A phase 3 study of PTC923 in subjects with phenylketonuria

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Primary:• To evaluate the efficacy of PTC923 in reducing blood phenylalanine (Phe) levels in subjects with phenylketonuria (PKU) as measured by mean change in blood Phe levels from baseline to Weeks 5 and 6 (ie, the average of each respective...

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

Summary

ID

NL-OMON51999

Source
ToetsingOnline

Brief title
PTC923-MD-003-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

The primary efficacy measure will be reduction in blood Phe levels in subjects with PKU as measured by mean change in Phe levels from baseline to Part 2 Weeks 5 and 6 (ie, the average of the 2-week period at the target dose of double-blind treatment). Baseline blood Phe level will be the mean of Day -1 and Day 1 blood Phe levels.

Secondary outcome

The secondary efficacy endpoints are the proportion of subjects with baseline Phe levels >=600 µmol/L who achieve Phe levels <600 µmol/L at the end of the double-blind treatment period and the change from baseline in mean blood Phe levels at each PTC923 dose level (ie, each 2-week period in Part 2).

Safety endpoints:

Safety and tolerability of PTC923 as measured by severity and number of treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, physical examinations, and electrocardiograms (ECGs) will be compared to placebo.

Pharmacokinetics endpoints:

Depending on the number of samples obtained, the following PK parameters of sepiapterin and BH4 for a given subject may be calculated using

noncompartmental methods: Cmax, Tmax, T1/2, area under the plasma concentration-time curve from time zero to 24 hours (AUC0-24h), area under the plasma concentration-time curve from time zero to infinity (AUC0-inf), apparent total clearance of the drug from plasma following oral administration (CL/F), and apparent volume of distribution during terminal phase after non-intravenous administration (Vz/F).

Additionally, depending on the number of samples collected and subject demography, a population PK analysis will be performed using all PK samples collected in the study to further characterize the PK of sepiapterin and BH4 to examine potential source of PK variability, such as age, and to explore the relationship between exposure and response.

The exploratory efficacy endpoint is the change from baseline in blood Tyr over time, including the Phe:Tyr ratio.

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 individuals with 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 Phe control (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 study to assess the efficacy of PTC923 in reducing blood Phe levels in subjects with PKU. It is anticipated that a greater reduction in Phe will be observed in subjects with PKU who receive PTC923 versus those who receive placebo. This Phase 3 study is designed to support registration of PTC923 in subjects with PKU.

Study objective

Primary:
• To evaluate the efficacy of PTC923 in reducing blood phenylalanine (Phe) levels in subjects with phenylketonuria (PKU) as measured by mean change in blood Phe levels from baseline to Weeks 5 and 6 (ie, the average of each respective treatment dose 2-week period of double-blind treatment).

Secondary:
• To evaluate the proportion of subjects with baseline Phe levels >=600 µmol/L who achieve Phe levels <600 µmol/L at the end of the double-blind treatment period.
• To evaluate the effect of PTC923 dose response on reducing blood Phe levels in subjects with PKU.
• To evaluate the pharmacokinetics (PK) of PTC923 in subjects with PKU.
• To assess the safety of PTC923 in subjects with PKU.

Exploratory Objectives:
• To evaluate changes in blood tyrosine (Tyr) overtime, including the Phe:Tyr ratio.

Study design

Study PTC923-MD-003-PKU is a phase 3, double-blind, randomized study that compares PTC923 plus
SoC to placebo plus SoC. Standard of care in PKU is a Phe-restricted diet.

The study is set up in 2 parts and lasts in total 122 days.

During Part 1 (the open-label Responsiveness Test), subjects with PKU will be enrolled and receive PTC923 for 14 days to identify subjects with >=15% reduction from baseline in blood Phe levels.

Subjects will receive the following doses of PTC923 for 14 days:
- Subjects 0 to <6 months of age - 7.5 mg/kg
- Subjects 6 to <12 months of age - 15 mg/kg
- Subjects 12 months to <2 years of age - 30 mg/kg
- Subjects >=2 years - 60 mg/kg

Subjects who experience <15% reduction in blood Phe levels will be classified

as nonresponsive and will be contacted to schedule an Early
Termination Visit (ETV) (on or between Day 28 to Day 35 of last dose).

Subjects <2 years of age who experience a >=15% reduction in blood Phe levels will be offered
the option to enroll directly into an open-label extension study.

PTC923-responsive subjects >=2 years of age will be entered into Part 2.
Part 2 (double-blind, randomized (1:1), placebo controlled):
Subjects in the PTC923 treatment arm will receive:
- PTC923 20 mg/kg daily for 14 days,
- PTC923 40 mg/kg daily for 14 days and
- PTC923 60 mg/kg daily for 14 days.
As dosing is weight-based and to maintain the blind, subjects in the placebo arm will receive equivalent quantities of placebo to match the 20 to 40 to 60 mg/kg dose escalation of the PTC923 treatment arm.

After 6 weeks of treatment with either PTC923 or placebo, subjects will be offered the option to enter an open-label extension study.

Intervention

PTC923 is a powder for oral use and will be suspended in water or apple juice prior to administration.

In part 1 (open label) of the study the subjects will receive PTC923 once daily for 2 weeks:
- Subjects 0 to <6 months of age - 7.5 mg/kg
- Subjects 6 to <12 months of age - 15 mg/kg
- Subjects 12 months to <2 years of age - 30 mg/kg
- Subjects >=2 years - 60 mg/kg

In part 2 (double-blind, randomized) of the study the subjects will receive:
- PTC923 20 mg/kg daily for 14 days,
- PTC923 40 mg/kg daily for 14 days and
- PTC923 60 mg/kg daily for 14 days.
As dosing is weight-based and to maintain the blind, subjects in the placebo arm will receive equivalent quantities of placebo to match the 20 to 40 to 60 mg/kg dose escalation of the PTC923 treatment arm.

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).
Study PTC923-MD-003-PKU is a Phase 3 study to assess the efficacy of PTC923 in reducing blood Phe levels in subjects with PKU. It is anticipated that a greater reduction in Phe will be observed in subjects with PKU who receive PTC923 versus those who receive placebo.

PTC923 is provided as a powder for suspension in water or apple juice.

Side effects of PTC923 are: Constipation, Diarrhea, Abdominal Pain, Vomiting, Gas, Stomach discomfort, Worsening of gastrointestinal 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, part 1 - day 1, part 2 - day 1 and 42 and at the Early termination visit (part 1 and 2 - day 1 pre- and post-dose);
- physcial examination at screening, part 1 - day 1, part 2 - day 1 and 42 and at the Early termination visit;
- ECG at part 1 - day 1, part 2 - day 42 and Early termination visit. For subjects in the PK sub-study ECGs will be performed on part 1 - day 1 at 2, 4, 6 and 8 hours post-dose as well;
- Questionnaires to be completed on day 1 of part II: PKU Quality of Life (subjects as of age 6 years) and EQ-5D (subjects as of age 3 years).
- Venous blood draw: at screening, part 1 day 1, part 2 - days 1 and 42 or early termination visit.
Blood samples will be collected for PK analysis from subjects participating PK sub-study at the following timepoints. In Part 1, subjects >=2 years, samples will be collected at Part 1 Day 1 (predose, and 0.5, 1, 2, 4, 6, 8, and 24 hours postdose).
In Part 1, subjects <2 years, samples will be collected at Part 1 Day 1 (predose and 4 hours postdose), Part 1 Day 14 (2 and 6 hours postdose).
In Part 2 (all ages), samples will be collected pre-dose and 4 hours post dose on Day 1, Part 2 Day 14, Part 2 Day 28 , Part 2 Day 42.
For subjects participating in the PK sub-study, additional, blood Phe and Tyr samples will be collected at all timepoints from the PK samples prior to plasma harvesting in Part 1.
- Dried blood spot for participants <2 years:
- screening: 1 time 0.12 mL and/or 3 times 0.12 mL (washout period);
- part 1: 8 times 0.12 mL and/or 4 times 0.25 mL (in case of PK-substudy);
- part 2: 11 times 0.12 mL

- Dried blood spot for participants >= 2 years <12 years:
- screening: 1 time 0.12 mL and/or 3 times 0.12 mL (washout period);
- part 1: 8 times 0.12 mL and/or 8 times 0.25 mL (in case of PK-substudy);
- part 2: 11 times 0.12 mL
- Dried blood spot for participants >= 12 years:
- screening: 1 time 0.12 mL and/or 3 times 0.12 mL (washout period);
- part 1: 8 times 0.12 mL and/or 8 times 0.25 mL (in case of PK-substudy);
- part 2: 11 times 0.12 mL

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

Contacts

Public
PTC Therapeutics Inc.

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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)

Inclusion criteria

Informed consent and assent (if necessary, at the investigator*s discretion [ie, for children and/or subjects who are mentally impaired secondary to disease]) with parental/legal guardian consent
2. Male or female subjects of any age
3. Uncontrolled blood Phe level >=360 µmol/L on current therapy anytime 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 subject*s medical history (inclusive of the Screening value)
4. Clinical diagnosis of PKU with hyperphenylalaninemia (HPA) 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):
• 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).

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 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

Exclusion criteria

1. The individual, in the opinion of the investigator, is unwilling or unable to adhere to
the requirements of the study
2. 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
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
subject*s ability to participate in the study or increase the risk of participation for that
subject

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 subjects >=18 years of age, the Modification of Diet in Renal Disease Equation should be used to determine GFR.
In subjects <18 years, the Bedside Schwartz Equation should be used to determine GFR.
12. Requirement for concomitant treatment 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 GTP cyclohydrolase I,
sepiapterin reductase, quinoid dihydropteridine reductase, or pterin-4-alphacarbinolamine
dehydratase genes
14. Major surgery within the prior 90 days of screening
15. Concomitant treatment with BH4 supplementation (eg, sapropterin dihydrochloride,
KUVAN) or pegvaliase-pqpz (PALYNZIQ)
16. Unwillingness to washout from BH4 supplementation (eg, sapropterin dihydrochloride,
KUVAN) or pegvaliase-pqpz (PALYNZIQ)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-08-2022
Enrollment:	5
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	14-04-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-08-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2023
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
EudraCT	EUCTR2021-000474-29-NL
ClinicalTrials.gov	NCT05099640
CCMO	NL77504.042.22