A phase 3 open-label study of PTC923 (Sepiapterin) in Phenylketonuria

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This study has been transitioned to CTIS with ID 2023-509229-31-00 check the CTIS register for the current data. Primary:• To evaluate the long-term safety of PTC923 in subjects with phenylketonuria (PKU)• To evaluate changes from baseline in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Protein and amino acid metabolism disorders NEC
Study type	Interventional

Summary

ID

NL-OMON53510

Source
ToetsingOnline

Brief title
PTC923-MD-004-PKU

Condition

- Protein and amino acid metabolism disorders NEC

Synonym
hyperphenylalaninemia, Phenylketonuria

Research involving
Human

Sponsors and support

Primary sponsor: PTC Therapeutics Inc.
Source(s) of monetary or material Support: PTC Therapeutics Inc.

Intervention

Keyword: Hyperphenylalaninemia, Phenylketonuria, PTC923

Outcome measures

Primary outcome

Safety is a primary endpoint: Safety of long-term treatment with PTC923 will be measured by number of treatment-emergent adverse events (TEAEs), including assessment of severity of TEAEs, clinical laboratory tests, vital signs, and physical examinations.

The primary efficacy endpoint is the change from baseline in dietary Phe/protein consumption measured during Dietary Phe Tolerance Assessment period:

• Dietary Phe tolerance evaluated at Baseline and every 2 weeks over the course of 26 weeks assessment period

Secondary outcome

Secondary measures will be evaluated at 6-month intervals starting at M8D1 and will include the following:

• Changes from baseline in QOL using PKU-QOL questionnaire in the subset of subjects who are able to complete the PKU-QOL (ie, subjects whose primary language is English [British or American], Turkish, Dutch, German, Spanish, Italian, Portuguese, or French) (ages 6 to 8 years Parent PKU-QOL; ages 9 to 11 years Child PKU-QOL; ages 12 to 17 years Adolescent PKU-QOL; ages >=18 years Adult PKU-QOL)

• Changes from baseline in QOL using the EQ-5D (EQ-5D-Y Proxy Version 1 [3 to 7 years]; EQ-5D-Y [8 to 15 years]; EQ-5D-5L ([>=16 years])

• PK assessment of sepiapterin and BH4 concentrations in plasma following

dosing of sepiapterin

Study description

Background summary

Phenylketonuria (PKU) is an autosomal-recessive inborn error of metabolism characterized by deficiency of the enzyme phenylalanine hydroxylase (PAH), which metabolizes phenylalanine (Phe). Gene mutations of PAH result in decreased catalytic activity leading to hyperphenylalaninemia (HPA). High levels of Phe are toxic to the brain and are associated with cognitive dysfunction, memory impairment, and can lead to psychiatric and behavioral problems. If left untreated, severe and irreversible intellectual disability can occur. Phenylketonuria is diagnosed at birth with the near universal adoption of newborn screening. Phenylketonuria has been described in all ethnic groups, and its incidence worldwide varies widely, but is estimated to occur in approximately 1 in every 23930 births.

Currently, there is no cure for PKU. Initial treatment consists of prompt institution of stringent Phe dietary restriction supplemented with specifically designed medical foods. Dietary control is considered the standard of care (SoC). The restriction in protein requires exclusion of natural foods such as meat, fish, milk, cheese, bread, nuts, and many other common food items. Even the intake of vegetables is limited.
The success of dietary control, however, comes at high personal cost to affected individuals and their families. Compliance with a restrictive diet and Phe monitoring can be difficult for older children, adolescents, and adults and it is accepted that dietary burden does not improve with age. Lifelong management of Phe levels is critical to avoid neurocognitive decline and other comorbidities.

Synthetic tetrahydrobiopterin (BH4) (eg, sapropterin dihydrochloride), is commercially available as an approved drug for the treatment of HPA in PKU. However, international experts concluded that most people with PKU have little or no benefit from sapropterin dihydrochloride, and evidence of long-term clinical improvements was lacking. They further concluded that *new drugs that are safe, efficacious, and impacting a larger proportion of individualswith PKU are needed*.

PALYNZIQ (pegvaliase-pqpz) is a commercially available product that was recently approved for the treatment of adult patients with PKU (aged 16 years and older in the European Union [EU]) who have inadequate blood Phecontrol

(blood Phe levels greater than 600 µmol/L) despite prior management with available treatment options including sapropterin. While effective at helping lower blood Phe levels to <600 µmol/L, it requires a daily injection and patients in clinical studies experienced significant adverse reactions to PALYNZIQ treatment (e.g. anaphylactic reaction, hypersensitivity, etc.). PALYNZIQ is not indicated for patients <=18 years of age in the United States and <=16 years of age in the EU, and accordingly does not address the unmet need for new medications that are safe and efficacious for children and adolescents.

PTC923 is a new molecular entity and synthetic form of sepiapterin. Sepiapterin serves as a substrate for de novo synthesis of BH4 via the pterin salvage pathway, making sepiapterin a naturally occurring precursor for BH4.Tetrahydrobiopterin is an essential cofactor for enzymes including PAH and tyrosine (Tyr) hydroxylase. Following oral administration, PTC923 is rapidly converted to BH4 intracellularly, the natural cofactor of PAH, and is intended to restore BH4 to physiological levels in patients who lack endogenous BH4, increase BH4 levels in patients who have lower than normal physiological levels of BH4, or enhance the chaperone effect on PAH in PAH-deficient patients by providing pharmacological levels of BH4 while also directly enhancing the thermal stability of PAH.

Study PTC923-MD-003-PKU is a Phase 3 registration study to assess the efficacy of PTC923 in reducing blood Phe levels in subjects with PKU. All subjects who successfully complete a PTC Therapeutics (PTC)-sponsored Phase 3 study in PKU, including Study PTC923-MD-003-PKU, will be eligible for the PTC923-MD-004-PKU study as feeder subject. Additionally, subjects with PKU who have not completed a feeder study (non-feeder subjects) will be considered eligible if they fulfill the inclusion and exclusion criteria. This open-label study will provide important long-term safety data in subjects who will receive PTC923 for a minimum of 12 months or until PTC923 is authorized and commercially available in the specific country.

Study objective

This study has been transitioned to CTIS with ID 2023-509229-31-00 check the CTIS register for the current data.

Primary:
• To evaluate the long-term safety of PTC923 in subjects with phenylketonuria (PKU)
• To evaluate changes from baseline in dietary phenylalanine (Phe)/protein consumption

Secondary:
• To evaluate PTC923 effect on quality of life (QOL) using the Phenylketonuria-quality of life (PKU-QOL) questionnaire in the subset of subjects who are able to complete the PKU-QOL (ie, subjects whose primary

language is English [British or American], Turkish, Dutch, German, Spanish, Italian, Portuguese, or French) (ages 6 to 8 years Parent PKU-QOL; ages 9 to 11 years Child PKU-QOL; ages 12 to 17 years Adolescent PKU-QOL; ages >=18 years Adult PKU-QOL)
• To evaluate PTC923 effect of QOL using the European Quality of Life 5 Dimensions (EQ-5D) (EQ-5D for Youth [EQ-5D-Y] Proxy Version 1 [3 to 7 years]; EQ-5D-Y [8 to 15 years]; EQ-5D-5 Levels (EQ-5D-5L) ([>=16 years])
• To evaluate the pharmacokinetics (PK) of sepiapterin and tetrahydrobiopterin (BH4) following PTC923 dosing

Exploratory:
• To evaluate changes in blood Phe and tyrosine (Tyr) over time
• To assess the taste, palatability, and acceptability of PTC923 (non-feeder subjects <18 years)

Study design

This is a Phase 3 open-label study of PTC923 for subjects with PKU. Eligible subjects are:
- Feeder subjects: those who have completed a Phase 3 PTC Therapeutics (PTC)-sponsored feeder study (including Study PTC923-MD-003-PKU.
At select sites only, the following subjects are eligible:
- Non-feeder controlled subjects: those who have not completed a feeder study and have blood Phe levels <360 µmol/L at study entry
- Non-feeder uncontrolled subjects: those who have not completed a feeder study and have blood Phe levels >=360 µmol/L at study entry
All potential non-feeder subjects will undergo screening procedures. After successful screening, for subjects who have not completed a feeder study and have controlled blood Phe levels (<360 µmol/L), a protein loading test will be performed to test for PTC923 responsiveness (responsiveness defined as >=15% reduction in blood Phe levels at any timepoint (1, 8, or 24 hours) post- PTC923 dose compared to pre-PTC923 dose baseline). These subjects will be classified as responsive and should continue into the study immediately or within 14 days of determination of ascertainment of responsiveness.

For all the subjects, the treatment phase of the study consists of open-label treatment with PTC923 administered orally once a day for a minimum of 12 months or until subject experiences lack of efficacy, adverse events (AEs) that lead to discontinuation, withdraws from treatment, or PTC923 is authorized and commercially available in the specific country.
Upon entry to the study, subjects will be eligible for the following age-based dose escalation:
• 0 to <6 months of age: up to 7.5 mg/kg/day
• 6 to <12 months of age: up to 15 mg/kg/day
• 12 months to <2 years of age: up to 30 mg/kg/day
• >=2 years old of age: up to 60 mg/kg/day

All subjects will provide blood Phe samples at M1D5, 10, 14, 19, 24, and 28. During this period, all subjects will continue their usual diet and will maintain 3-day diet records once every 2 weeks. To determine qualification for the 26-week concurrent Dietary Phe Tolerance Assessment, subjects* mean blood Phe concentrations averaged from M1D5, M1D10, and M1D14 will be analyzed (if only 2 values are available, these will be averaged; and if only 1 value is available, this will be used) and provided to the clinical site prior to the in-clinic M2D1 visit. If on M2D1 there are no blood Phe values from M1D5, M1D10 or M1D14, then the determination of the subject*s participation into the Dietary Phe Tolerance Assessment will be made upon receipt of the initial post-PTC923 treatment M1 blood Phe value and the subject will begin participation in the Dietary Phe Tolerance Assessment at the earliest convenience for the site and subject, but no later than M3D1.
During the Dietary Phe Tolerance Assessment, dietary Phe adjustments will be performed in 2-week intervals for 26 weeks. Once participation in the Dietary Phe Tolerance Assessment concludes, subjects will revert to monthly blood sampling (samples will be collected on Day 1 of each month, where possible), and subjects or parent(s)/legal guardian(s) will complete a 3-day diet record quarterly (the week prior to the scheduled quarterly visit).

Intervention

The test product is PTC923 Powder for Oral Use. All subjects will receive PTC923 (administered with food) daily:
• 7.5 mg/kg/day for subjects 0 to <6 months of age
• 15 mg/kg/day for subjects 6 to <12 months of age
• 30 mg/kg/day for subjects 12 months to <2 years of age
• 60 mg/kg/day for subjects >=2 years of age

Study burden and risks

Currently, there is no cure for PKU. Initial treatment consists of prompt institution of stringent Phe dietary restriction supplemented with specifically designed medical foods. Dietary control is considered the standard of care (SoC).

Side effects of PTC923 are: Constipation, Diarrhea, Abdominal Pain, Vomiting, Gas, Stomach discomfort, Worsening ofgastrointestinal reflux disease, Painful periods, Fatigue, Decreased appetite, Conjunctivitis (pink eye), Headache, Dizziness

Risks associated to study assessments:
- Blood draws can cause pain, bruising, inflammation and swelling of the vein, bleeding or even an infection at the puncture site.
- ECG: Skin reactions to the sticky pads may occur, such as redness, itching or discomfort. Some hair loss may be associated with the glue at the placement

sites of the ECG pads.

The following procedures are performed:
- measurement of vital signs;
- physcial examination;
- ECG;
- Questionnaires;
- Venous blood draw, including PK and Phe/Tyr samples.

Subjects or subject's legal representative will be asked to maintain a 3-days diet diary in study which will be collected by the site staff for review by a dietician.

Contacts

Public
PTC Therapeutics Inc.

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US
Scientific
PTC Therapeutics Inc.

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Children (2-11 years)
Elderly (65 years and older)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

Individuals are eligible to participate if they meet all the following inclusion criteria:
1. Informed consent and assent (if necessary, at the investigator*s discretion [ie, for children]) with parental/legal guardian consent
2. Male or female subjects of any age.
3. Clinical diagnosis of PKU with hyperphenylalaninemia (HPA) documented by past medical history of at least 2 blood Phe measurements >=600 µmol/L
4. Women of childbearing potential, as defined in (CTFG 2020), must have a negative
pregnancy test at study entry 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):
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
* Oral
* Intravaginal
* Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation:
* Oral
* Injectable
* Implantable
• Intrauterine device
• Intrauterine hormone-releasing system
• Bilateral tubal occlusion
• 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).
5. 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 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.
6. Willing and able to comply with the protocol and study procedures
7. Willing to continue current diet unchanged while participating in the study (unless specifically instructed to change diet during the study by the investigator)

Exclusion criteria

Individuals are not eligible to participate if they meet any of the following exclusion criteria:
1. The individual, in the opinion of the investigator, is unwilling or unable to adhere to
the requirements of the study
2. Inability to tolerate oral medication
3. A female who is pregnant or breastfeeding, or considering pregnancy
4. Serious neuropsychiatric illness (eg, major depression) not currently under medical
control, that in the opinion of the investigator or sponsor, would interfere with the
subject*s ability to participate in the study or increase the risk of participation for that
subject
5. Past medical history and/or evidence of renal impairment and/or condition including
moderate/severe renal insufficiency (glomerular filtration rate [GFR] <60 mL/min as
estimated most recently during qualifying participation in a feeder study) and/or under
care of a nephrologist
6. Any other condition that in the opinion of the investigator or sponsor, would interfere
with the subject*s ability to participate in the study or increase the risk of participation
for that subject
7. Requirement for concomitant treatment with any drug known to inhibit folate synthesis
(eg, methotrexate)
8. Concomitant treatment with BH4 supplementation (eg, sapropterin dihydrochloride,
KUVAN) or pegvaliase-pqpz (PALYNZIQ)
Additional criteria for subjects who did not participate in a feeder study:
9. Gastrointestinal disease (such as irritable bowel syndrome, inflammatory

bowel disease, chronic gastritis, and peptic ulcer disease, etc) that could affect the absorption of study drug
10. History of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy
11. History of allergies or adverse reactions to synthetic BH4 or sepiapterin
12. Current participation in any other investigational drug study or use of any investigational agent within 30 days prior to Screening
13. 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
14. Any abnormal physical examination and/or laboratory findings indicative of signs or symptoms of renal disease, including calculated GFR <60 mL/min/1.73 m2. In subjects >=18 years of age, the Modification of Diet in Renal Disease Equation should be used to determine GFR.
In subjects <18 years of age, the Bedside Schwartz Equation should be used to determine GFR.
15. Confirmed diagnosis of a primary BH4 deficiency as evidenced by biallelic pathogenic mutations in 6-pyruvoyltetrahydropterin synthase, recessive GTP cyclohydrolase I, sepiapterin reductase, quinoid dihydropteridine reductase, or pterin-4-alpha-carbinolamine dehydratase genes
16. Major surgery within the prior 90 days of screening
17. Unwillingness to washout from BH4 supplementation (eg, sapropterin dihydrochloride, KUVAN) or pegvaliase-pqpz (PALYNZIQ)

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-10-2023

Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PTC923
Generic name:	PTC923

Ethics review

Approved WMO Date:	15-09-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-04-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-04-2023
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-509229-31-00
EudraCT	EUCTR2021-000497-28-NL
ClinicalTrials.gov	NCT05166161
CCMO	NL82363.042.22