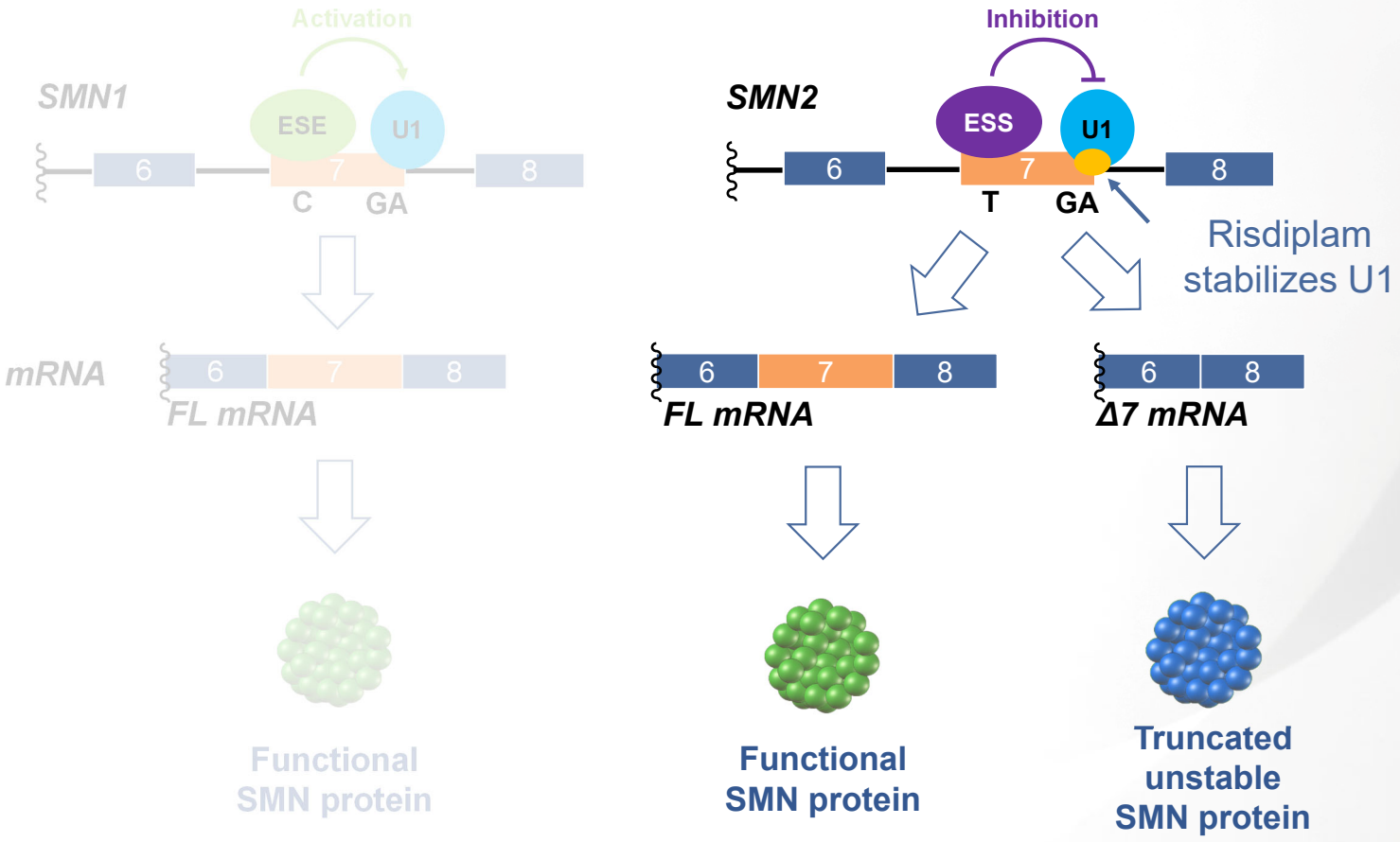
- Spinal muscular atrophy
- Familial dysautonomia
- Huntington's disease

Many additional targets

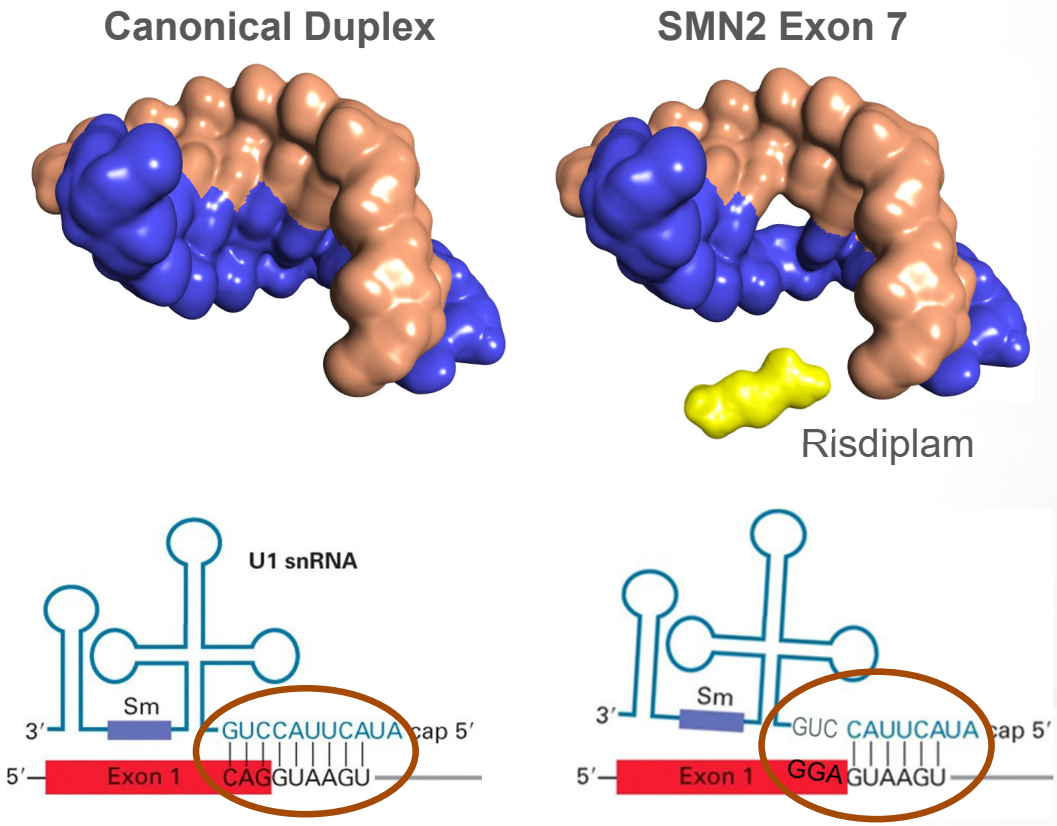
Recognition of Pre-mRNA is Mediated by U-snRNP Complexes U1 and U2



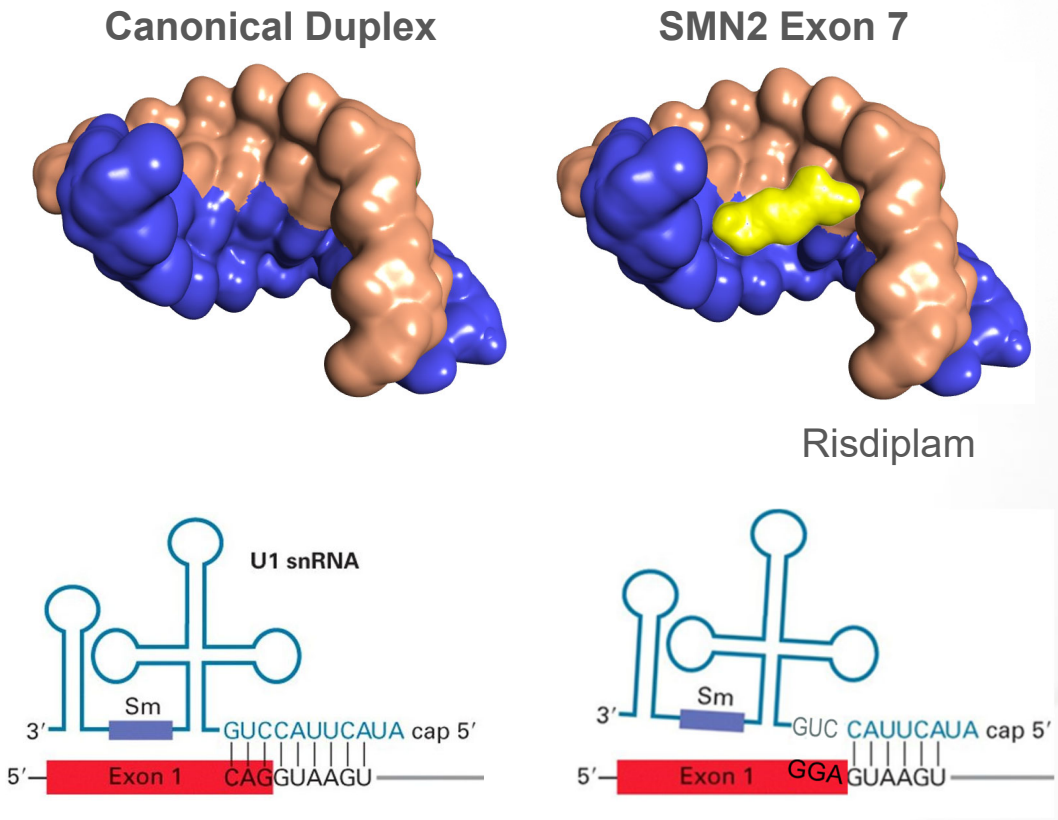
Targeting Alternative Splicing of SMN2 in SMA by Targeting the U1 Site



The SMN2 5'-Splice Site Presents a Unique Structural Interface for Small Molecule

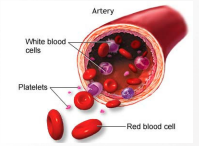


Risdiplam SMN2 Improves the Ability of the 5’-Splice Site to Promote Splicing

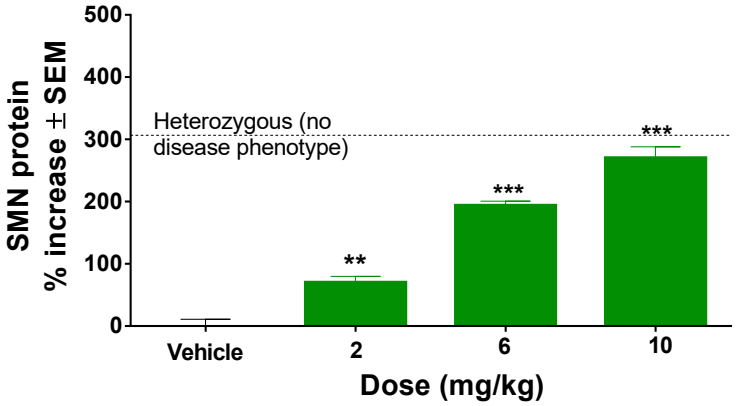


Risdiplam Increases SMN Protein in Multiple Tissues to Near or Above Heterozygous Levels

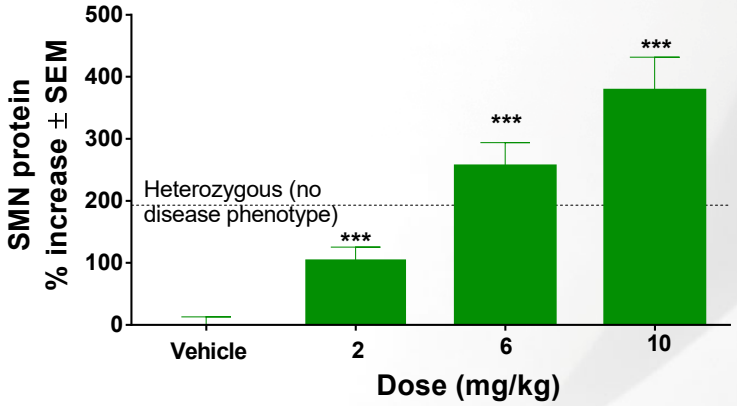
Oral dosing for 10 days in mild SMA mouse model



Brain



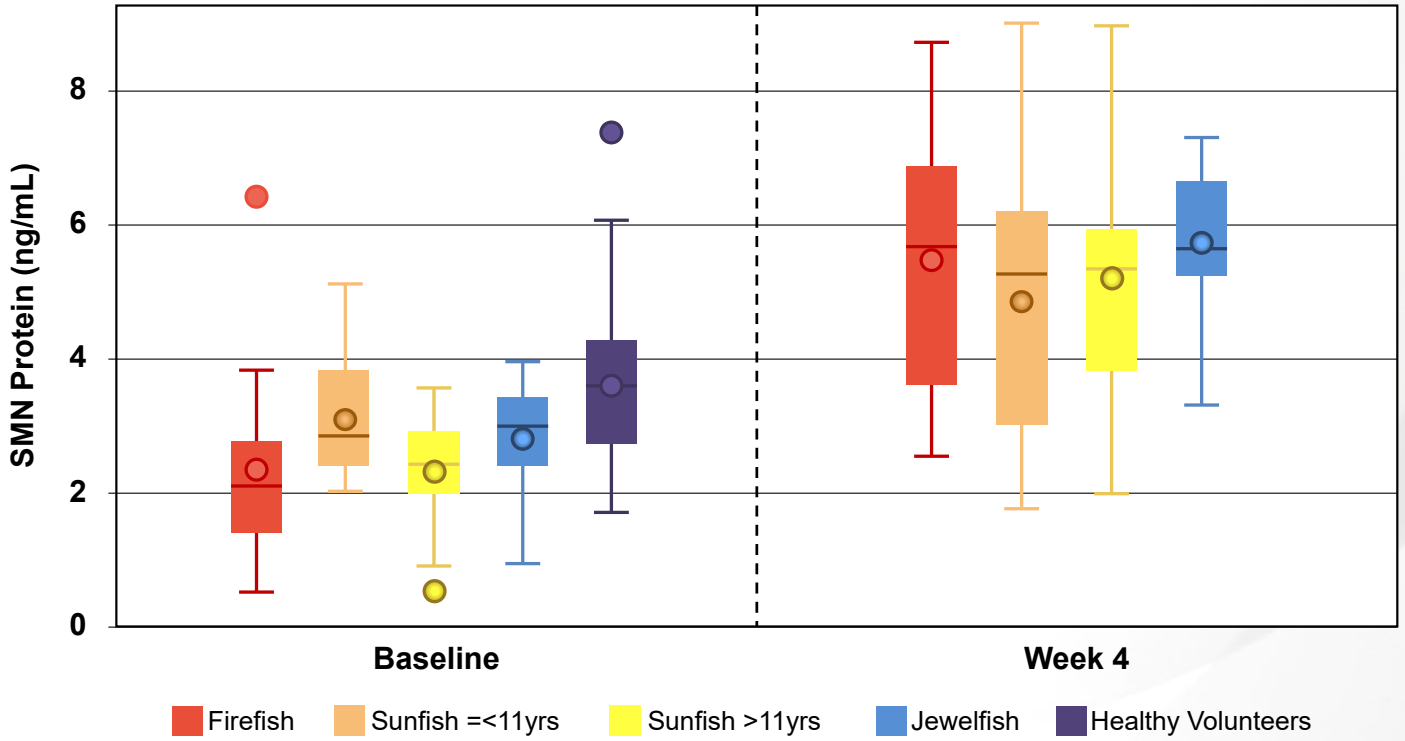
Peripheral Blood Mononuclear Cells



- SMN protein levels in peripheral blood cells correlate to those in brain
- Similar increases in SMN observed in spinal cord, muscle, heart, liver, skin

Naryshkin et al. Science 2014

Risdiplam Increases SMN Protein Levels in All SMA Types to the Level in Adult Healthy Subjects

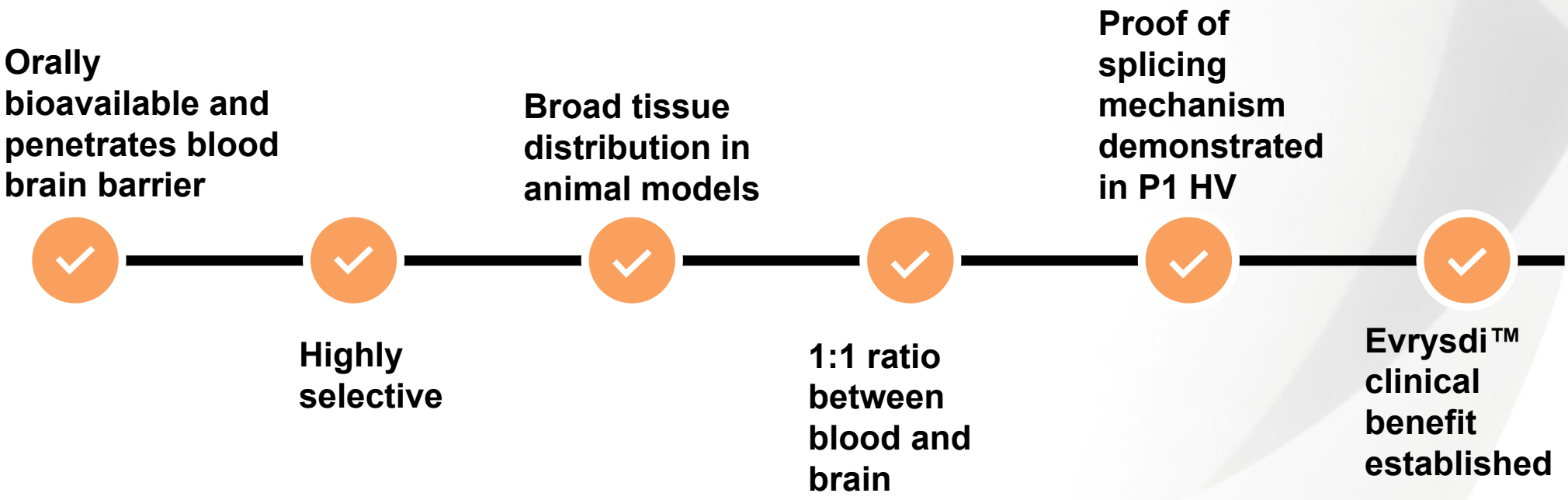


Healthy subjects: n=49, age 18-60 years. Patients with SMA: n=84, age 3.3 months to 52 years. FIREFISH part 1 (n=21), SUNFISH part 1 (n=51), JEWELFISH (n=12). Patients on all dose levels of risdiplam have been included

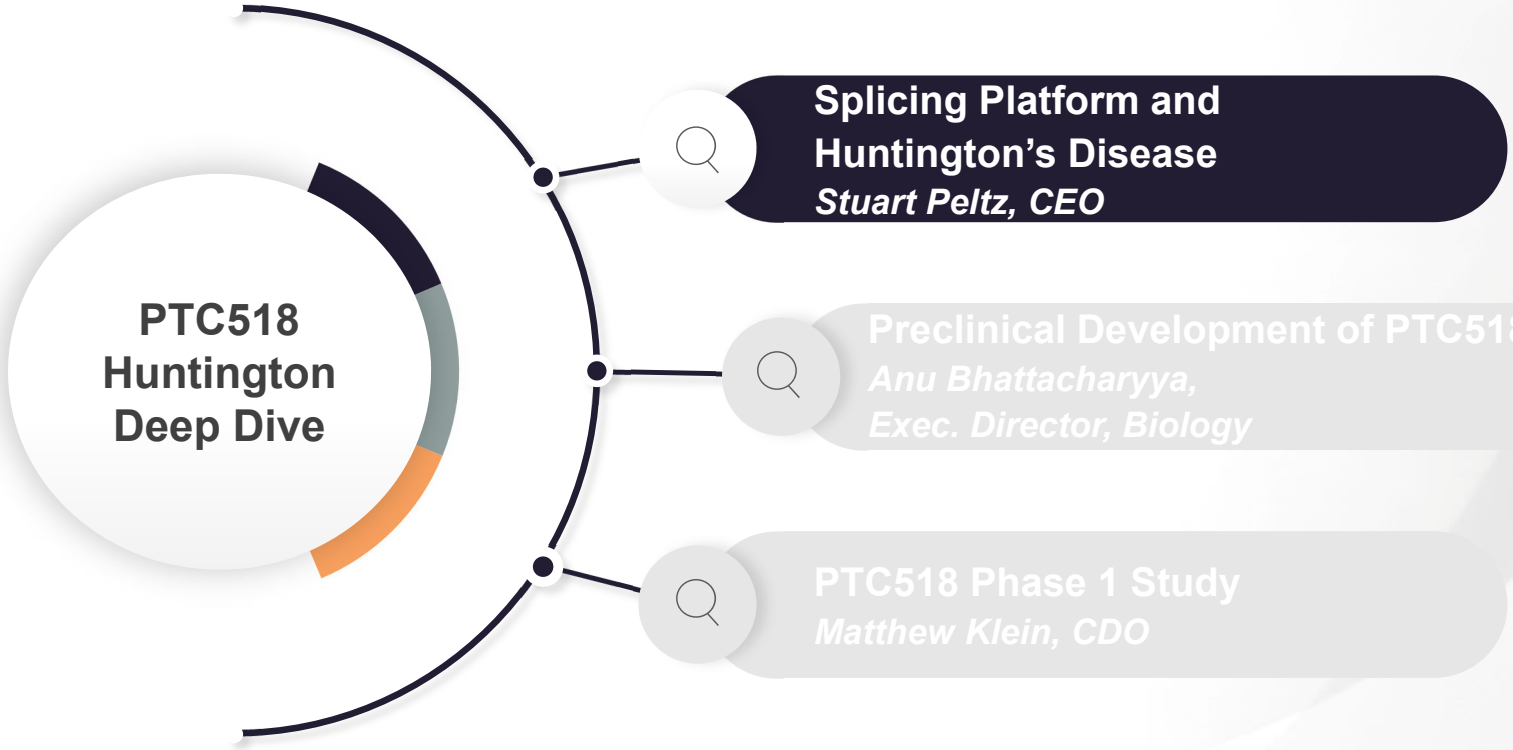
SMA, spinal muscular atrophy; SMN, spinal motor neuron.

Kletzl H, et al. 23rd International Annual Congress of World Muscle Society; October 2-6, 2018; Mendoza, Argentina.

Evrysdi™ Roadmap to Success



PTC518 Huntington's Disease Deep Dive Agenda



PTC518 Huntington's Disease Key Focus Areas

- Overview of Huntington's Disease
- Different treatment modalities
- Why is the blood a good marker that correlates with the CNS?
- Can mHTT in CSF accurately verify target engagement in brain?
- What evidence supports partial lowering of wild type HTT?
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Huntington's Disease is a Debilitating Neurodegenerative Disorder with No Available Disease Modifying Treatments

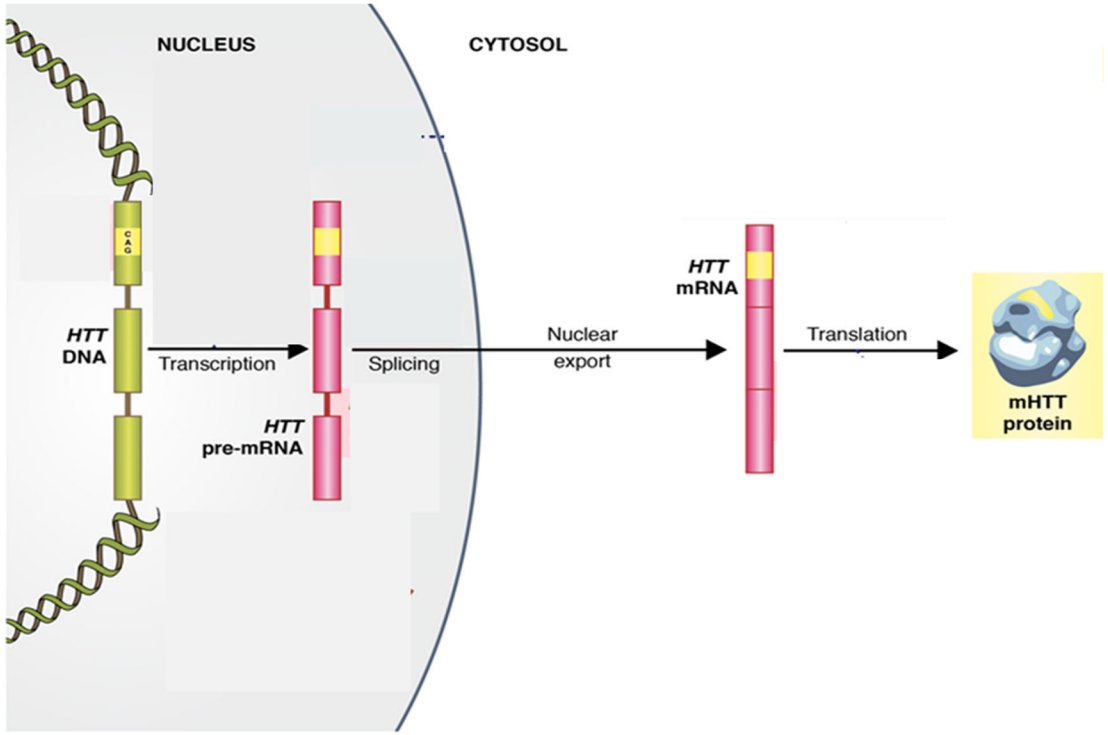
Huntington's Disease

- Caused by a monogenic defect; autosomal dominant inheritance
- Expansion of CAG trinucleotide repeat in the huntingtin (HTT) gene
- Leads to movement, psychiatric and cognitive disorders

Current Treatments

- No approved disease modifying therapies

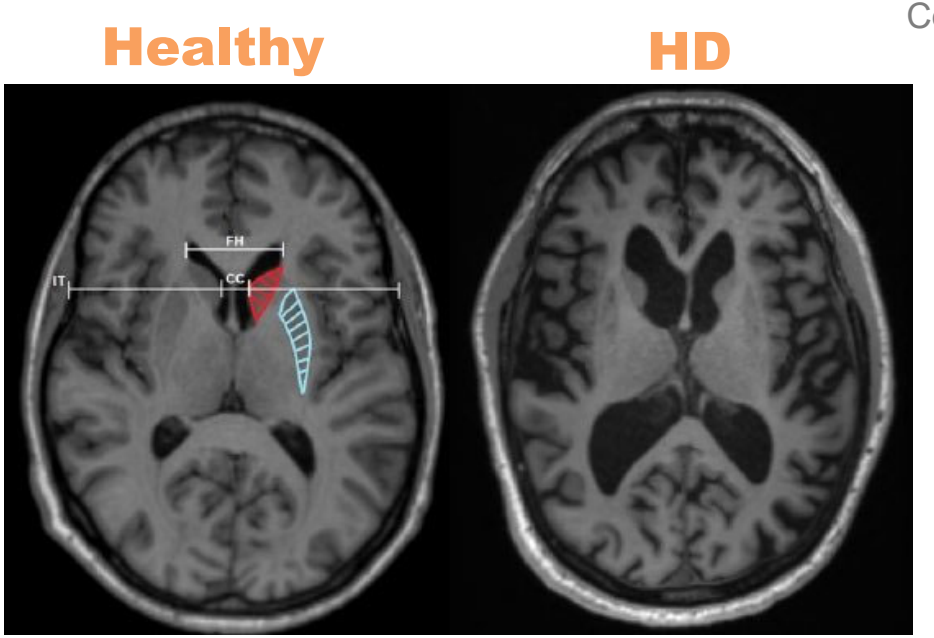
Molecular Basis of Huntington's Disease is Well Understood

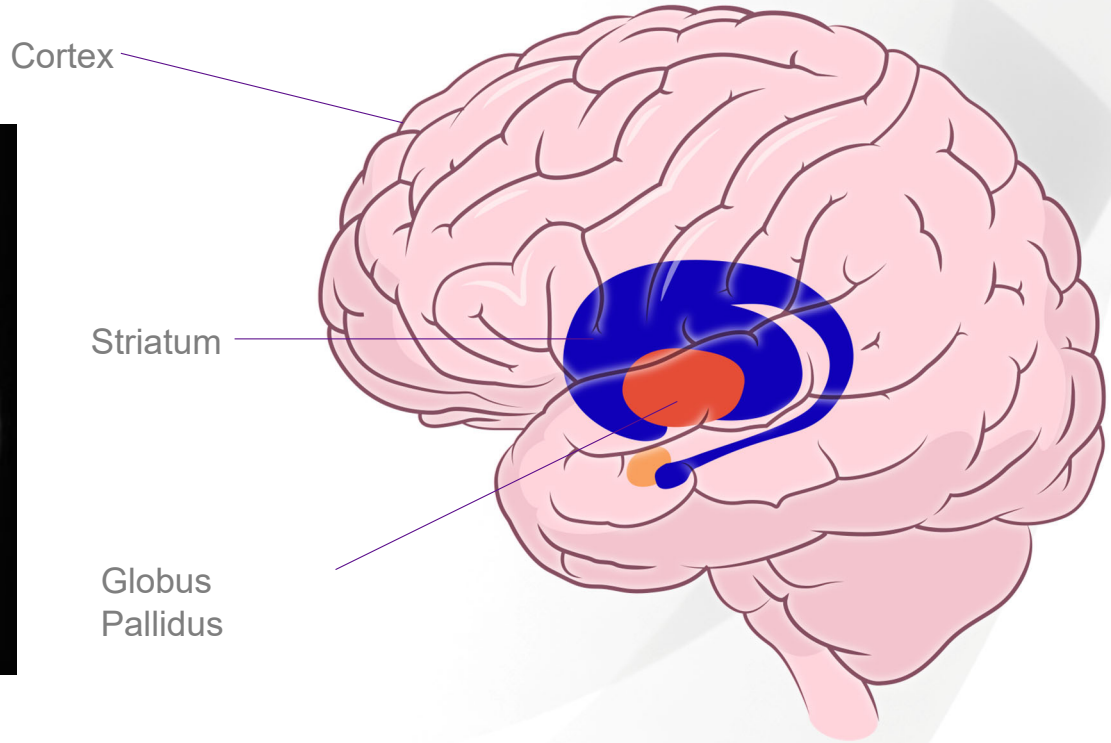


Repeat Count	Classification	Disease Status
<28	Normal	Unaffected
28–35	Intermediate	Unaffected
36–39	Reduced Penetrance	+/- Affected
40-above	Full Penetrance	Affected

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

Progressive Neuronal Degeneration Occurs Throughout the Brain

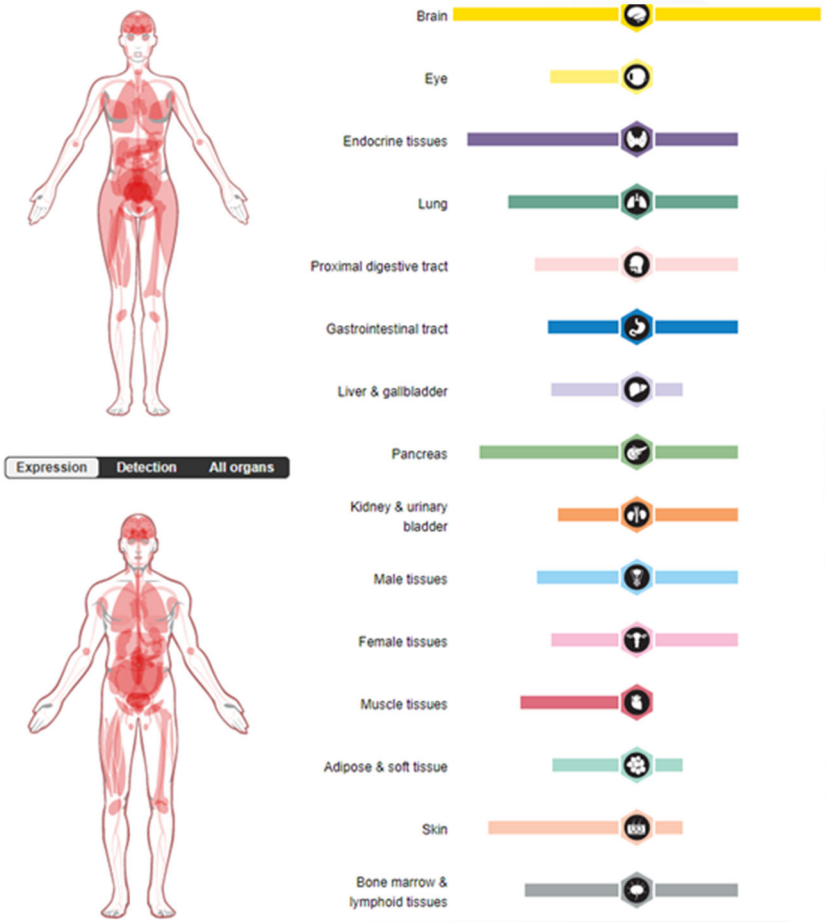




Goh et al. *Aus Psychiatry*. 2018

HTT is Ubiquitously Expressed and Involved in Many Cellular Processes

- Predominantly an intra-cellular protein
- Required during embryonic development
- Ubiquitously expressed throughout development and in all adult tissues



 Uhlén M et al., *Science* (2015); www.proteinatlas.org

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Lowering mHTT Expression to Target Root Cause of Pathogenesis

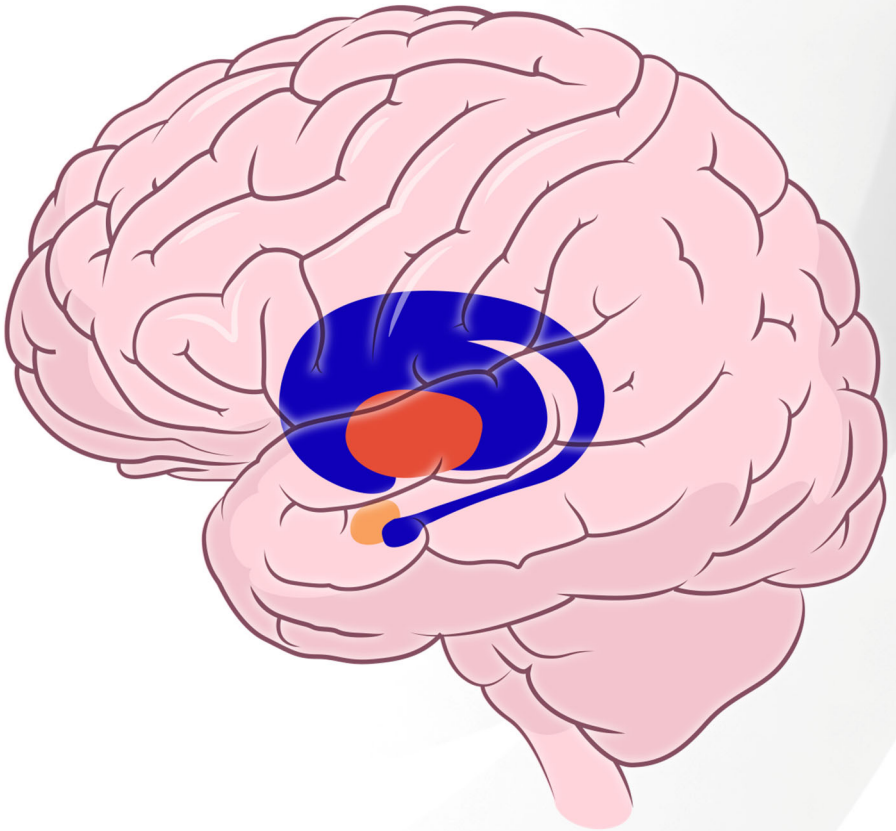
Toxic gain of function mutation

↓

Huntington's disease
Whole brain atrophy
HTT protein aggregates

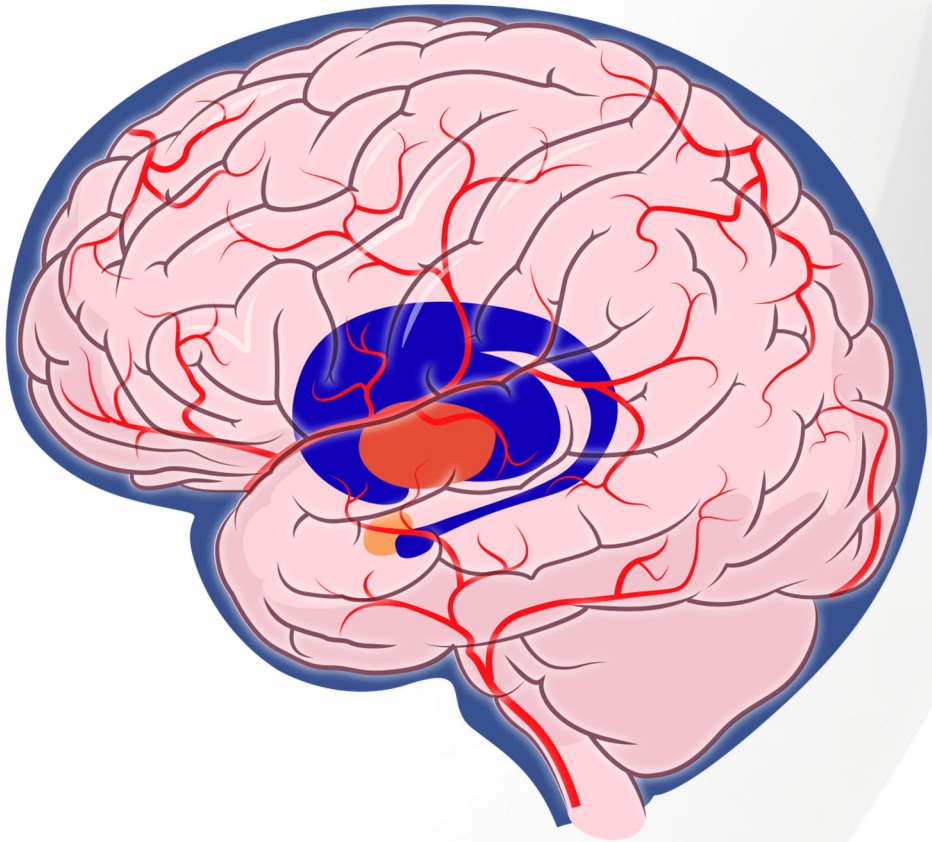
↓

Make less HTT



Oral Treatment has Uniform Lowering Across the Key Regions of the Brain

Property	Small molecules
Delivery	Oral
CNS lowering	Equal across the key areas of the brain
Peripheral lowering	Yes
Reversible	Yes

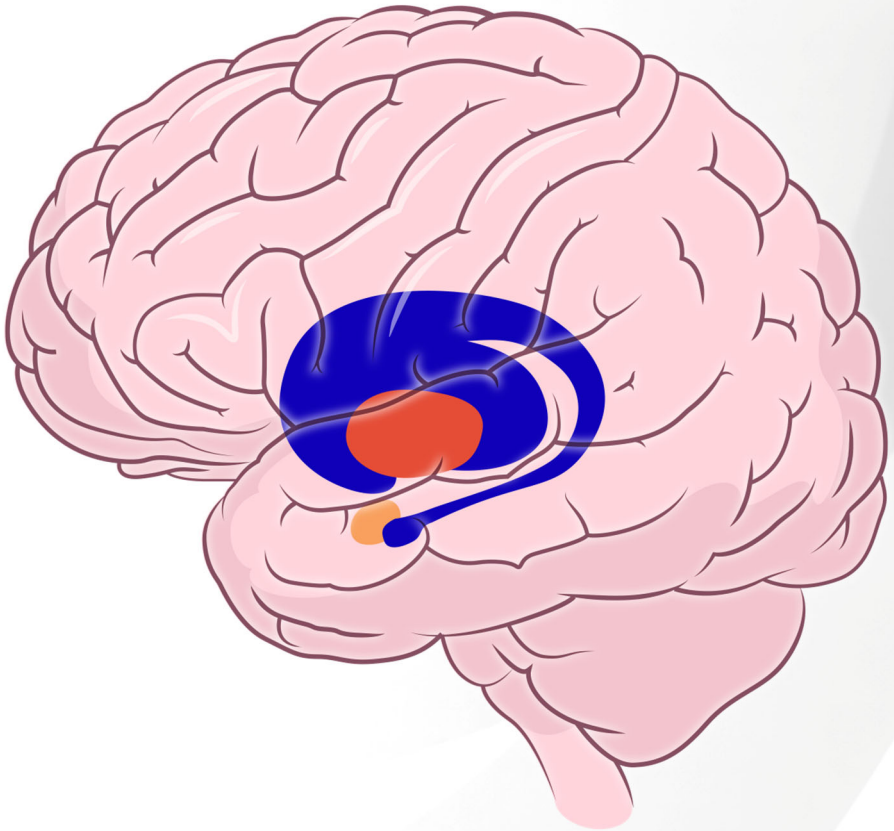


Antisense Oligonucleotide Treatment has More Lowering in the Cortex Compared to the Striatum

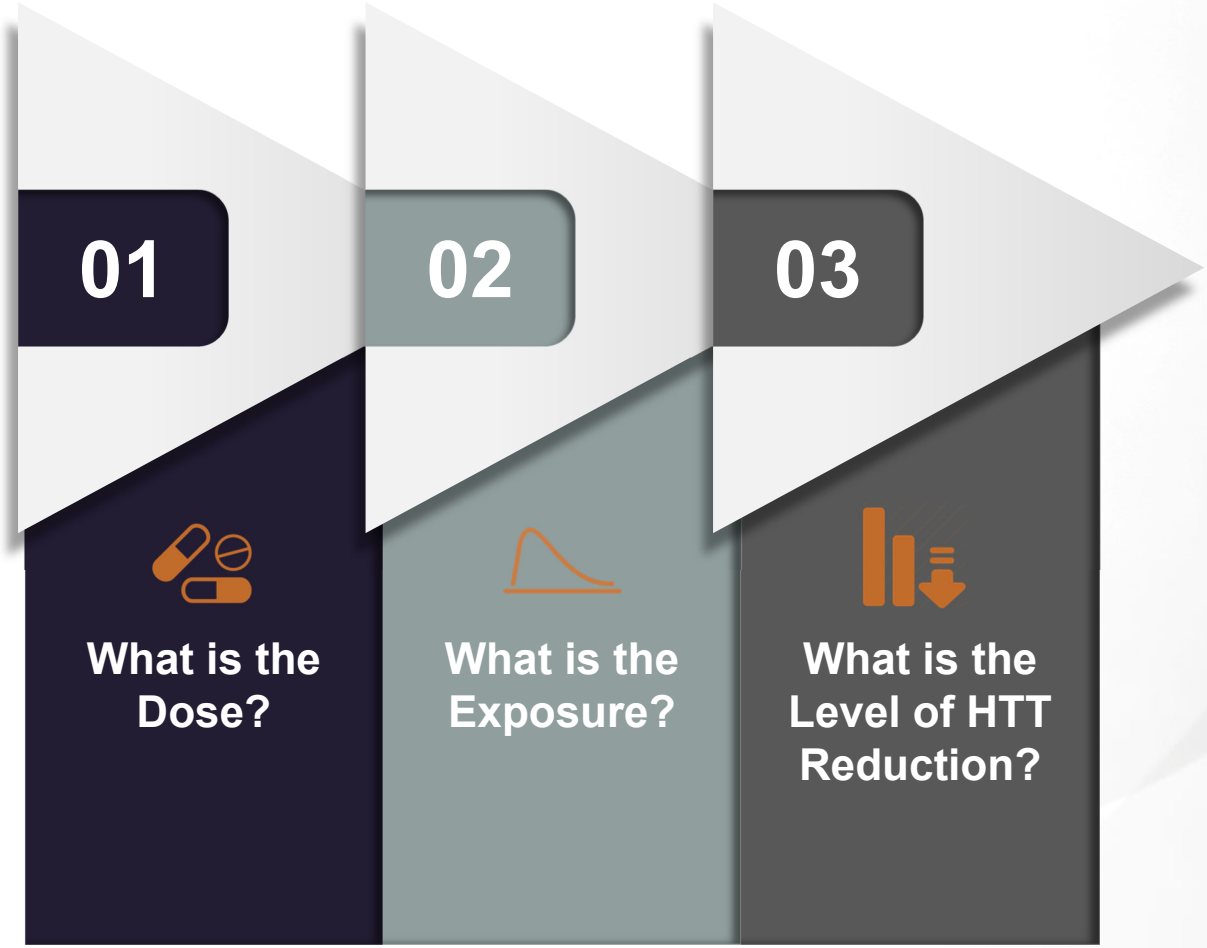
Property	ASOs
Delivery	Intrathecal
CNS lowering	Less reduction in the striatum compared to cortex
Peripheral lowering	No
Reversible	Yes

Gene Therapy Treatment has More Lowering in the Striatum Compared to the Cortex

Property	RNAi
Delivery	Striatum/Thalamus
CNS lowering	Less reduction in the cortex compared to striatum
Peripheral lowering	No
Reversible	No



PTC518 Drug Development Objectives



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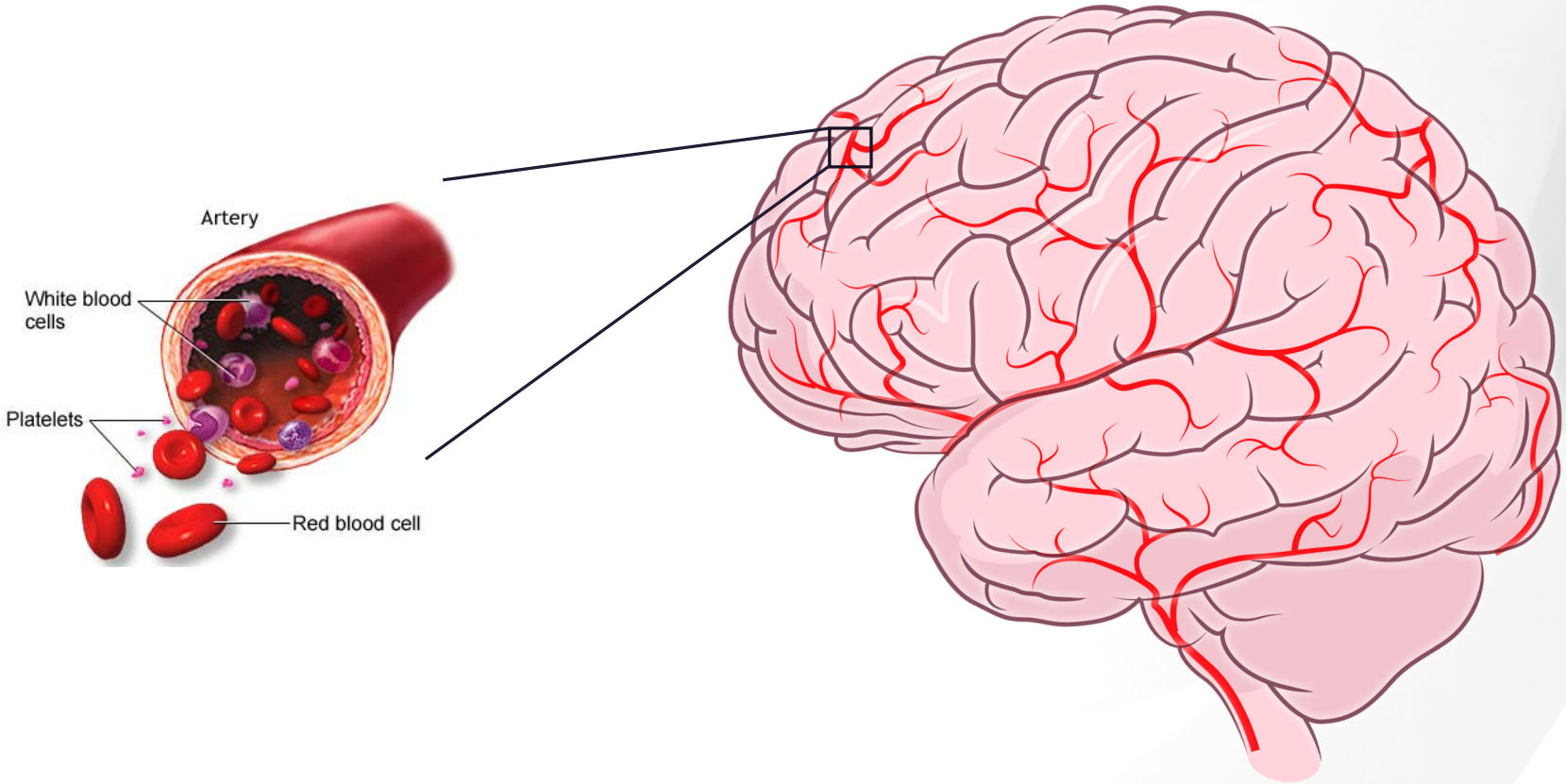
Distribution Through the Blood Effectively Targets the Whole Brain



Purves D, Augustine GJ, et al., editors. Sunderland (MA): Sinauer Associates; 2001.

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The Cerebrospinal Fluid Cushions the Brain

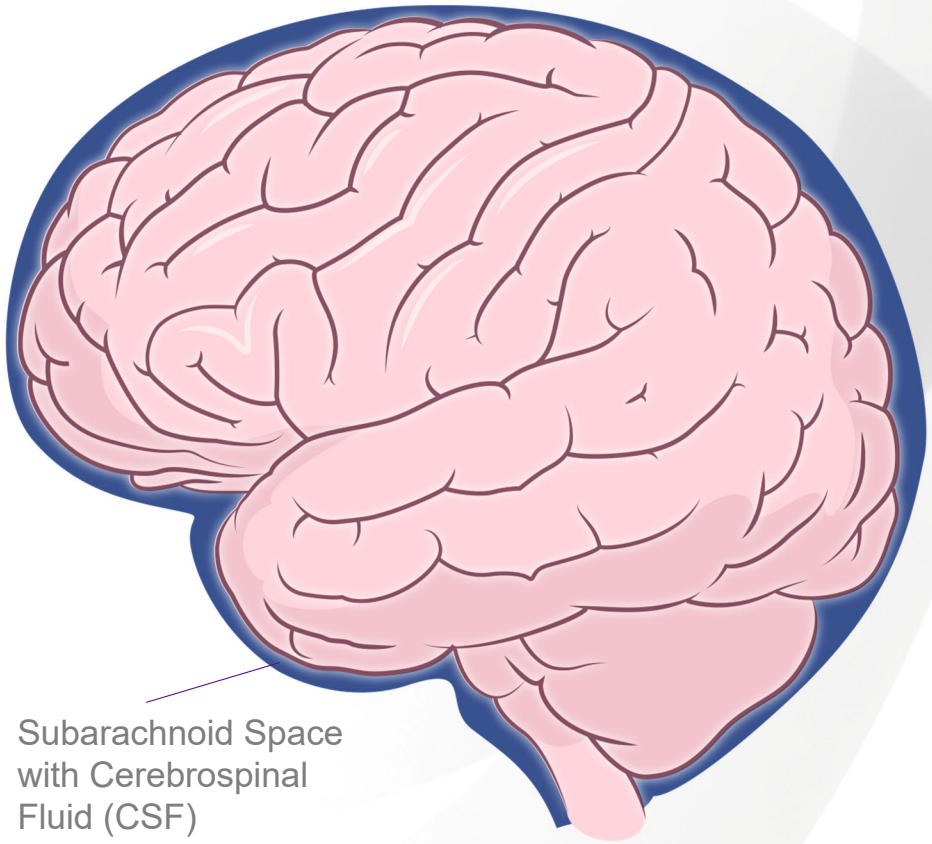
In healthy people, the cerebrospinal fluid (CSF):

Does

- Cushion the brain
- Provide immune surveillance
- Remove metabolic waste

Does not

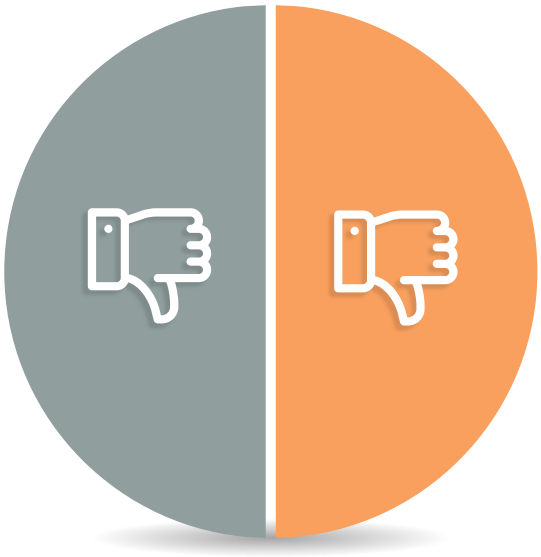
- Interact with most neurons directly
- Contain very much protein (35 mg/dL, compared to 7000 mg/dL in serum)



Limitations of CSF HTT Measurement as a Pharmacodynamic Marker for HTT lowering

What We Know

- Brain mHTT levels >100X CSF mHTT levels
- Very low levels of CSF mHTT – an ultra sensitive assay (low fM) required for measurement
- Assay inconsistency and variability
- Lack of strong correlation between brain and CSF lowering with different modalities



Unknowns

- The origin of CSF mHTT
- Specific contributions of brain regions to CSF mHTT levels
- Not enough data to understand a meaningful treatment related change in levels over assay variability

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Multiple Models Demonstrate Partial Reduction of Wild Type HTT Is Well Tolerated

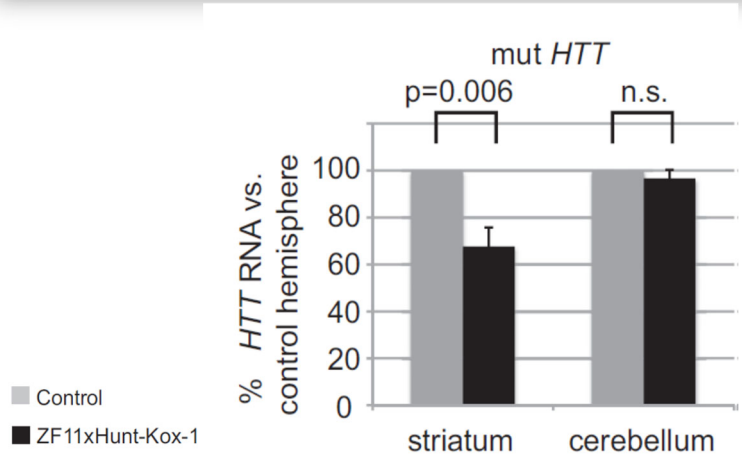
Species	Magnitude of wild type HTT change	Phenotype
Human	Loss of one normal HTT allele ~50%	No detectable abnormal phenotype
Adult Nonhuman Primates	~50%	No alterations in motor function; No abnormal histopathologic findings
Adult Rodents	~50%	No alterations in motor performance or activity

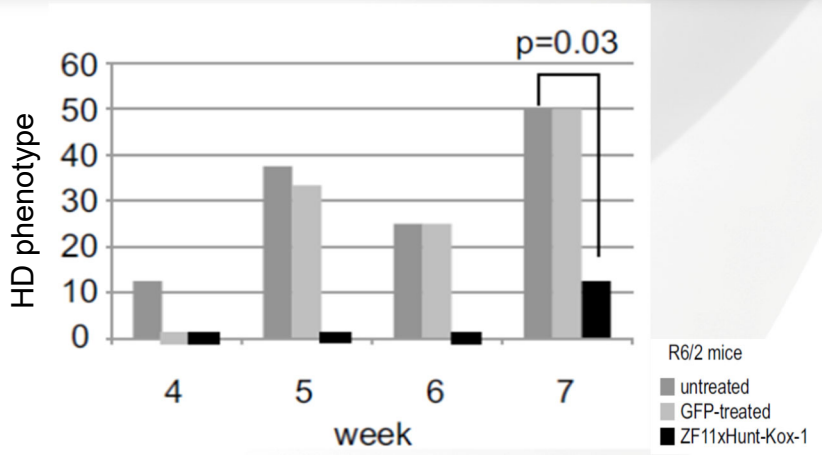
Leavitt et. al. JAMA Neurology 2020 doi:10.1001/jamaneurol.2020.0299

HTT Reduction Correlates with Clinical Benefit

Human data: ~50% reduction in *HTT* transcriptional activity results in mean delay of age of onset by 9.3 years

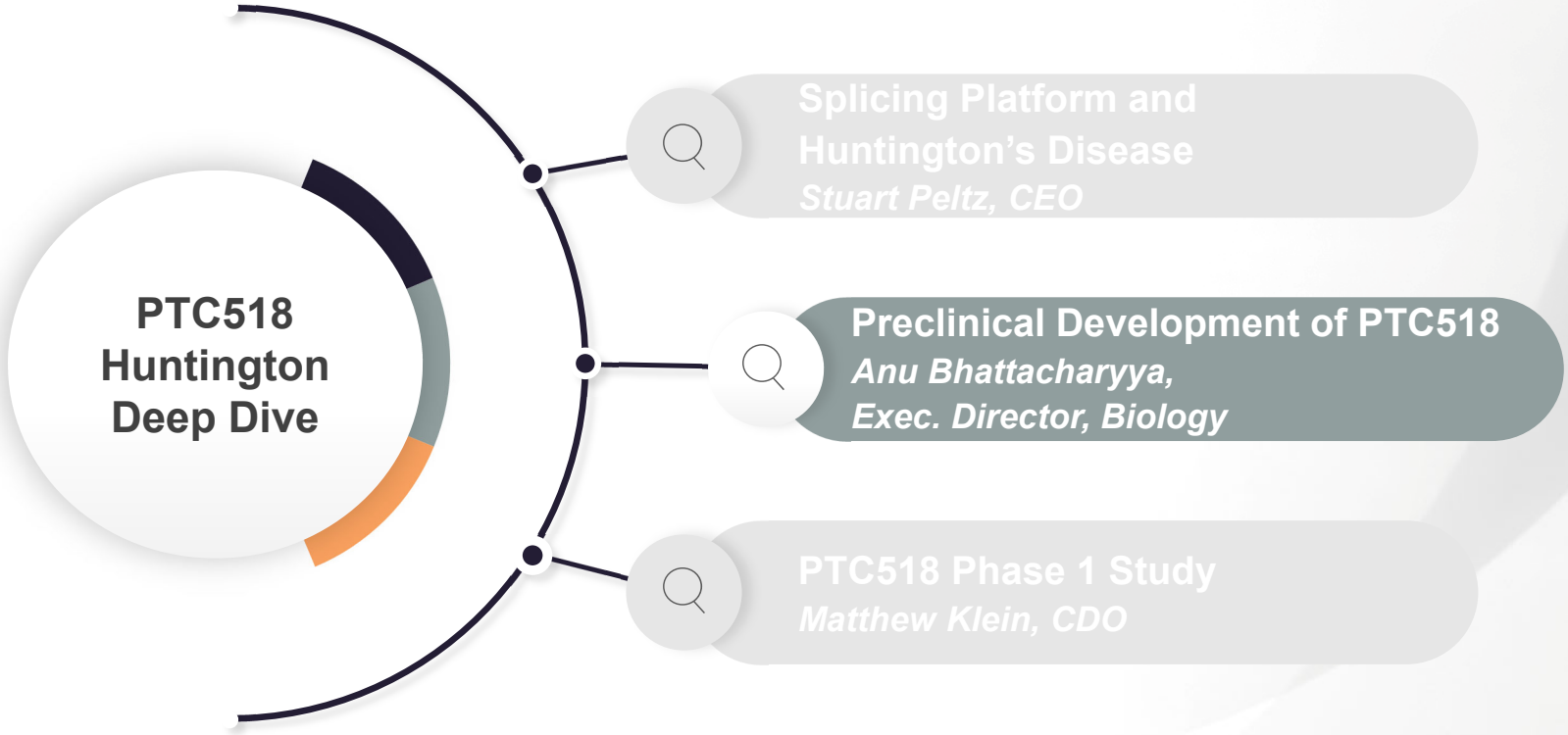
Mouse data: 30-40% reduction in m*HTT* expression translates to beneficial effects



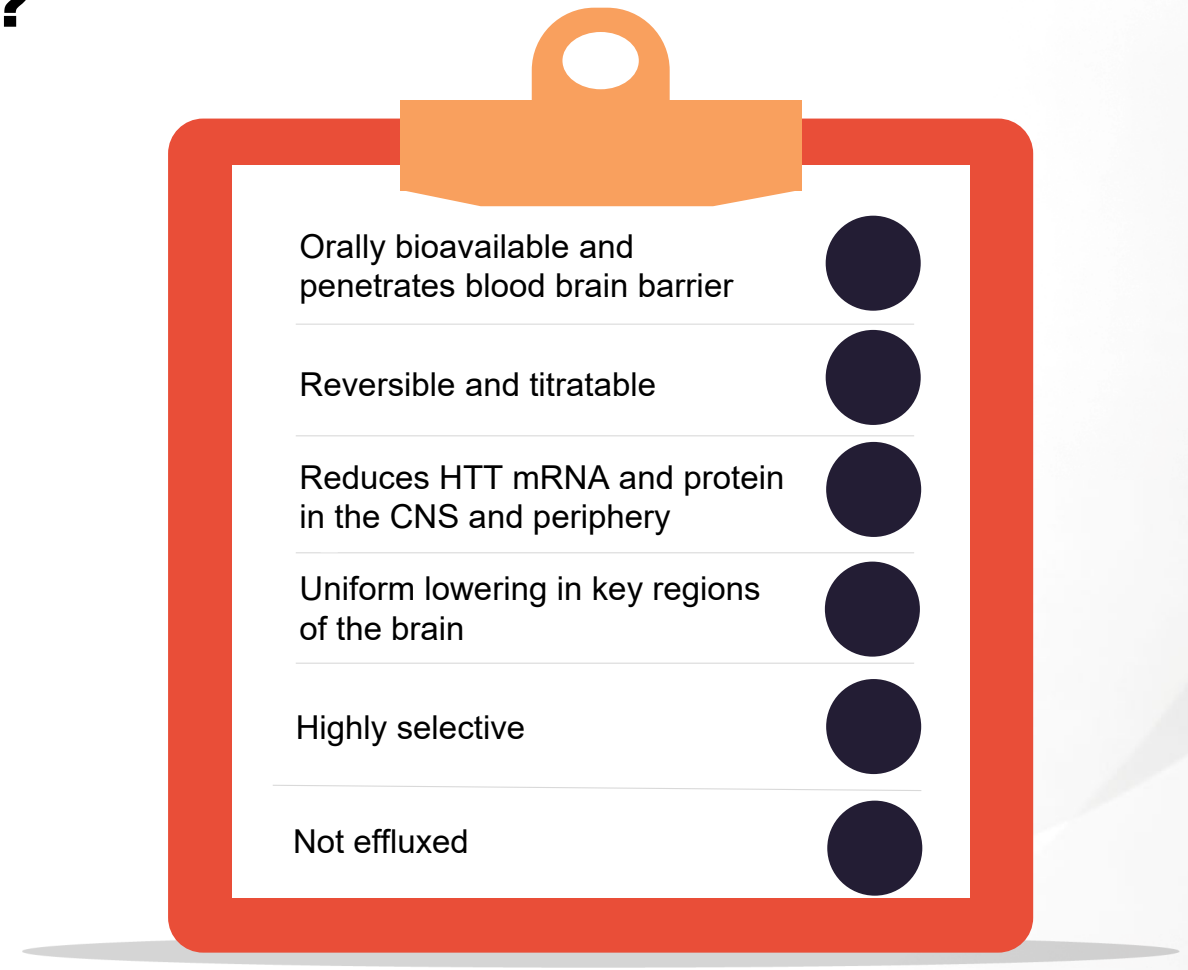


Becanovic et. al. Nat Neurosci. 2015. doi:10.1038/nn.4014
Garriga-Canut et. al. PNAS 2012 doi.org/10.1073/pnas.1206506109

PTC518 Huntington's Disease Deep Dive Agenda



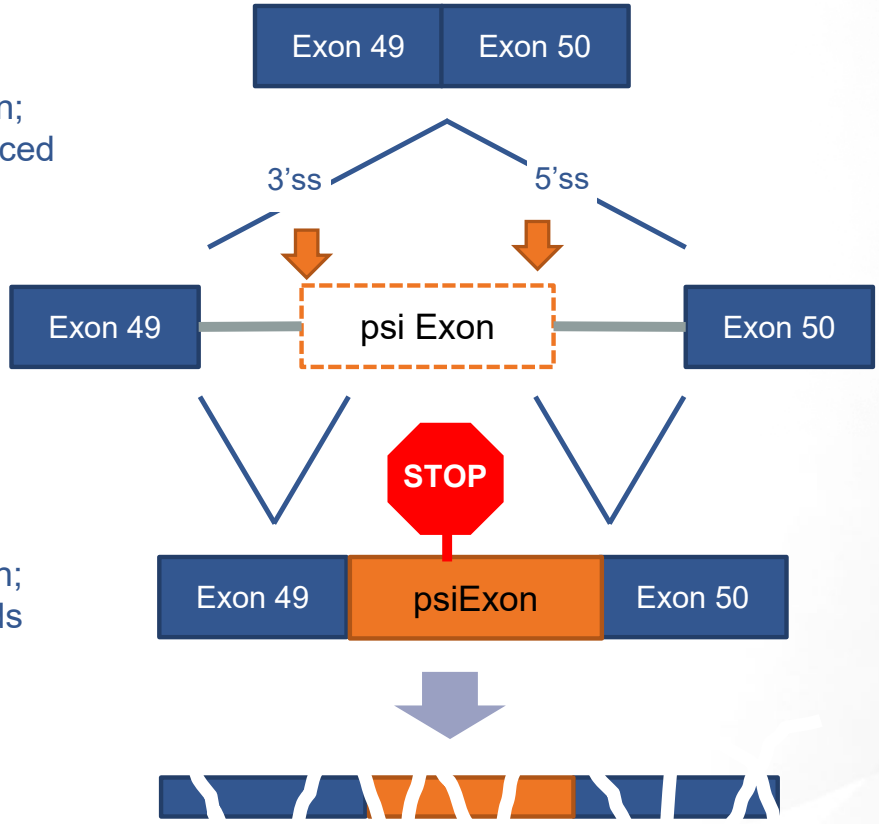
What are the Characteristics of a Promising HD Therapeutic?



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

Key Preclinical Proof Points

DMPK

Reduce metabolism

Maximize oral bioavailability and exposure *in vivo*

Cellular Activity

Do the molecules lower HTT levels in cells?

Do the molecules lower both HTT mRNA and protein levels?

Pharmacology

Assess protein expression *in vivo*

Establish PK/PD correlation

Toxicology

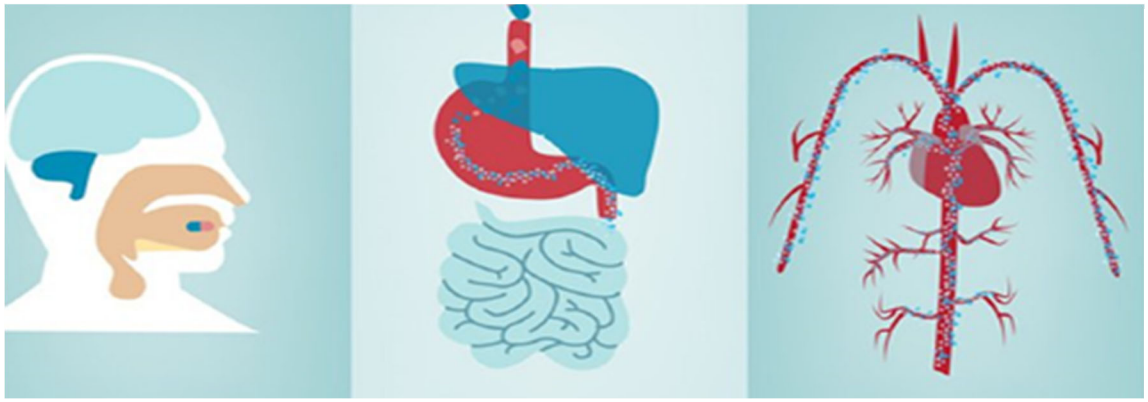
Reduce cellular toxicity, mutagenicity, and key off target activity

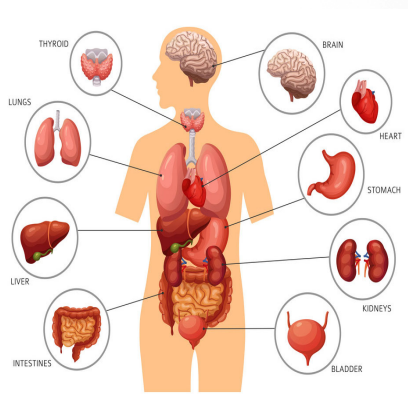
Monitor short and long-term safety in animals

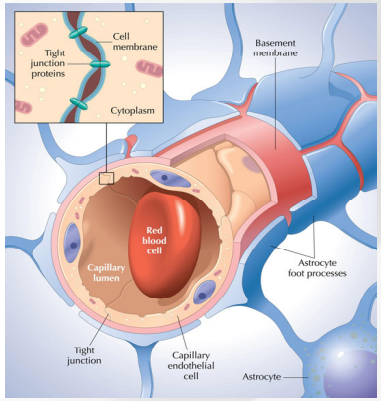
Animal Models Were Selected to Best Show PK and PD

Model	Purpose	Pros	Cons
BACHD mouse	PK-PD-distribution/ HTT lowering biomarker	Human Genomic Locus Full-length HTT/PsiExon target	Subtle & late onset phenotype/ Increased body weight
WT Mouse	PK-distribution	Availability; commonly used; quick PK	NO PsiExon target
WT NHP	PK-distribution	Large brain; study efflux (CSF PK)	NO PsiExon target

PTC518 is Orally Bioavailable and Crosses the Blood Brain Barrier







After swallowing, it makes its way to the stomach

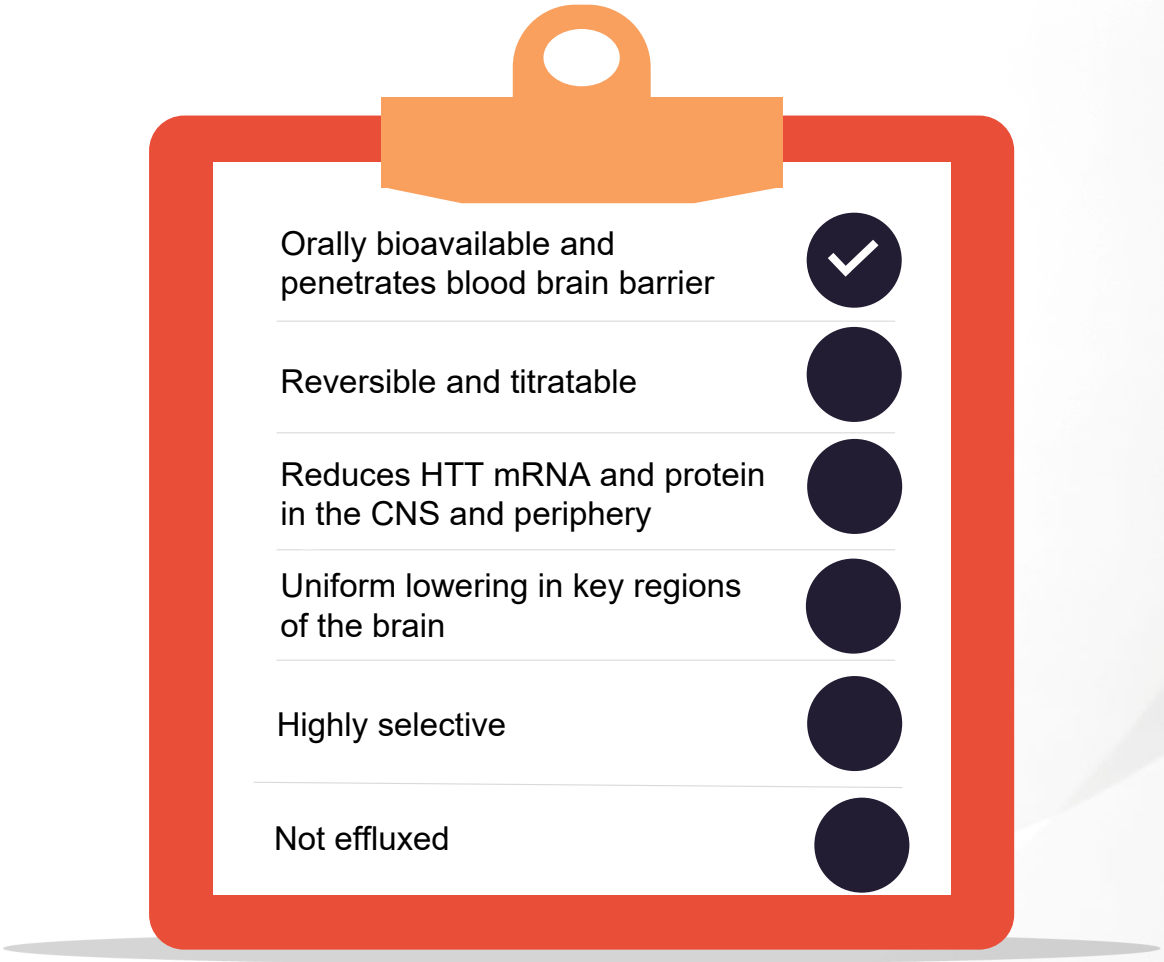
Broken down in the stomach, small intestine, and liver

Circulates through the bloodstream

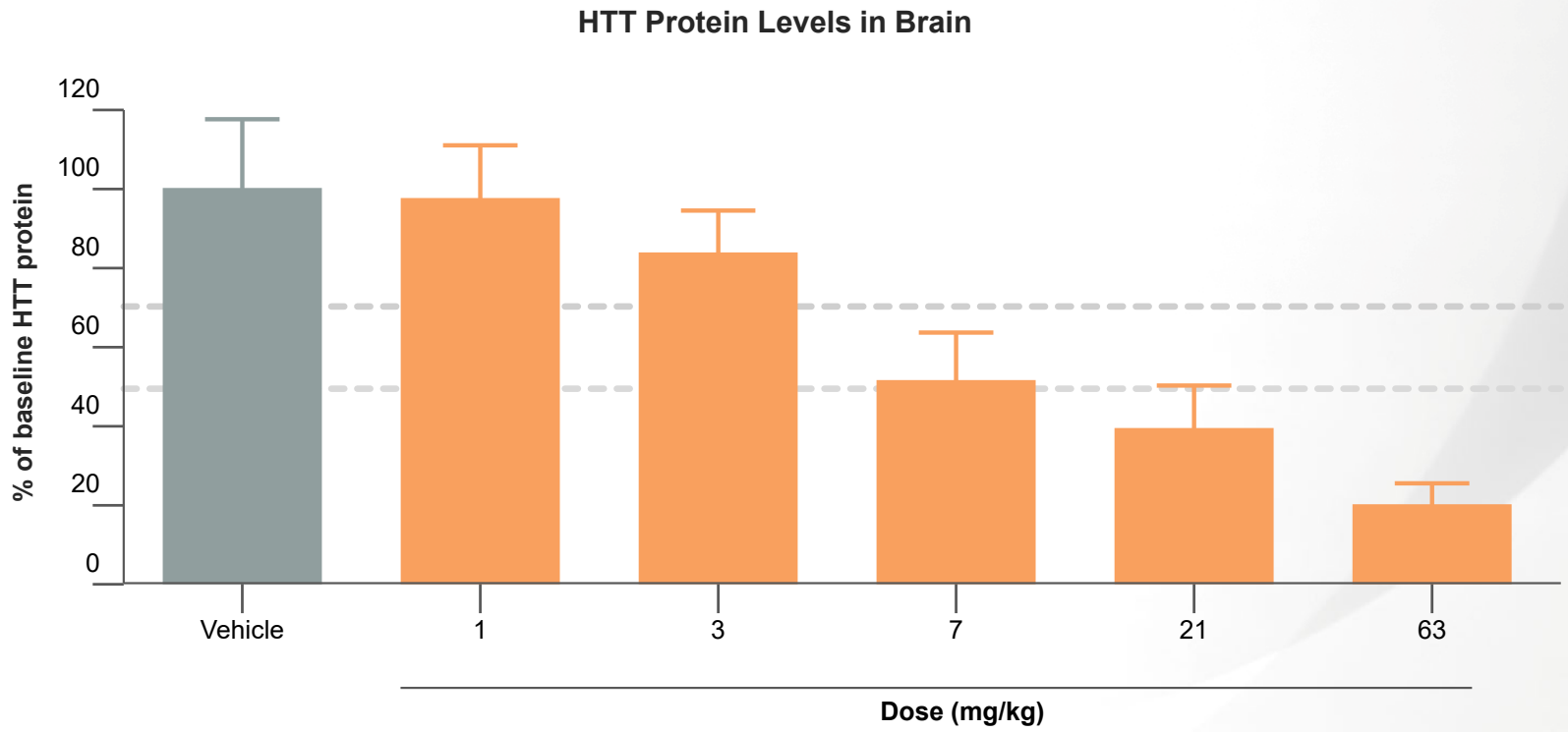
Distributed through the body

Crosses blood brain barrier to access neurons

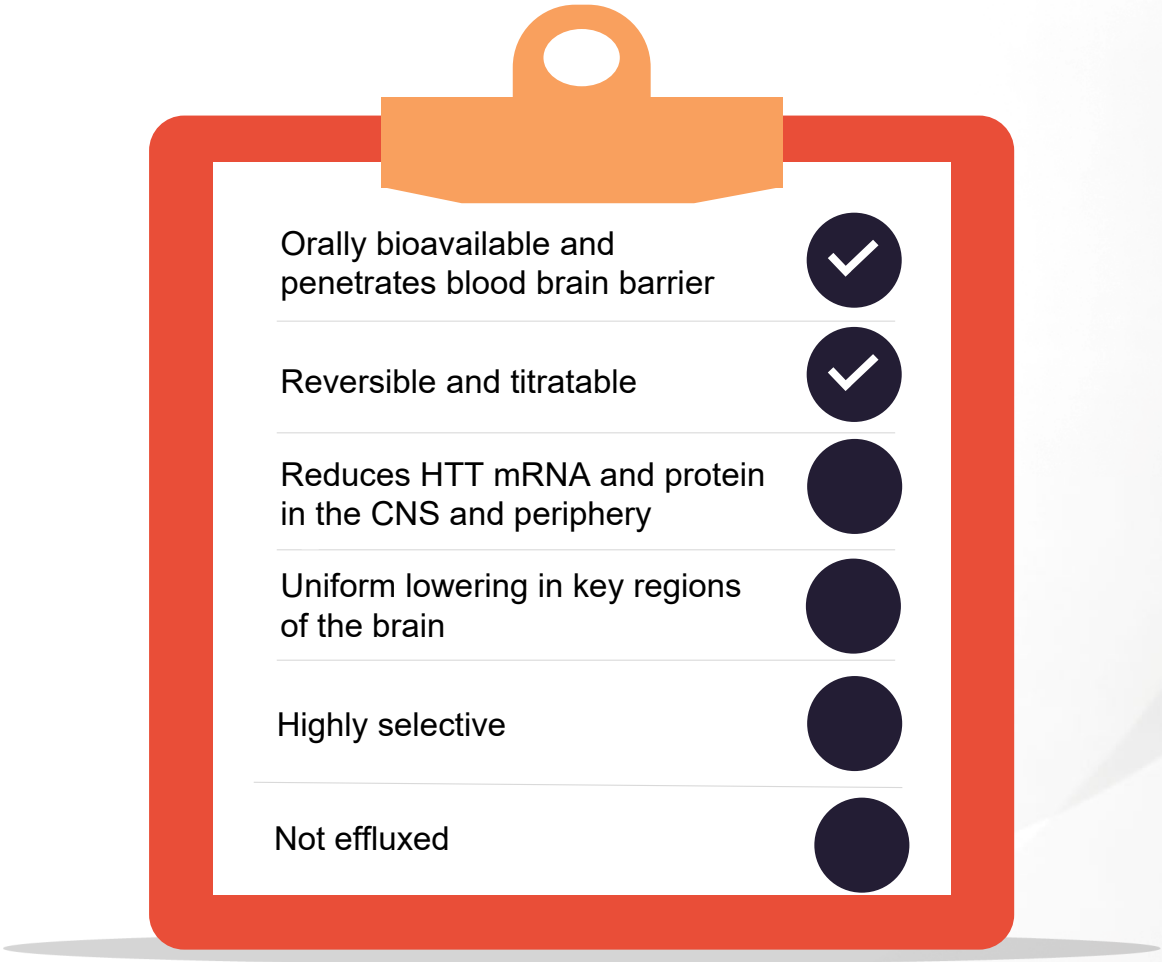
What are the Characteristics of PTC518?



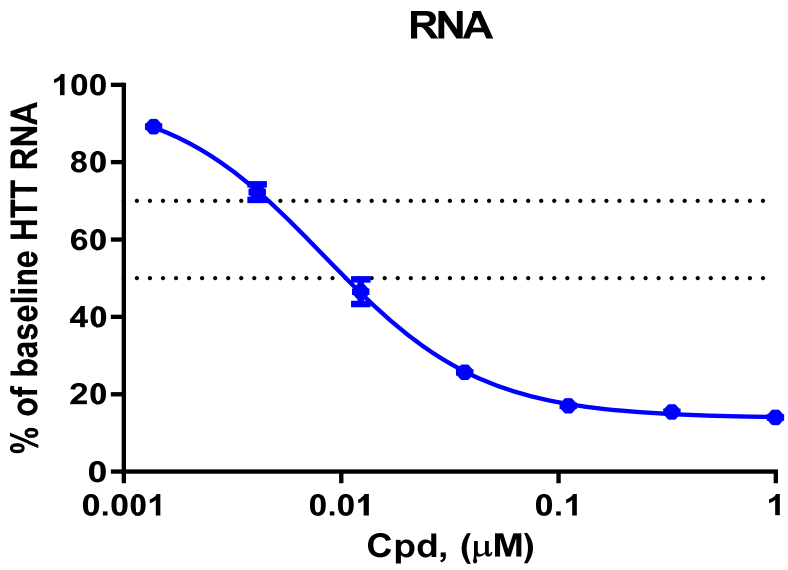
Dose Dependent HTT Lowering in the Brain of BACHD Mice



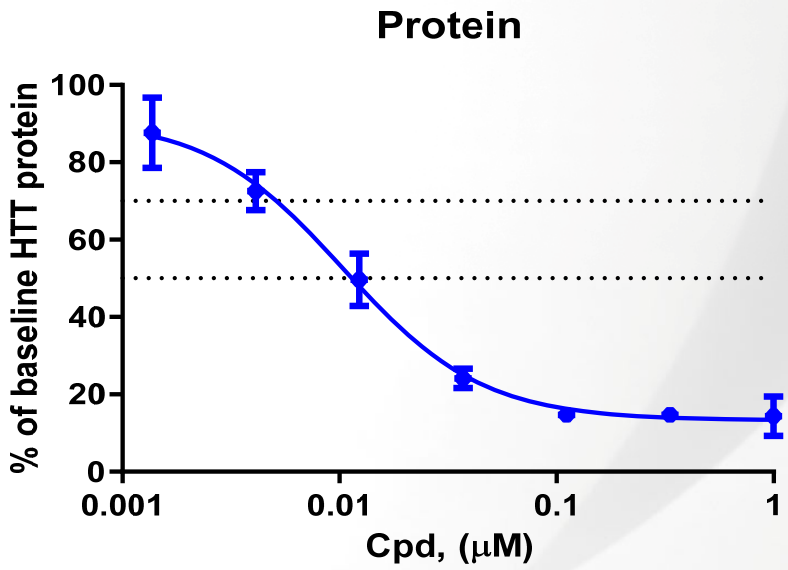
What are the Characteristics of PTC518?



PTC518 is Highly Potent in Promoting Splicing of *HTT* Pre-mRNA and Lowering HTT Protein Levels in Human Cells



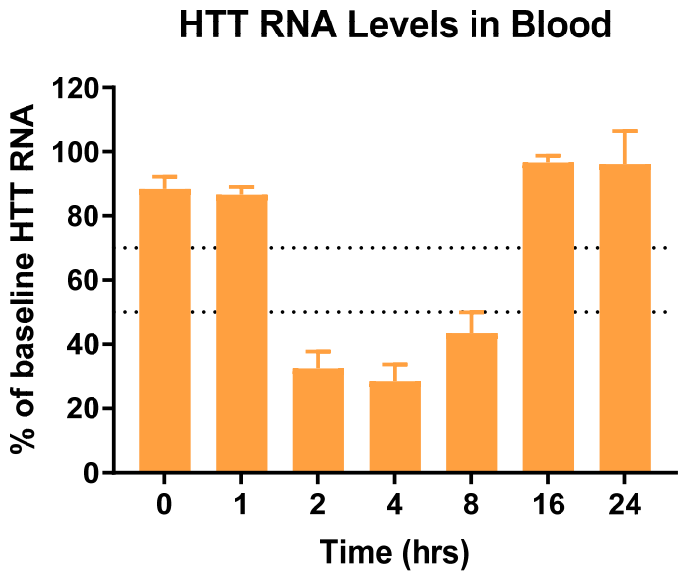
HTT pre-mRNA splicing

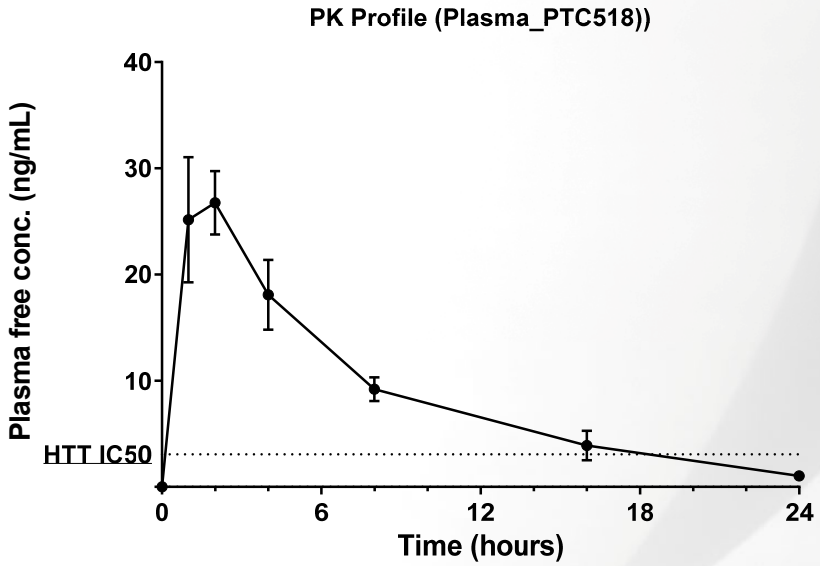


HTT protein lowering

 Data on file, human cells expressing endogenous HTT.

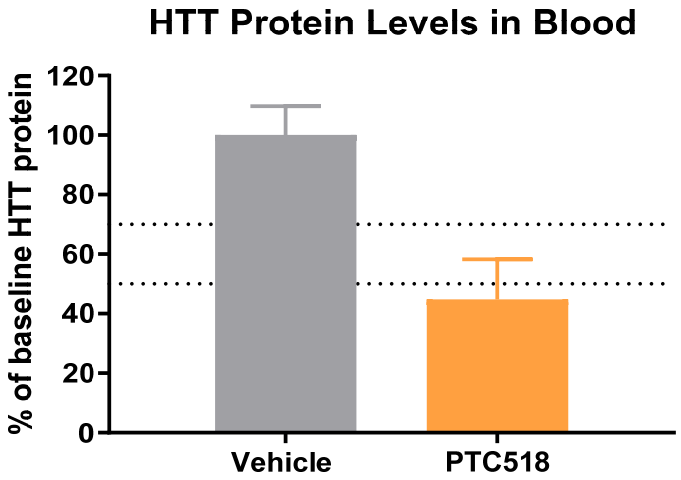
PTC518 Promotes Splicing of *HTT* Pre-mRNA in BACHD Mouse Whole Blood





Data on file

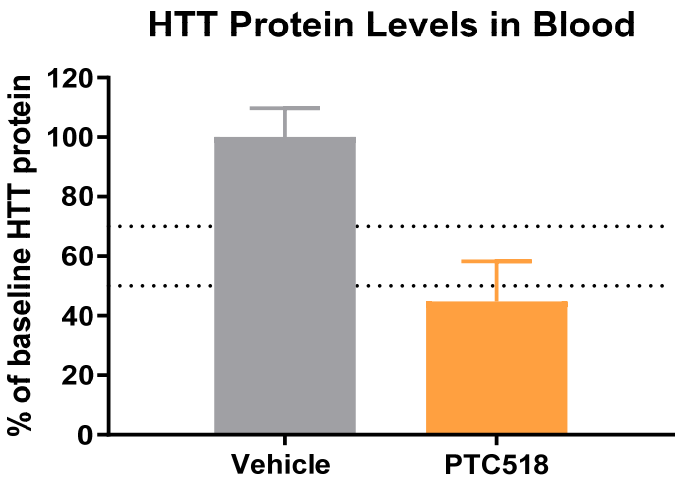
PTC518 Showed a Strong Correlation Between *HTT* mRNA Splicing and Protein Lowering in Blood of BACHD Mice

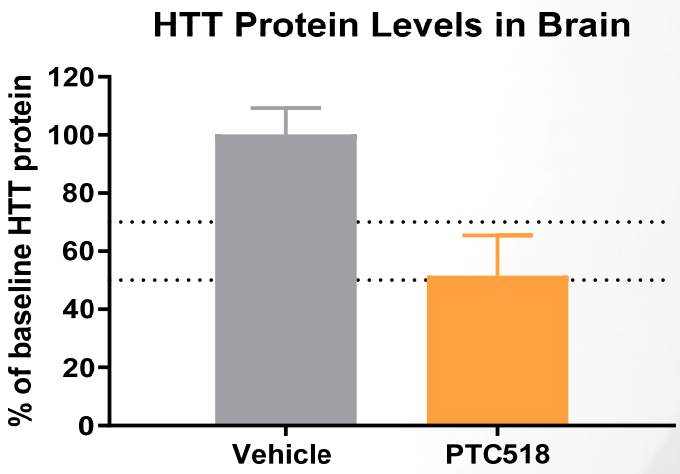


- HTT protein lowering in BACHD white blood cells
  - Time – 21 days; multiple doses; PD evaluated 2h post last dose

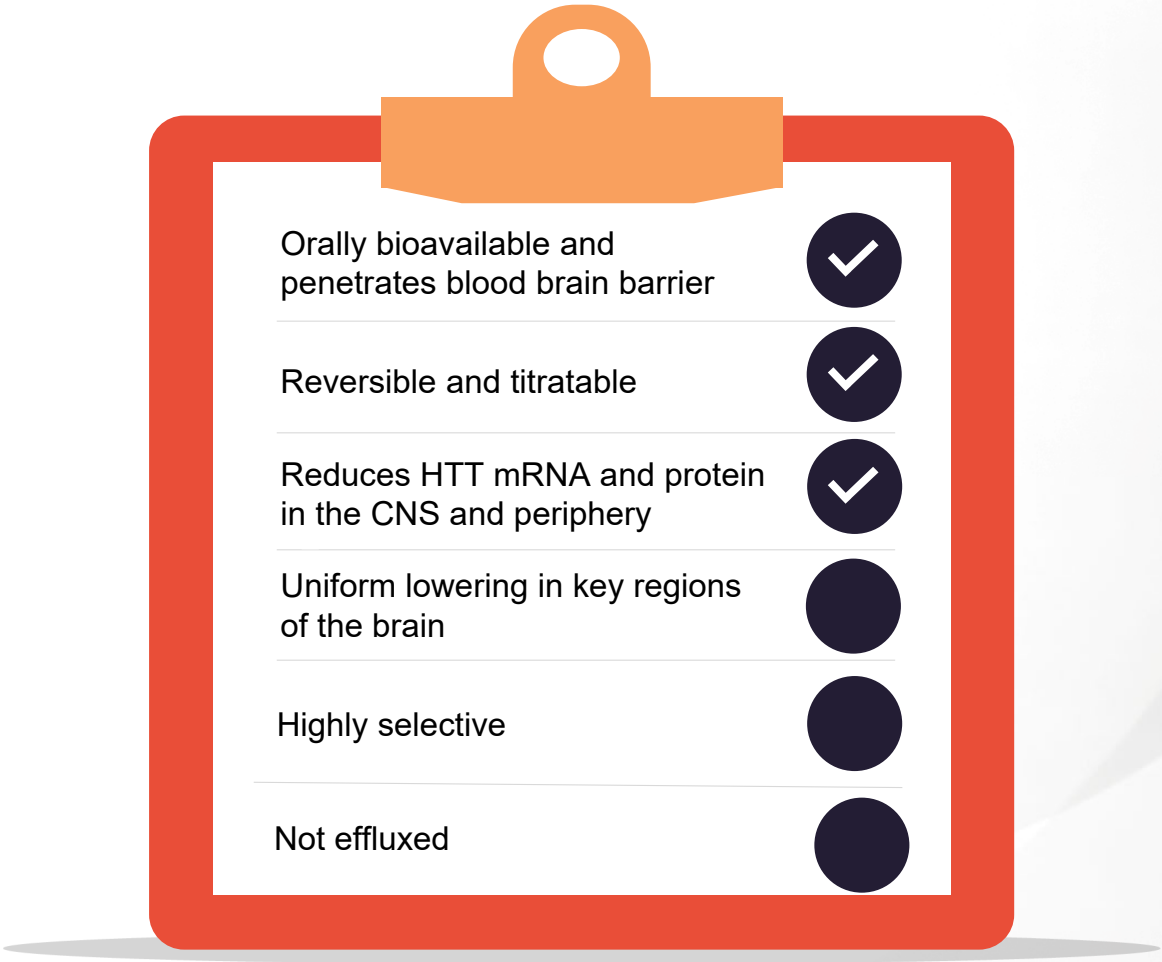
 Data on file

PTC518 Uniformly Lowers HTT Protein Levels in BACHD Mouse Brain and White Blood Cells



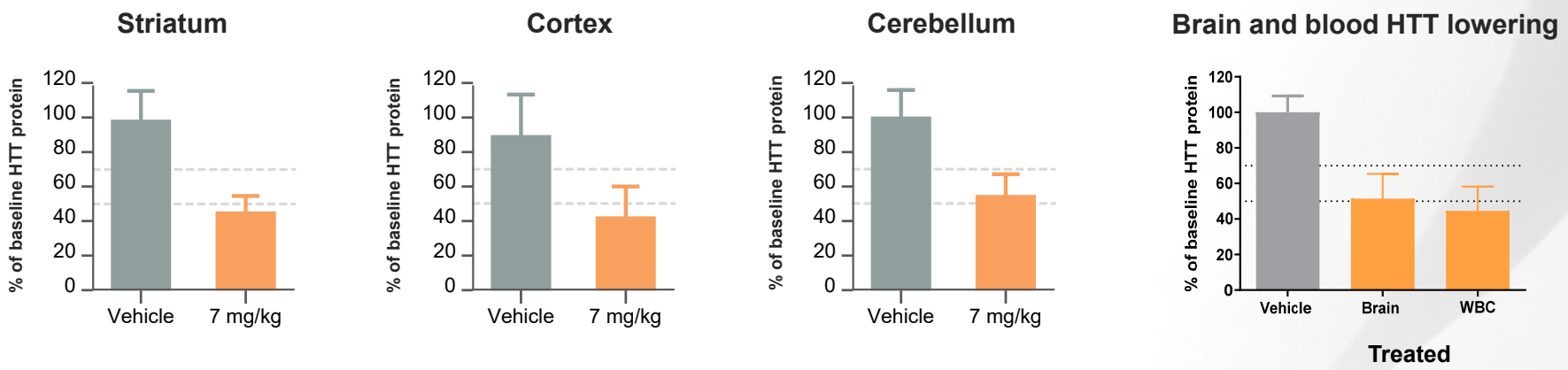


What are the Characteristics of PTC518?



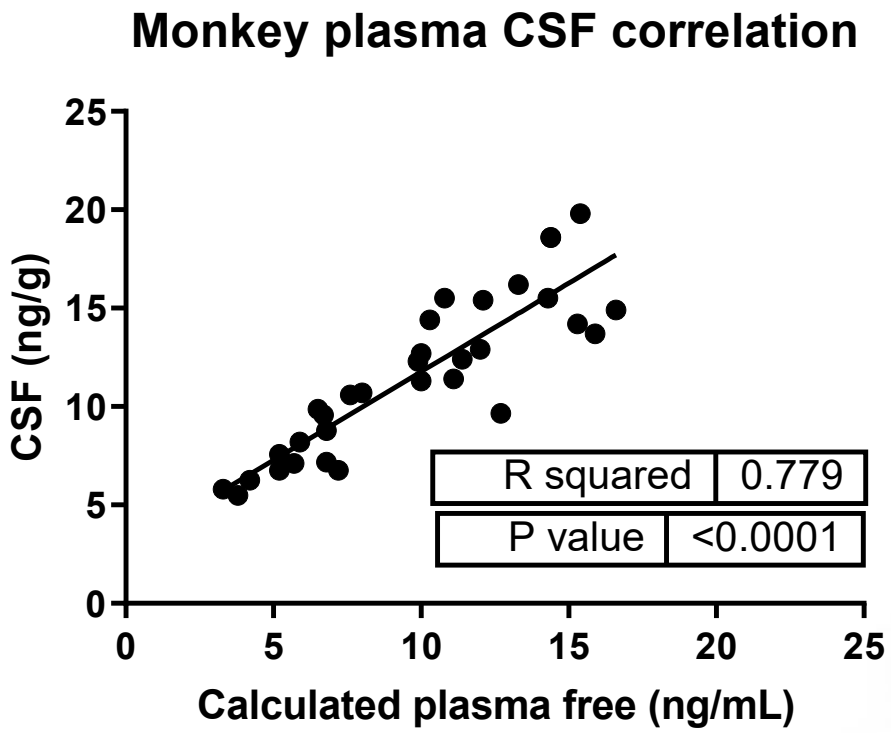
HD Splicing Small Molecules Demonstrate Robust HTT Reduction in BACHD Mouse Brain

Measurements demonstrate uniform HTT lowering across brain regions with ~1:1 brain and blood lowering effect



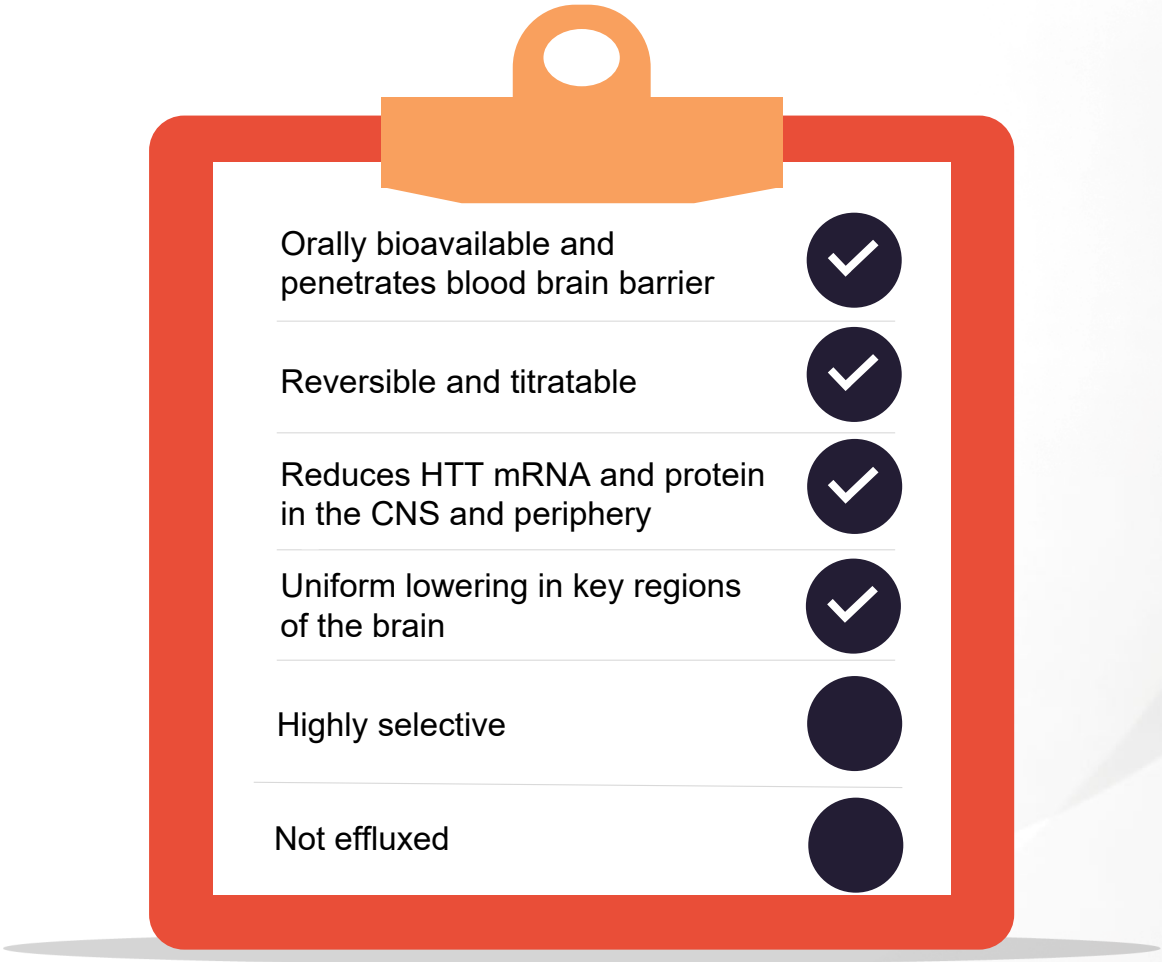
Data on file from multiple studies

PTC518 Crosses the Blood Brain Barrier in Non-Human Primates



 Data on file

What are the Characteristics of PTC518?



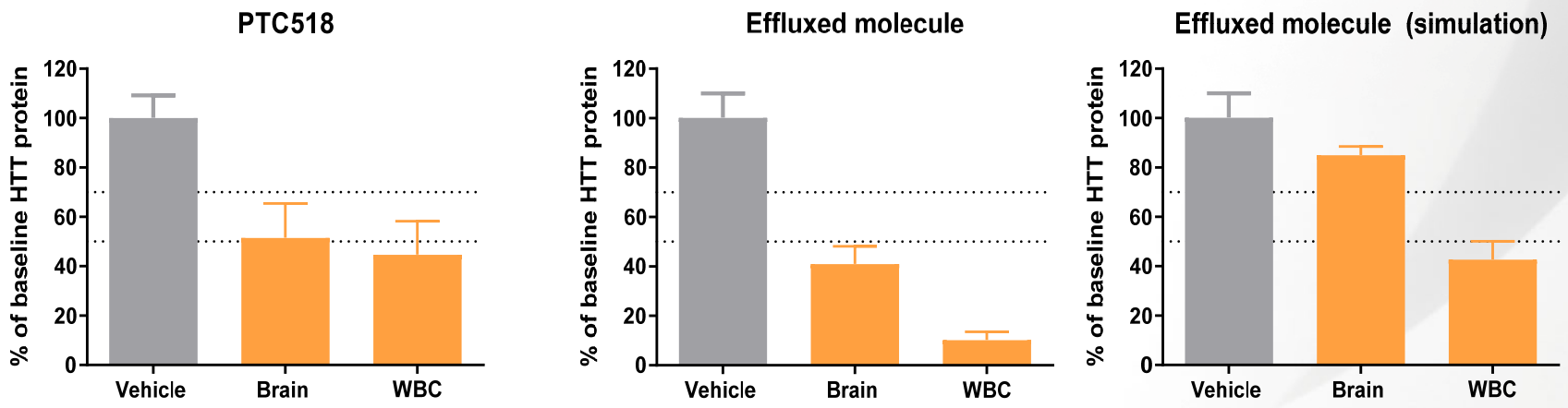
What are the Characteristics of PTC518?

Why is it Important to Reduce Efflux?

- Reducing efflux has several advantages:
  - Balancing the extent of peripheral vs brain lowering is critical
  - Increases the therapeutic window versus non target-related splicing in the periphery
  - Stronger correlation between blood (peripheral) and brain lowering

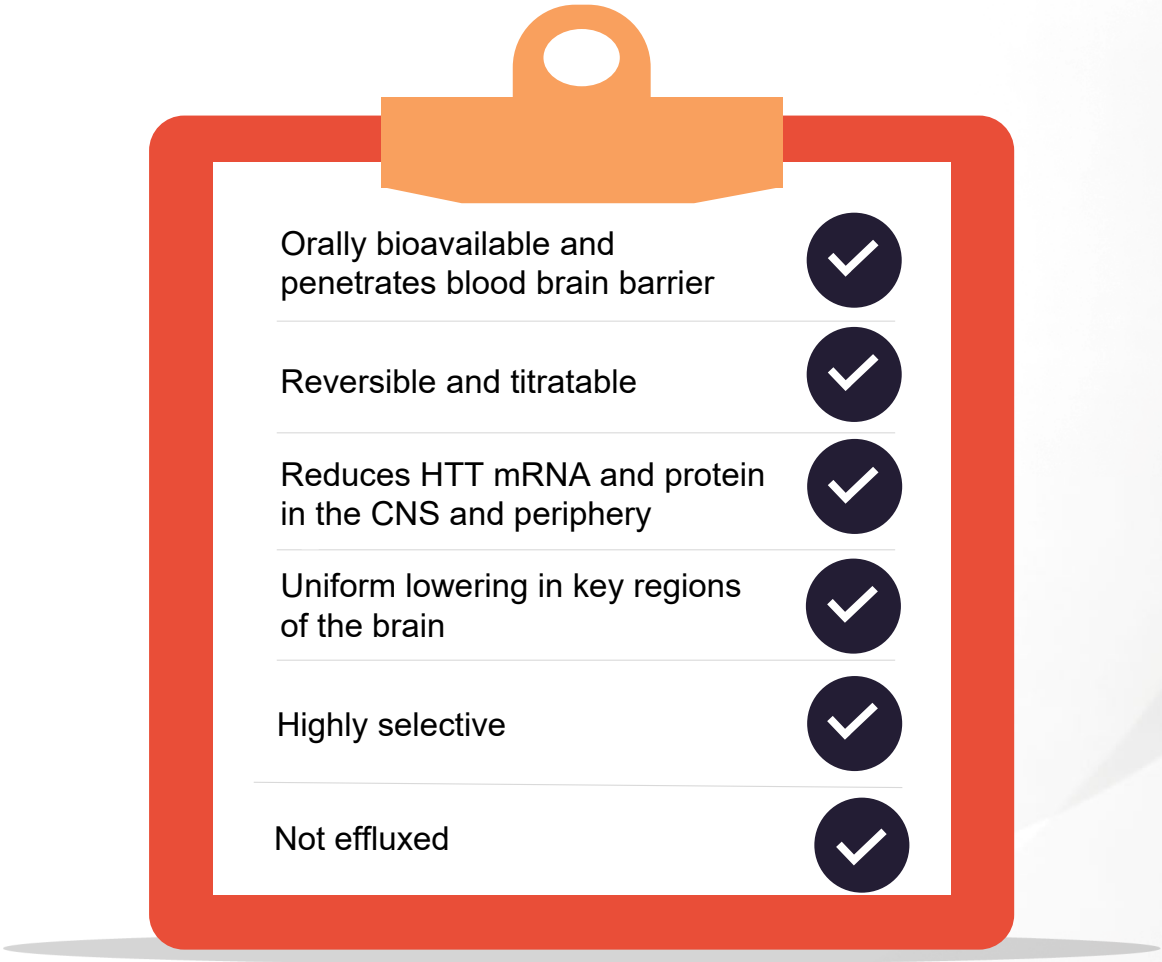
PTC518 is Not Effluxed Resulting In ~1:1 Brain and Blood Lowering Effect In BACHD Mice

PTC518	Effluxed Molecule
Peripheral ≈ Brain	Peripheral >> Brain

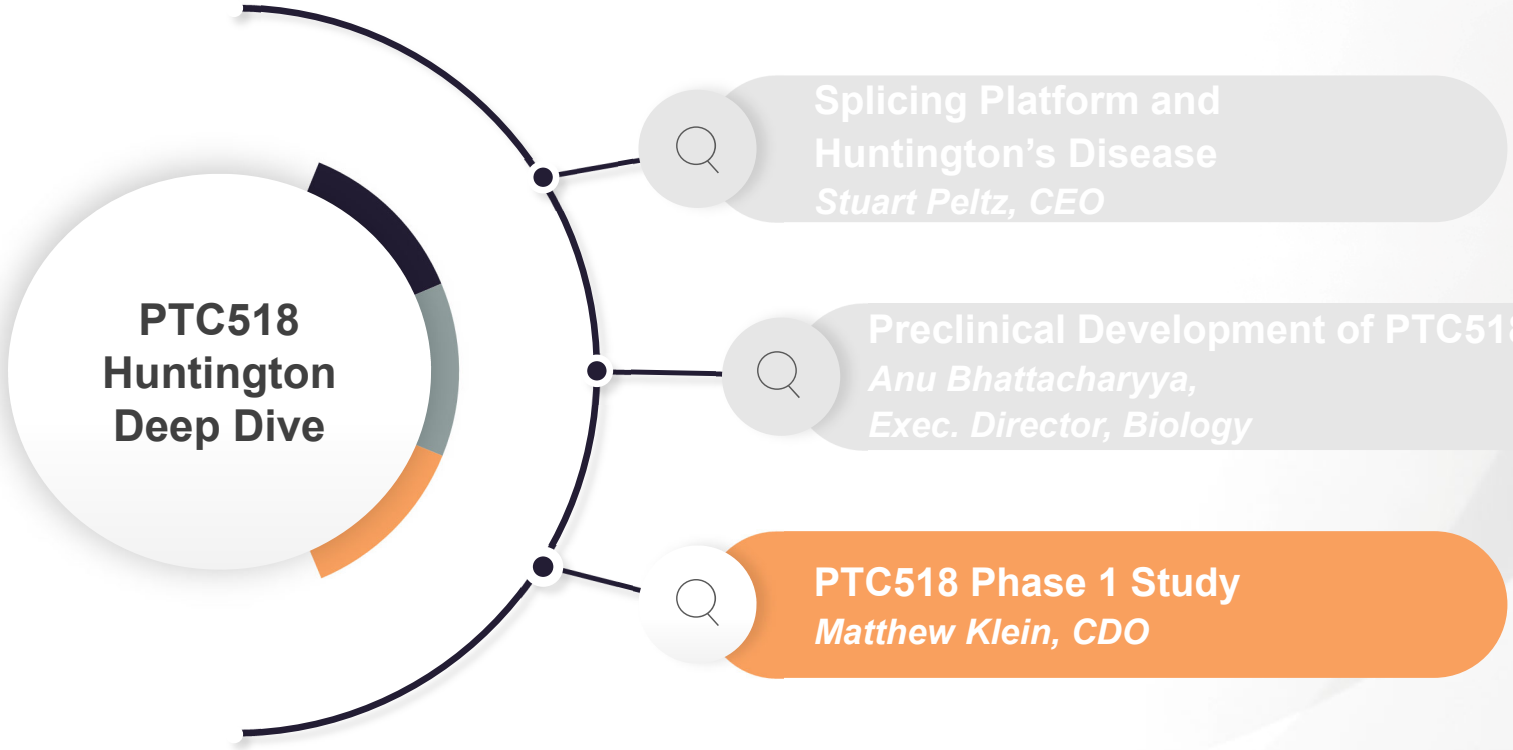


 Data on file

What are the Characteristics of PTC518?



PTC518 Huntington's Disease Deep Dive Agenda



The Phase 1 Trial is a 4-Part Study

Phase 1 trial in healthy volunteers is ongoing

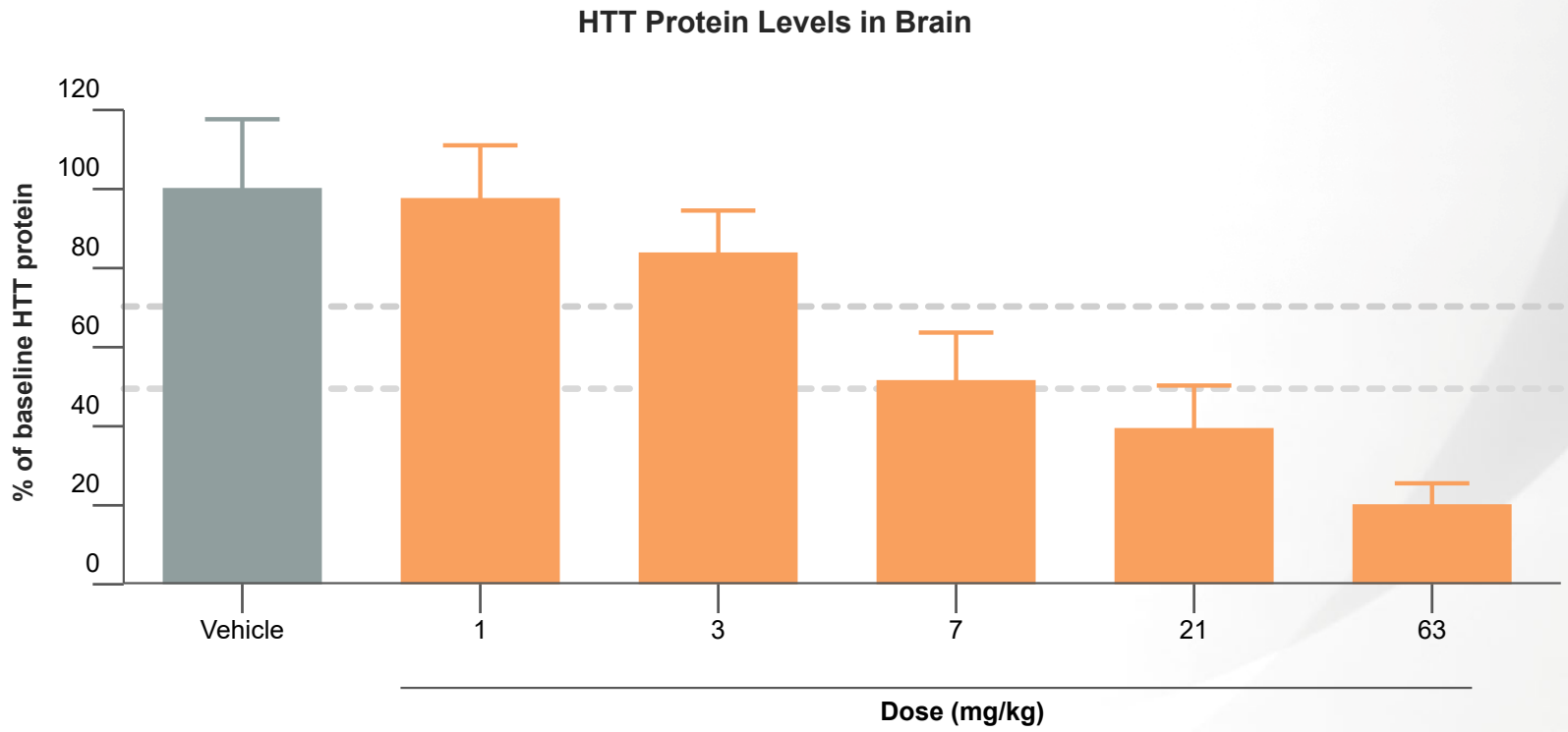
Single ascending dose
- Five cohorts of 8 healthy volunteers (6 active and 2 placebo)
- Evaluate safety & tolerability; HTT mRNA splicing

Multiple ascending dose
- Up to 5 cohorts of 8 healthy volunteers (6 active and 2 placebo)
- Evaluate safety & tolerability; HTT mRNA splicing & protein lowering

Food effect
- Crossover design
- Evaluate the effects of food on PTC518 pharmacokinetics

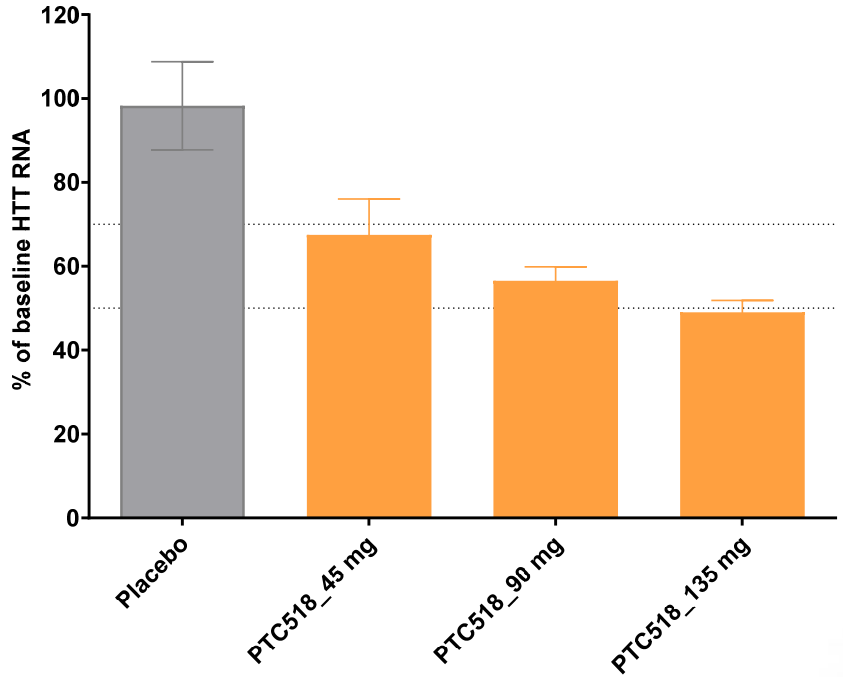
CSF sampling
- Evaluate pharmacokinetics of PTC518 in the CSF
- Compare drug levels in CSF with plasma compartment

Phase 1 Objective: Establish Dose Dependent HTT Lowering Similar to the BACHD Mouse



 Data on file

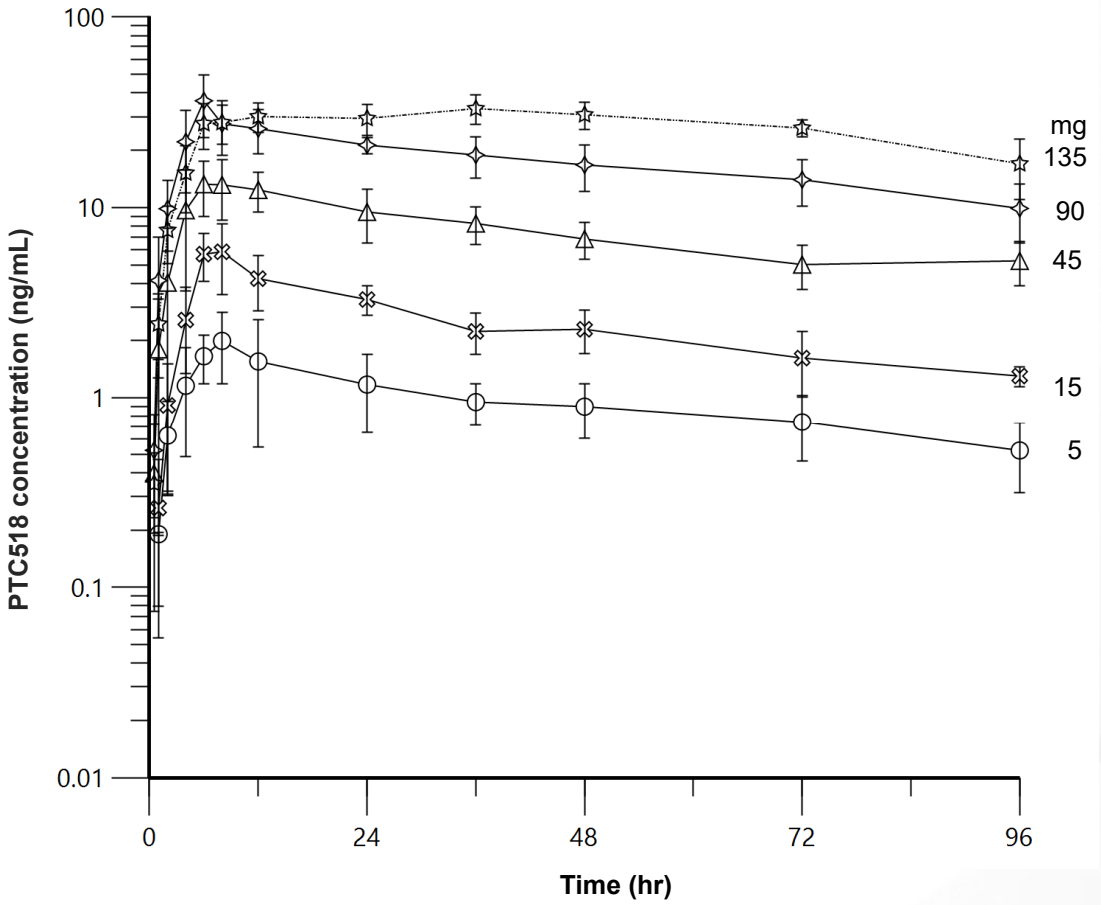
SAD Study: Proof of Mechanism of PTC518 Demonstrated By Dose-Dependent *HTT* Splicing



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

Data on file PTC518-CNS-001-HD

SAD PK Demonstrates Dose Predictable Drug Exposure

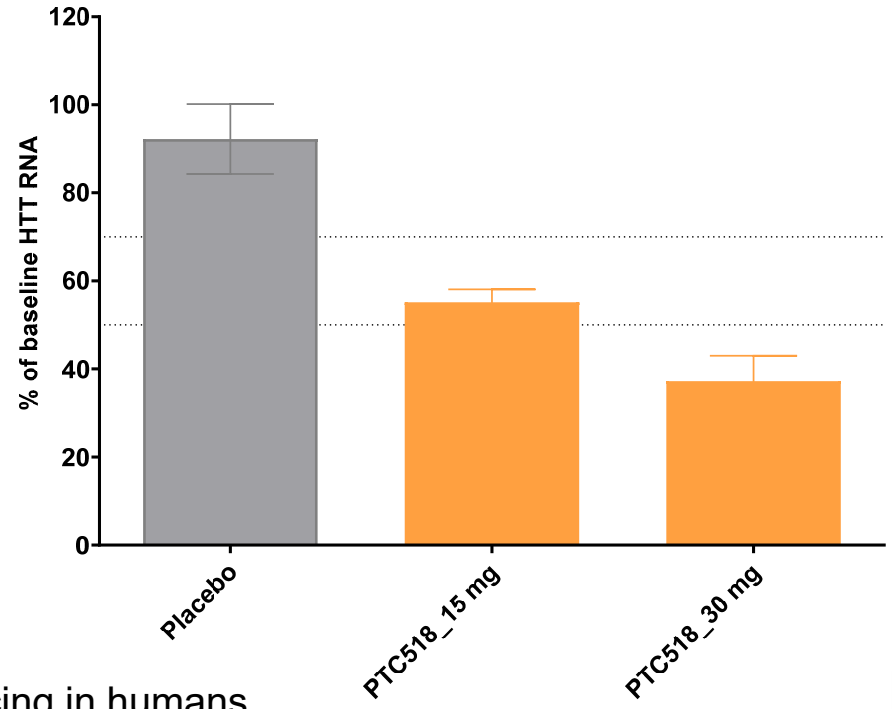


Data on file PTC518-CNS-001-HD

Phase 1 SAD Interim Results Summary

- Well-tolerated with no safety-related findings
- Predictable pharmacology
- Dose-dependent splicing of *HTT* mRNA
- Target splicing reduction achieved with single dose

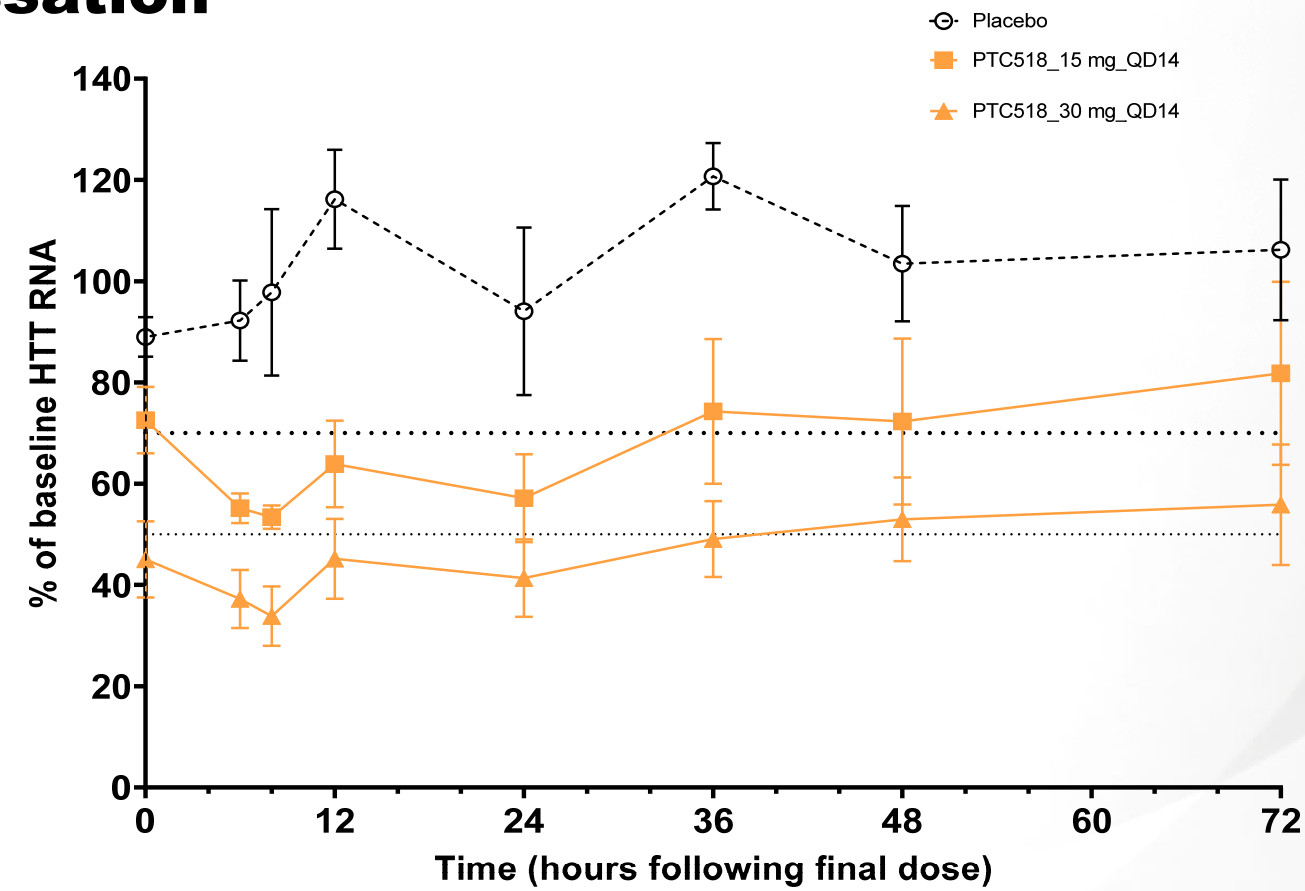
MAD Study: Proof of Mechanism of PTC518 Confirmed By Dose-Dependent *HTT* Splicing



- 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

Data on file PTC518-CNS-001-HD

Durability of Response: Splicing Activity Persists 72 hrs Post Cessation



HTT splicing monitored after the final dose at day 14 (calculated % HTT remaining from baseline (pre-dose_Day0))

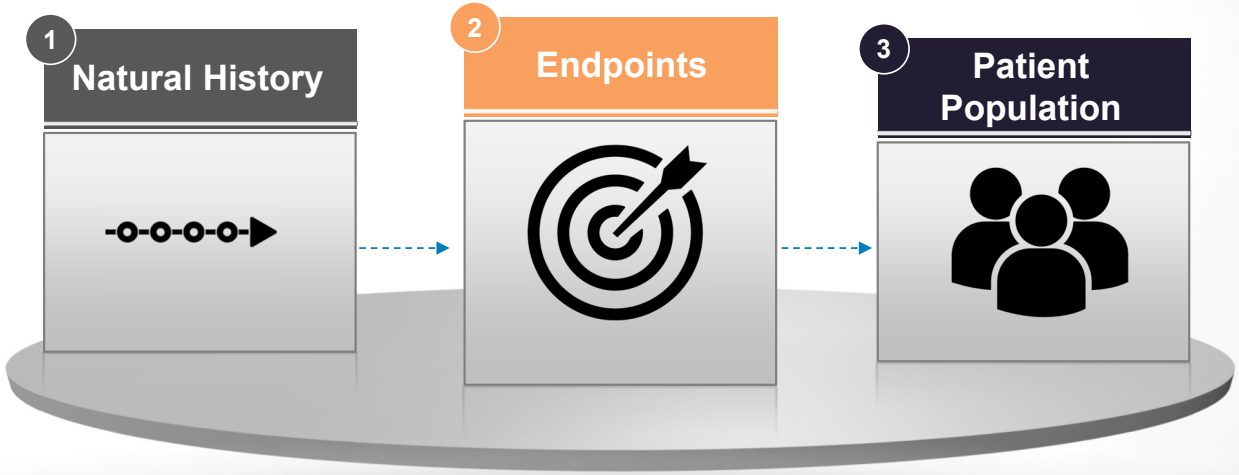
Phase 1 MAD Interim Results Summary

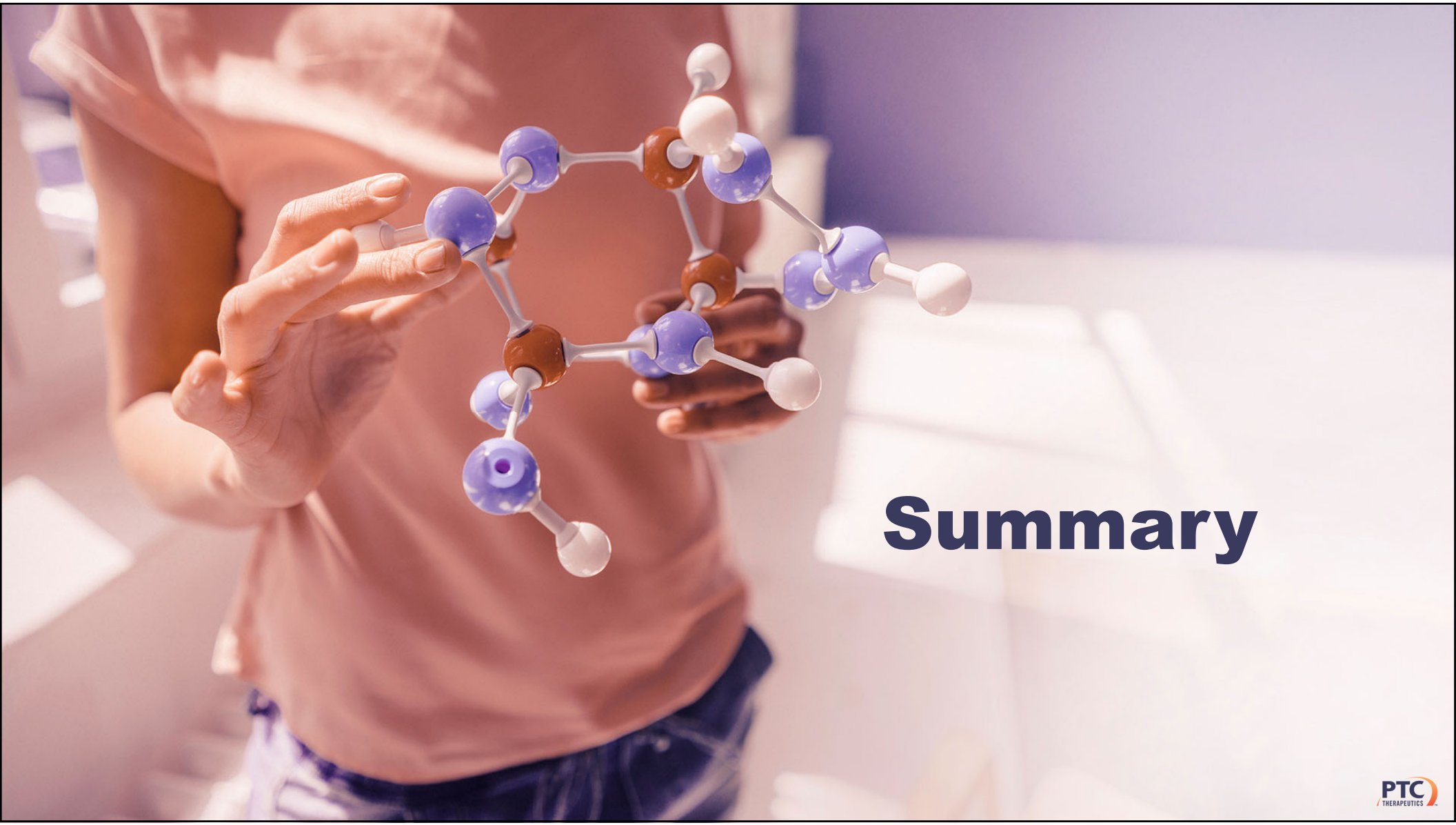
- Two cohorts completed; two to three additional planned
- Well-tolerated with no safety-related findings
- Dose dependent splicing of *HTT* mRNA
- Long-half life with maintenance of splicing up to 72 hours following last dose

Phase 1 Trial Next Steps

1. Complete Additional MAD Cohorts
2. Complete CSF Cohort
3. Complete Food Effect Cohort
4. Finalize Clinical Development Plan

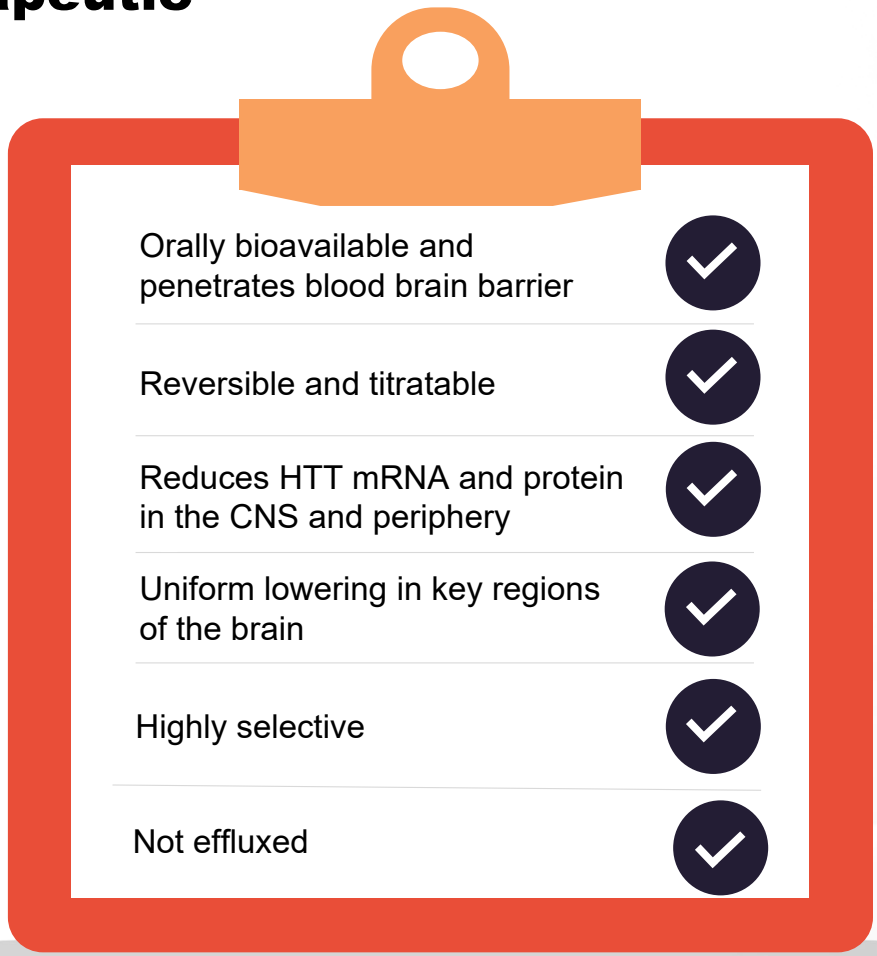
Defining Clinical Next Steps



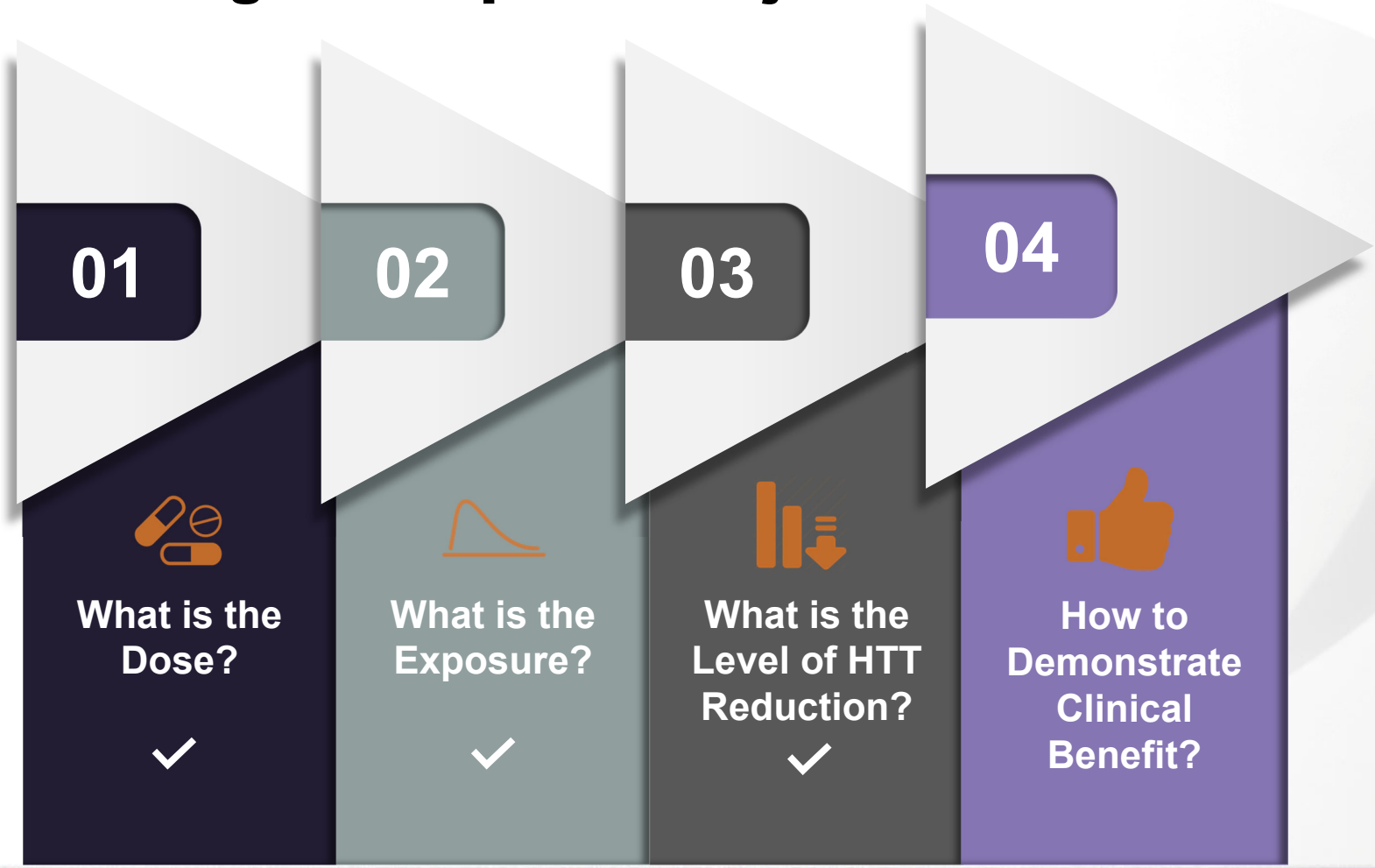


Summary

Preclinical Studies Show PTC518 Has all the Characteristics Of a Promising HD Therapeutic

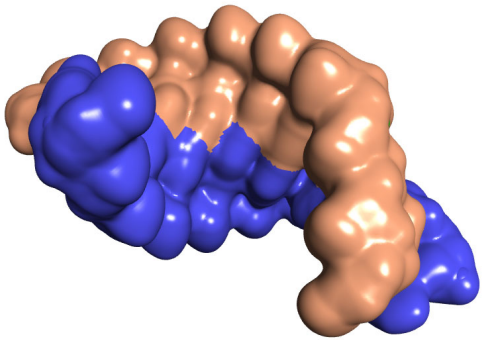


PTC518 Drug Development Objectives

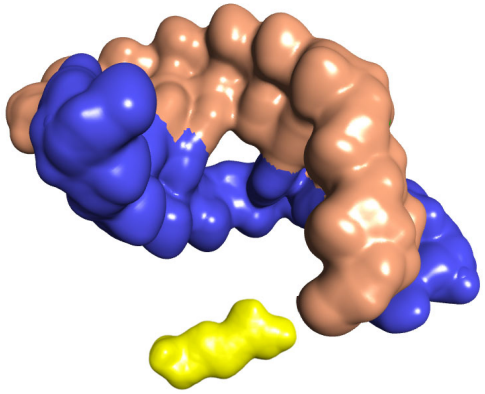


The Splicing Platform Has Proven to be a Robust Engine to Identify Development Candidates

Canonical duplex

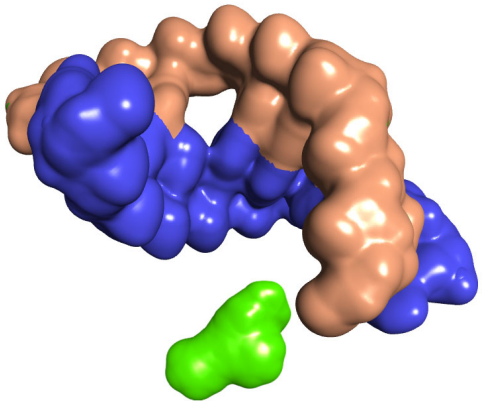


SMN2



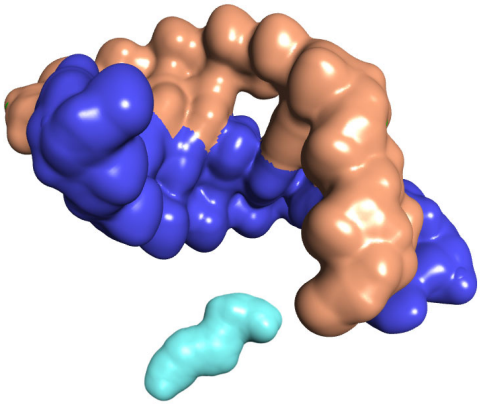
Risdiplam

HTT



PTC518

And the next one….



PTC-XXX

Molecules are designed to match a unique **pre-mRNA/U1** interface and serve as molecular glue to help initiate splicing events

Questions?