# A Phase III study of sepiapterin versus sapropterin in participants with phenylketonuria ≥2 years of age

Submission date	Recruitment status	[X] Prospectively registered
26/10/2023	No longer recruiting	[] Protocol
Registration date	Overall study status	[] Statistical analysis plan
29/01/2024	Completed	[_] Results
Last Edited	Condition category	Individual participant data
07/03/2025	Nutritional, Metabolic, Endocrine	[X] Record updated in last year

## Plain English summary of protocol

Background and study aims

Phenylketonuria (PKU) is an inherited disease in which the body cannot metabolize an amino acid called phenylalanine (Phe). The main purpose of this study is to see how the study drug, sepiapterin, affects blood Phe levels in the body compared with the maximum recommended daily dose of an already known and commercially available treatment called sapropterin in participants with PKU (≥2 years of age).

Who can participate? Patients aged 2 years and over with PKU

What does the study involve?

The study duration for each participant will be up to 173 days from Screening to the final study visit. Following a screening period of up to 45 days, all enrolled participants will receive sepiapterin for 2 weeks followed by a minimum 14-day sepiapterin washout period in Part 1. Participants with ≥20% reduction in blood Phe levels to sepiapterin will continue into Part 2 where they will receive sequential treatment with 4 weeks of sepiapterin and 4 weeks of sapropterin (order determined by randomisation) within each treatment period, separated by a 14-day washout. After completion of the second 14-day washout period, participants will be offered the option to enrol directly into an open-label long-term Study PTC923-MD-004-PKU. There will be approximately 100 participants enrolled in Part 1 and approximately 42 participants randomised into Part 2 of this study.

What are the possible benefits and risks of participating? Benefits

Participation in this study may not benefit study participants, but the knowledge gained from this study may benefit others in the future.

Sepiapterin has been evaluated in a previous study of 24 participants with a significant decrease in Phe levels of participants who maintained the same diet. Not all study participants may be able to see this decrease in their Phe levels, and the amount of the decrease may be different. Risks

Side effects that may occur with administration of sepiapterin and their estimated frequencies include: headache, diarrhoea, upper respiratory tract infection (very common, may occur in ≥10% participants ), and faeces discoloured, abdominal pain (common, may occur in 1% to <10% participants).

In addition to these side effects, when sepiapterin is administered together with certain drugs (e. g., methotrexate, pemetrexed, pralatrexate, trimetrexate) there is a potential risk that a drugdrug interaction between them may occur due to the decrease in a protein involved in their metabolism called dihydrofolate reductase (DHFR). For this reason, coadministration of sepiapterin with these drugs is not permitted.

For information regarding the side effects and risks of sapropterin please see the separate leaflet attached to the PIS-ICF (Adult / Parent(s)/Legal Guardian(s).

All medications can cause allergic reactions that can be mild or more serious and can result in death. Common symptoms of allergic reactions are listed in the PIS and participants are advised to seek medical attention immediately.

Where is the study run from? PTC Therapeutics, Inc. (USA)

When is the study starting and how long is it expected to run for? October 2023 to March 2025

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

Who is the main contact? Medinfo@ptcbio.com

# **Contact information**

**Type(s)** Principal Investigator

**Contact name** Dr Suresh Vijayaraghavan

# **Contact details**

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Scientific

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## Type(s)

Public

**Contact name** Dr Med Info

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# Additional identifiers

EudraCT/CTIS number 2023-506238-61

**IRAS number** 1008747

**ClinicalTrials.gov number** Nil known

Secondary identifying numbers PTC923-PKU-301, IRAS 1008747

# Study information

# Scientific Title

A Phase III, randomized, crossover, open-label, active-controlled study of sepiapterin versus sapropterin in participants with phenylketonuria ≥2 years of age

# Study objectives

Primary objective: To compare the efficacy of sepiapterin to sapropterin in reducing blood phenylalanine (Phe) levels in participants with phenylketonuria (PKU) Secondary objectives:

1. To evaluate the efficacy of sepiapterin in reducing blood Phe levels

2. To assess the safety and tolerability of sepiapterin

Ethics approval required

Ethics approval required

#### Ethics approval(s)

Approved 13/12/2023, London - Hampstead Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8248, (0)207 104 8284, (0)207 104 8227; hampstead.rec@hra.nhs.uk), ref: 23/LO/0939

Study design

Open randomized active-controlled cross-over trial

**Primary study design** Interventional

**Secondary study design** Randomised cross over trial

Study setting(s) Hospital

**Study type(s)** Safety, Efficacy

Participant information sheet

Health condition(s) or problem(s) studied Phenylketonuria (PKU)

#### Interventions

The study consists of two parts: In Part 1 all enrolled participants will receive 60 mg/kg per day of the study drug sepiapterin for 2 weeks followed by a minimum 14-day sepiapterin washout period.

Participants with ≥20% reduction in blood Phe levels to sepiapterin will continue into Part 2 where they will receive sequential treatment with 4 weeks of 60 mg/kg sepiapterin per day and 4 weeks of 20 mg/kg sapropterin per day (order determined by randomisation) within each treatment period. Each 4-week treatment period is followed by a 14-day washout. Randomisation will occur via the online tool Interactive Response Technology (IRT).

Additionally, a phone follow-up visit will occur 30 (±3) days after the last dose of study drug.

After completion of the second 14-day washout period in Part 2, participants will be offered the option to enrol directly into an open-label long-term Study PTC923-MD-004-PKU.

Samples will be collected using the VAMS technology by utilizing the Mitra microsampling devices. Blood phenylalanine levels will be measured at the timepoints indicated in Table 7,

Table 8, and Table 9 of the protocol, i.e.: 1. Screening Period: Day 1 & BH4 Washout: Days 1, 4, 7 2. Part 1: Day -1, 1, 7, 10, 14, 19, 24, 28 3. Part 2: During Treatment Periods 1 and 2: Days -1, 1, 7, 10, 14, 19, 24, 28 4. During Washout for Treatment Periods 1 & 2: Days 5, 10, 14

#### Intervention Type

Drug

#### Pharmaceutical study type(s)

Therapy

**Phase** Phase III

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

Sepiapterin, sapropterin

## Primary outcome measure

Mean change in blood phenylalanine levels is measured using an HPLC/MS/MS method from baseline to Weeks 3 and 4 (i.e., the average of the 2-week treatment period of each treatment). Dried blood spots (DBS) will be collected on Days -1, 1, 7, 10, 14, 19, 24, & 28 in Part 2, Treatment Periods 1 and 2.

## Secondary outcome measures

1. The proportion of participants with baseline blood phenylalanine (Phe) levels ≥600 µmol/L who achieve Phe levels <600 µmol/L after each treatment period is measured by an HPLC/MS /MS method. Dried blood spots (DBS) will be collected on Days -1, 1, 7, 10, 14, 19, 24, & 28 in Part 2. Treatment Periods 1 and 2.

2. The proportion of participants reaching blood Phe <360 µmol/L after each treatment period is measured by an HPLC/MS/MS method. DBS will be collected on Days -1, 1, 7, 10, 14, 19, 24, & 28 in Part 2, Treatment Periods 1 and 2.

3. Adverse events measured using records that are collected throughout the study.

4. Physical examinations are assessed at Screening, Part 1 Day 1; Part 2 Treatment Periods 1 and 2 – Days 1 and 28, Early Termination Visit (if applicable), and End of Study Visit

5. Vital signs are assessed at Screening, Part 1 Day 1; Part 2 Treatment Periods 1 and 2 – Days 1 and 28, Early Termination Visit (if applicable), and End of Study Visit

6. 12-lead ECGs are assessed at Part 1 Day 1; Part 2 Treatment Periods 1 and 2 – Day 28, Early Termination Visit (if applicable), and End of Study Visit

7. Clinical laboratory assessments are assessed at Screening, Part 1 Day 1; Part 2 Treatment Periods 1 and 2 – Days 1 and 28, Early Termination Visit (if applicable), and End of Study Visit

# Overall study start date

24/10/2023

# Completion date

12/03/2025

# Eligibility

## Key inclusion criteria

Participants with any PAH mutation are permitted to screen and enroll into the study. However, participants with biochemically diagnosed classical PKU will be capped at 30% of the total study population. Biochemically diagnosed classical PKU includes those with ≥2 historical blood Phe concentrations ≥1200 µmol/L in their medical history. Furthermore, participants with initial newborn screen performed >3 days after birth demonstrating values ≥1200 µmol/L may have these values excluded from the ≥2 historical blood Phe concentration requirement. Genotyping will not be required for study eligibility; however, all participants will undergo genotyping unless documented in their medical history, and these data will be collected for analysis.

Participants are eligible to be included in the study only if all the following criteria apply: 1. Informed consent, and if necessary, assent (with parent/legally designated representative consent)

2. Male or female participants ≥2 years of age

3. Uncontrolled blood Phe level ≥360 µmol/L on current therapy at any time during Screening and uncontrolled blood Phe level ≥360 µmol/L on current therapy when taking the average of the 3 most recent Phe levels from the participant's medical history (inclusive of the Screening value)

4. Clinical diagnosis of PKU with hyperphenylalaninemia documented by past medical history of at least 2 blood Phe measurements ≥600 μmol/L

5. Women of childbearing potential, as defined in (CTFG 2020), must have a negative pregnancy test at Screening and agree to abstinence or the use of at least one highly effective form of contraception (with a failure rate of <1% per year when used consistently and correctly): 5.1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with

- inhibition of ovulation:
- 5.1.1. Oral
- 5.1.2. Intravaginal
- 5.1.3. Transdermal

5.2. Progestogen-only hormonal contraception associated with inhibition of ovulation:

- 5.2.1. Oral
- 5.2.2. Injectable
- 5.2.3. Implantable
- 5.3. Intrauterine device
- 5.4. Intrauterine hormone-releasing system
- 5.5. Bilateral tubal occlusion
- 5.6. Vasectomized partner with confirmed azoospermia

Highly effective contraception or abstinence must be continued for the duration of the study and for up to 90 days after the last dose of the study drug.

All females will be considered of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea in the appropriate age group without other known or suspected cause) or have been permanently sterilized surgically (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).

6. Males who are sexually active with women of childbearing potential who have not had a vasectomy must agree to use a barrier method of birth control during the study and for up to 90 days after the last dose of the study drug. Males must also refrain from sperm donations during this time period. Males who are abstinent will not be required to use a contraceptive method unless they become sexually active. Males who have undergone a vasectomy are not required to use a contraceptive method if at least 16 weeks post-procedure.

7. Willing and able to comply with the protocol and study procedures

8. Willing to continue current diet unchanged while participating in the study

# Participant type(s)

Patient

# Age group

Mixed

# Lower age limit

2 Years

#### **Sex** Both

both

# Target number of participants

121

# Total final enrolment

83

# Key exclusion criteria

1. The individual, in the opinion of the investigator, is unwilling or unable to adhere to the requirements of the study. Incapacitated adults are not eligible for participation in this study. 2. Gastrointestinal disease (such as irritable bowel syndrome, inflammatory bowel disease, chronic gastritis, peptic ulcer disease, etc.) that could affect the absorption of study drug 3. History of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy

4. Inability to tolerate oral medication

5. History of allergies or adverse reactions to synthetic BH4 or sepiapterin

6. Current participation in any other investigational drug study or use of any investigational agent within 30 days prior to Screening

7. Any clinically significant laboratory abnormality as determined by the investigator. In general, each laboratory value from Screening and baseline chemistry and hematology panels should fall within the limits of the normal laboratory reference range, unless deemed not clinically significant by the investigator

8. A female who is pregnant or breastfeeding, or considering pregnancy

9. Serious neuropsychiatric illness (eg, major depression) not currently under medical control, that in the opinion of the investigator or sponsor would interfere with the participant's ability to participate in the study or increase the risk of participation for that participant

10. Past medical history and/or evidence of renal impairment and/or condition including moderate/severe renal insufficiency (glomerular filtration rate [GFR] <60 mL/min) and/or under care of a nephrologist

11. Any abnormal physical examination and/or laboratory findings indicative of signs or symptoms of renal disease, including calculated GFR <60 mL/min/1.73m2

In participants ≥18 years of age, the Modification of Diet in Renal Disease Equation should be used to determine GFR.

In participants <18 years, the Bedside Schwartz Equation should be used to determine GFR. 12. Requirement for concomitant treatment with levodopa or with any drug known to inhibit folate synthesis (eg, methotrexate)

13. Confirmed diagnosis of a primary BH4 deficiency as evidenced by biallelic pathogenic mutations in 6-pyruvoyltetrahydropterin synthase, recessive guanosine triphosphate (GTP) cyclohydrolase I, sepiapterin reductase, quinoid dihydropteridine reductase, or pterin 4-alpha-carbinolamine dehydratase genes

14. Major surgery within the prior 90 days of Screening

15. Unwillingness to washout from BH4 supplementation (eg, sapropterin dihydrochloride, KUVAN)

16. Use of pegvaliase-pqpz (PALYNZIQ) concurrently or within the 60 days prior to Screening 17. Greater than 20% variance in dietary Phe consumption as measured by mandatory weekly 3day diet record collection for 4 consecutive weeks (Dietary Control Observation Period during Screening)

# Date of first enrolment

31/01/2024

# Date of final enrolment

09/09/2024

# Locations

#### **Countries of recruitment** Australia

Canada

Czech Republic

Denmark

England

France

Germany

Italy

Netherlands

Poland

Slovenia

Spain

**Study participating centre Great Ormond Street Hospital** Great Ormond Street London United Kingdom WC1N 3JH

#### **Study participating centre Birmingham Children's Hospital** Steelhouse Lane Birmingham

United Kingdom B4 6NW

#### **Study participating centre Fakultní nemocnice Královské Vinohrady** Šrobárova 50 Prague Czech Republic 100 34

#### Study participating centre Copenhagen University Hospital BoerneUngeAfdelingen 4062 Blegdamsvej 9 Copenhagen Denmark 2100

#### **Study participating centre CHRU Hôpitaux de Tours - Hôpital Bretonneau** 2 Boulevard Tonnellé Tours France 37044

**Study participating centre Assistance Publique – Hôpitaux de Paris (AP-HP) - Hôpital Necker-Enfants Malades** 149 rue de Sèvres Paris France 75743

#### **Study participating centre Universitätsklinikum Hamburg-Eppendorf** Martinistraße 52

Hamburg Germany 20246

**Study participating centre Universitätsklinikum Münster** Albert-Schweitzer-Campus I, Building D Münster Germany 48149

Study participating centre Azienda Ospedaliera di Padova Via Orus, 2/B Padova Italy

**Study participating centre Pomorski Uniwersytet Medyczny w Szczecinie** Unii Lubelskiej 1 Szczecin Poland 71-252

**Study participating centre Univerzitetni klinicni center Ljubljana** Zaloška cesta 7 Ljubljana Slovenia 1000

**Study participating centre Hospital Universitario Ramón y Cajal** Ctra. Colmenar, Km 9100 Madrid Spain 28034

#### **Study participating centre Hospital Universitario Virgen del Rocío** Av. Manuel Siurot s/n Sevilla Spain 41013

**Study participating centre UMCG, Beatrix Children's Hospital** Hanzeplein 1 Groningen Netherlands 9713 GZ

# Sponsor information

**Organisation** PTC Therapeutics (United States)

Sponsor details 500 Warren Corporate Center Drive Warren United States of America NJ 07059 +1 (0)908 222 7000 Medinfo@ptcbio.com

Sponsor type Industry

Website https://www.ptcbio.com/

ROR https://ror.org/03jz67a83

# 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

- 1. Peer-reviewed scientific journals
- 2. Internal report
- 3. Conference presentation
- 4. Publication on website
- 5. Submission to regulatory authorities

# Intention to publish date

31/03/2026

# Individual participant data (IPD) sharing plan

The data-sharing plans for the current study are unknown and will be made available at a later date.

## IPD sharing plan summary

Data sharing statement to be made available at a later date