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A study to evaluate the safety and efficacy of PTC518 in participants with Huntington's disease (HD)

Submission date	Recruitment status	[_] Prospectively registered
03/03/2022	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
08/08/2022	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
08/04/2025	Genetic Diseases	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The safety and efficacy of three doses of PTC518 (investigational medicine), for participants with Huntington's Disease (HD), will be studied in this Clinical Trial.
PTC518 is being studied to determine if it can slow the progression of HD and its associated symptoms by reducing the production of an abnormal version of a protein called huntingtin protein (sometimes called a mutant version or mHTT).

Who can participate?
Approximately 252 participants, aged 25 years and older will participate across approximately 20 sites in North America, Europe, and Australia.

What does the study involve?
The study is divided into the below periods:
- Screening period (to check participant eligibility to join the study)
- Baseline visit (to further confirm participant eligibility and initial dosing)
- Treatment period
- Safety follow-up period (to check participants' overall health and safety)

The study medicine comes in tablet form and is to be taken orally, in the morning, at least 2 hours before the first meal of the day (fasting).

Participation in the study will last up to 18 months, from screening to the final follow-up visit. The study treatment period will last approximately 12 months. Participation is voluntary. Participants will be expected to attend clinic visit whereby study assessments will take place e. g., blood and urine collection, vital signs monitoring, assessments of motor function & gait, cognition & behavioral and mental health, and completion of questionnaires.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
PTC Therapeutics International Limited (Ireland)

When is the study starting and how long is it expected to run for?
September 2021 to August 2025

Who is funding the study?
PTC Therapeutics, Inc. (USA)

Who is the main contact?
Dr Sarah Tabrizi, s.tabrizi@ucl.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2021-003852-18

IRAS number
1004960

ClinicalTrials.gov number
NCT05358717

Secondary identifying numbers
PTC518-CNS-002-HD, IRAS 1004960, CPMS 51614

Study information

Scientific Title
A Phase 2a, randomized, placebo-controlled, dose-ranging study to evaluate the safety and efficacy of PTC518 in subjects with Huntington's disease

Acronym
PIVOT HD

Study objectives
Current study hypothesis as of 25/07/2023:
Primary objective:
• Evaluate the safety of PTC518 compared with placebo in participants with Huntington's Disease (HD)
• Evaluate the pharmacodynamic (PD) effects of PTC518 through the reduction in blood total huntingtin (tHTT) protein levels

Secondary Objectives:
• Assess the effects of PTC518 on change in caudate volume via volumetric magnetic resonance imaging (vMRI) (key secondary)
• Assess the effects of PTC518 on change in composite Unified Huntington’s Disease Rating Scale (cUHDRS)
• Determine the effect of PTC518 on mutant huntingtin (mHTT) protein in cerebrospinal fluid (CSF) at Month 12
• Determine the effect of PTC518 on blood mHTT levels at Month 12

Previous study hypothesis:
Primary objective:
• Evaluate the safety and pharmacodynamic effects of 3 different doses of PTC518 and placebo in subjects with Huntington's Disease (HD)

Secondary Objectives:
• Determine the effect of PTC518 on huntingtin (HTT) mRNA in blood and mHTT protein in CSF
• Reduction in blood mHTT levels

Exploratory Objectives:
• Assess the effect of PTC518 on change in whole brain, caudate, and putamen volume via volumetric magnetic resonance imaging (vMRI)
• Assess the effect of PTC518 on change in ventricular volume via vMRI
• Assess change after 12 weeks of treatment in clinical scales

Pharmacokinetic Objective:
• Evaluate the concentration of PTC518 in subjects with HD

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/05/2022, London Research Ethics Committee (80 London Road, Skipton House, London, SE1 6LH, UK; +44 (0)2071048387; londonbridge.rec@hra.nhs.uk), ref: 22/LO/0229

Study design
Interventional double-blind randomized parallel group placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Huntington’s disease is an illness caused by a faulty gene in the DNA. Huntington’s affects the body’s nervous system – which can cause changes in movement, learning, thinking and emotions.

Interventions
Current interventions as of 25/07/2023:
Participants will first be randomized to Part A or Part B or Parts D or E in a 1:1 randomization ratio, depending on their Huntington’s disease Integrated Staging System (HD-ISS) staging criteria and then to active treatment (PTC518 5 mg in Parts A and D and 10 mg in Parts B and E) or matching placebo within each part in a 2:1 ratio of active treatment to placebo. A Drug Safety Monitoring Board (DSMB) will undertake an unblinded review of safety data from the 5 and 10 mg dosing groups and provide a recommendation on when Parts C and F (with a 20 mg active treatment arm) can be initiated. At that time, participants will be randomized to any study Part that is currently open for enrollment, and then to either active treatment or placebo (in a 2:1 ratio) within that Part. The participant will receive the assigned treatment for approximately 12 months. After the treatment period ends, there is a safety follow-up period for all arms with follow-up safety visits at Month 13, Month 16, and Month 18.

Previous interventions:
There are three treatment arms: 1) Part A (5 mg or placebo), 2 Part B (10 mg or placebo), and 3) Part C (20 mg or placebo). Participants will be assigned to either Part A, Part B, or Part C based

on which parts of the study are open at the time of consent. A computer program (an interactive response technology system) will do the part assignment and assign the participant to either the study drug or placebo. The participant will have a 2 in 3 chance of receiving the study drug versus placebo. The subject will receive the assigned treatment for approximately 85 days or 12 weeks. After the treatment period ends, there is a safety follow-up period for all arms. The safety follow-up period includes two visits on Day 113 (approximately one month after the treatment period ends) and Day 185 (approximately 4 months after the treatment period ends.)

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacodynamic

Phase
Phase II

Drug/device/biological/vaccine name(s)
PTC518

Primary outcome measure
Current primary outcome measures as of 25/07/2023:
1. Number of participants with adverse events (AEs) [time frame: baseline up to month 18]
2. Change from baseline in blood total huntingtin protein (tHTT) at Month 3 [time frame: baseline, month 3]

Previous primary outcome measures:
Primary Safety Endpoints:
1. Safety profile as characterized by TEAEs, laboratory abnormalities, NfL levels in plasma and CSF, YKL-40 levels in CSF, ECG, vital signs, slit lamp eye examination, and physical examination

Primary Efficacy Endpoint:
2. Change from Baseline in blood tHTT protein at Day 85

Secondary outcome measures
Current secondary outcome measures as of 25/07/2023:
1. Change from baseline in caudate volume as assessed via vMRI at month 12 [time frame: baseline, month 12]
2. Change from baseline in Composite Unified Huntington's Disease Rating Scale (cUHDRS) Scores at month 12 [time frame: baseline, month 12]
3. Change from baseline in blood tHTT protein at month 12 [time frame: baseline, month 12]
4. Change from baseline in CSF mHTT at month 12 [time frame: baseline, month 12]
5. Change from baseline in blood mHTT protein at month 12 [time frame: baseline, month 12]

Previous secondary outcome measures:
1. Change from Baseline in blood HTT mRNA at Days 29, 57, and 85
2. Change from Baseline in CSF mHTT at Day 85
3. Change from Baseline in blood mHTT protein at Day 85

Exploratory Endpoints
4. Change from Baseline in whole brain, caudate, putamen, and ventricular volume (as assessed

by vMRI) at Day 85
5. Change from Baseline in UHDRS scores, with the exception of Behavioral Examination, at Day 85
6. Change from Baseline in the short form of the Problem Behaviors Assessment (PBA-s) at Day 85 (substituting for the UHDRS Behavioral Examination)
7. Change from Baseline in wearable accelerometer assessment of Timed Up and Go (TUG), 2-minute walk distance, and postural sway at Day 85
8. Change from Baseline in the FuRST 2.0 questionnaire at Day 85

Pharmacokinetic Endpoints
9. Plasma trough concentration (Ctrough) and accumulation ratio of PTC518 in plasma at Visits 3, 4, and 5 and accumulation ratio of PTC518 in CSF at Visit 5

Overall study start date
21/09/2021

Completion date
15/08/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 25/07/2023:
Key Inclusion Criteria:
1. Genetically confirmed HD diagnosis with a cytosine-adenine-guanine (CAG) repeat length from 40 to 50, inclusive

Eligibility for HD-ISS Stage 2 Group (Parts A, B, and C):
1. A Unified Huntington's Disease Rating Scale (UHDRS)-Independence Scale (IS) score of 100
2. A UHDRS Total Functional Capacity (TFC) score of 13
3. A score between 0.18 and 4.93 inclusive on the normed version of the HD prognostic index (PINHD)

Eligibility for HD-ISS Mild Stage 3 Group (Parts D, E, and F):
1. A UHDRS Total Functional Capacity (TFC) score of 11 or 12, or a UHDRS TFC score of 13 with an UHDRS IS score of <100

Note: Other inclusion criteria may apply.

Previous inclusion criteria:
1. Ambulatory male or female patients aged 25 years and older, inclusive
2. Subject (or legally authorized representative) is willing and able to provide informed consent and comply with all protocol requirements
3. Genetically confirmed HD diagnosis with a CAG repeat length from 42 to 50, inclusive
4. A UHDRS-IS score of 100
5. A UHDRS TFC score of 13
6. A score between 0.18 and 4.93 inclusive on the normed version of the HD prognostic index (PINHD)
7. Women of childbearing potential (WOCBP) must agree to use highly effective methods of contraception during dosing and for 6 months after stopping the study medication.
8. Sexually active and fertile males must agree to use a condom during intercourse while taking

the study drug and for 6 months after stopping the study drug and should neither father a child nor donate sperm in this period. A condom is required to be used also by vasectomized men in order to prevent the potential delivery of the drug via seminal fluid.

Participant type(s)
Patient

Age group
Adult

Lower age limit
25 Years

Sex
Both

Target number of participants
252

Total final enrolment
159

Key exclusion criteria
Current exclusion criteria as of 25/07/2023:
Key Exclusion Criteria:
1. Receipt of an experimental agent within 90 days or 5 half-lives prior to Screening or anytime over the duration of this study, including ribonucleic acid (RNA)- or deoxyribonucleic acid (DNA)-targeted HD-specific investigational agents such as antisense oligonucleotides, cell transplantation, or any other experimental brain surgery
2. Any history of gene therapy exposure for the treatment of HD
3. Participation in an investigational study or investigational paradigm (such as exercise/physical activity, cognitive therapy, brain stimulation, etc) within 90 days prior to Screening or anytime over the duration of this study
4. Any medical history of brain or spinal disease that would interfere with the lumbar puncture process safety assessments
5. Any medical history or condition that would interfere with the ability to complete the protocol-specified assessments (for example, implanted shunt, conditions precluding magnetic resonance imaging [MRI] scans)
6. Pregnancy, planning on becoming pregnant during the course of the study or within 6 months of the end of treatment, or currently breastfeeding

Note: Other exclusion criteria may apply.

Previous exclusion criteria:
1. Inability or unwillingness to swallow oral tablets
2. Receipt of an experimental agent within 90 days or 5 half-lives prior to Screening or anytime over the duration of this study, RNA- or DNA-targeted HD-specific investigational agents such as antisense oligonucleotides, cell transplantation, or any other experimental brain surgery
3. Any history of gene therapy exposure for the treatment of HD
4. Participation in an investigational study or investigational paradigm (such as exercise/physical activity, cognitive therapy, brain stimulation, etc) within 90 days prior to Screening or anytime

over the duration of this study
5. Presence of an implanted deep brain stimulation device
6. Family history of early onset cataracts or presence of cataracts at Baseline
7. Brain and spinal pathology that may interfere with CSF homeostasis and circulation, increased intracranial pressure (including presence of a shunt for the drainage of CSF or an implanted central nervous system catheter), malformations, and/or tumors
8. Hospitalization for any major medical or surgical procedure involving general anesthesia within 12 weeks of Screening or planned during the study
9. At significant risk of suicide as measured by the C-SSRS with a moderate risk rating or higher score
10. Risk of a major depressive episode, psychosis, confusional state, or violent behavior as assessed by the investigator
11. Any medical history of brain or spinal disease that would interfere with the lumbar puncture processor safety assessments
12. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
13. Any medical history or condition that would interfere with the ability to complete the protocol-specified assessments (eg, implanted shunt, conditions precluding MRI scans)
14. Antidepressant or benzodiazepine use, unless receiving a stable dose for at least 6 weeks prior to Screening and with a dose regimen that is not anticipated to change during the study
15. History of illicit/illegal drug use, or alcohol use in the high-risk category of risk drinking levels according to the World Health Organization for a duration of 1 month or longer that in the opinion of the investigator could compromise the interpretability of study results
16. Clinically significant medical condition, which in the opinion of the investigator could adversely affect the safety of the subject or impair the assessment of study results (e.g. inability to fast)
17. Current significant renal impairment defined as estimated glomerular filtration rate <60 mL /min/1.73 m^2 at Screening
18. Current hepatic impairment resulting in elevated liver function tests (aspartate transaminase [AST], alanine transaminase [ALT], alanine phosphatase [ALP]) at 3 times the upper limit of normal at Screening
19. Pregnancy, planning on becoming pregnant during the course of the study or within 6 months of end of treatment, or currently breastfeeding
20. Use of medications that are moderate or strong inhibitors of cytochrome P450 (CYP) 3A4 within 1 week of Screening or medications that are moderate or strong inducers of CYP3A4 within 2 weeks of Screening or planned use of moderate or strong CYP3A4 inhibitor or inducer medications during the study period.

Date of first enrolment
25/04/2022

Date of final enrolment
31/12/2023

Locations

Countries of recruitment
Australia

England

France

Germany

Netherlands

United Kingdom

United States of America

Wales

Study participating centre
UCL Queen Square Institute of Neurology National Hospital for Neurology Neurosurgery
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Study participating centre
Cardiff University Schools of Medicine and Biosciences
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Ruhr-Univ.Bochum St. Joseph-Hospital
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44791

Study participating centre
Ulm University, UKU, Dep. of Neurology
Ulm
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89081

Study participating centre
Centre Hospitalier Universitaire d'Angers
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49100

Study participating centre
Hôpital Universitaire de Marseille Hôpital de la Timone
Marseille
France
13385

Study participating centre
Brain and Spine Institute Paris
Paris
France
75013

Study participating centre
Westmead Hospital
Sydney
Australia
2145

Study participating centre
Monash Health
Clayton
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Sponsor information

Organisation
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Sponsor type
Industry

Funder(s)

Funder type
Industry

Funder Name
PTC Therapeutics

Alternative Name(s)
PTC Therapeutics Inc., PTC Therapeutics, Inc., PTC Therapeutics Incorporated, PTC Therapeutics, Inc, PTC

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Internal report
Conference presentation

Publication on website
Other publication
Submission to regulatory authorities

Intention to publish date
15/02/2026

Individual participant data (IPD) sharing plan
Study participants will provide appropriate consent to enable the sharing of study data. Through the consent form, participants will be informed of the possibility of their data being shared with other research teams and research collaborators in other countries.
All third parties involved with the research will have appropriate safeguards and confidentiality agreements in place to assure that same level of confidentiality as within the UK will be maintained.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No