Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Sephience

Active ingredient: sepiapterin

Sponsor: PTC Therapeutics Australia Pty Ltd

November 2025

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ARTG	Australian Register of Therapeutic Goods
BH4	Tetrahydrobiopterin
ASA	Australia-specific annex
AUC	Area under the concentration-time curve
CMI	Consumer Medicines Information
HPA	Hyperphenylalaninaemia
PAH	Phenylalanine hydroxylase
PI	Product Information
PKU	Phenylketonuria
PSUR	Periodic safety update report
RMP	Risk management plan
SD	Standard deviation
TEAEs	Treatment emergent adverse events
TGA	Therapeutic Goods Administration

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Sephience
Active ingredient:	sepiapterin
Decision:	Approved
Date of decision	14 July 2025
ARTG number(s):	453665 and 453666
▼*Black Triangle Scheme*	Yes
Sponsor's name and address:	PTC Therapeutics Australia Pty Limited, Suite 1617 & 1619, Level 16, 1 Denison Street North Sydney NSW 2060.
Dose form:	Oral powder
Strengths:	250 mg, 1000 mg
Container:	Sephience is supplied in individual heat-sealed laminated aluminium foil sachets comprising polyethylene terephthalate, white extruded polyethylene (polyester/foil bond), aluminium foil (moisture barrier) and a heat-seal ionomeric resin (adhesive).
Pack size:	Each carton contains 30 sachets.
Approved therapeutic use for the current submission:	Sephience is indicated for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients with phenylketonuria (PKU).
Route of administration:	Oral
Dosage:	The recommended dose of Sephience, to be administered orally once daily is based on age and body weight. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	Category B1 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is

available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by PTC Therapeutics Australia Pty Limited (the Sponsor) to register Sephience (sepiapterin) for the following proposed indication[1]

> *Treatment of hyperphenylalaninaemia in paediatric and adult patients with phenylketonuria*

Disease or condition

Phenylketonuria (PKU) is a metabolic disorder resulting from accumulation of phenylalanine. It is an autosomal recessive inherited disorder (i.e. an inborn error of metabolism).[2] It is caused by a deficiency in phenylalanine hydroxylase (PAH). Phenylalanine hydroxylase catalyses the hydroxylation of phenylalanine to tyrosine, the rate-limiting step in phenylalanine catabolism. The reaction is dependent on tetrahydrobiopterin (BH4), as a cofactor, molecular oxygen, and iron.

The incidence of PKU is 1 in 10,000 live births in Australia.[3] A more precise estimate of PKU prevalence in Australia is 1 in 1,1236 individuals and 2,216 patients with PKU.[4] Around half of patients with PKU are BH4 responsive, defined as a ≥30% reduction of blood Phe concentrations within 24-48 h after the administration of BH4 (20 mg/kg body weight)[5]. In Australia, 80% of patients are classic PKU, 14.1% are mild PKU and 5.4% are mild hyperphenylalaninaemia.

Individuals with classic PKU have residual PAH activity <20%, and individuals with activity >20% have mild PKU. Most variation in classical PKU is due to heterogeneity in the mutant alleles with many patients being compound heterozygotes rather than homozygotes for one particular mutant allele.

Normal mean (SD) blood phenylalanine concentrations are 58 (15) µmol/L in adults, 60 (13) µmol/L in teenagers, and 62 (18) µmol/L in childhood. In the newborn, the upper limit of normal is 120 µmol/L (2 mg/dL). In untreated classical PKU, blood concentrations as high as 2.4 mM/L can be measured.

If undiagnosed in infancy, progressive developmental delay is the most common manifestation, and in addition, untreated children in later infancy and childhood may also present with recurrent vomiting, mousy odour, eczema, seizures, severe behavioural disorders. Older children and adults who transition to a normal diet may develop poor focus and deteriorating cognitive skills. These individuals may also have evidence of white matter changes visible on magnetic resonance imaging and may experience an intelligence quotient decline of 10 points or more.

[1] This is the original indication proposed by the Sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.
[2] OMIM. https://www.omim.org/entry/261600?search=phenylketonuria&highlight=phenylketonuria. Accessed 20th October 2024.
[3] Human Genetics Society of Australasia (HGSA). The PKU Handbook. 2020.
[4] Hillert A, Anikster Y, Belanger-Quintana A, Burlina A, Burton BK, Carducci C, et al. The Genetic Landscape and Epidemiology of Phenylketonuria. Am J Hum Genet. 2020 Aug 6;107(2):234-250.
[5] Hillert A, 2020.

In Australia, general guidelines include the following with regard to target phenylalanine concentrations:[6]

- most clinics agree that for children up to 12 years old, Phe concentrations should be 120–360 µmol/L.
- for children over 12 years old, teenagers and adults, an informed decision to accept Phe levels above 360 µmol/L may be appropriate in some cases. However, lower levels are preferable.
- women planning a pregnancy or who are pregnant need to have Phe levels between 70 to 250 µmol/L to prevent injury to the foetus.

Current treatment options

PKU is managed by restricting protein and phenylalanine intake, and with BH4 supplementation in those patients who are responsive.[7] This can be quite restrictive as phenylalanine is found in all proteins.[8] Hence, the PKU diet consists of avoiding meat, dairy, nuts, tofu, and other foods that are high in protein. Infants with PKU need to be fed with a low-protein formula. Affected individuals are often limited to certain fruits and vegetables and foods containing fats and sugars (such as butter, jelly, pasta, and potato chips). The artificial sweeter aspartame, which is found in diet soda and many other low-calorie items, should be avoided as it contains high amounts of phenylalanine. The amount of phenylalanine that is safe to consume is different for each person. The diet should be overseen by a clinical dietitian in order to ensure adequate intake of nutrients including vitamins and minerals.

On diagnosis, the diet should be devoid of phenylalanine to enable a washout period. Following the washout period, there should be sufficient phenylalanine in the diet to enable normal protein synthesis, but excess Phe should be avoided. Adherence to diet is usually adequate but non-adherence can result in cognitive impairment.

Other dietary modifications include supplementation with large neutral amino acids (LNAAs) like arginine, histidine, isoleucine, lysine, methionine, threonine, tryptophan, tyrosine, and valine, which may compete with Phe for transport across the blood-brain barrier and reduce its influx into the brain.

There are two medicines for the treatment of PKU that are approved on the ARTG:

- Sapropterin (Kuvan): a synthetic formulation of BH4 registered on the ARTG in 2018 for "the treatment of hyperphenylalaninemia (HPA) in sapropterin-responsive adult and paediatric patients with phenylketonuria (PKU) or BH4 deficiency".
- Pegvaliase (Palynziq) is a subcutaneous injection of a pegylated recombinant phenylalanine ammonia lyase enzyme that converts phenylalanine to ammonia and cinnamic acid that are primarily eliminated by liver metabolism. Pegvaliase was registered in the ARTG in 2021 with the indication: "for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control despite prior management with available treatment options".

[6] HGSA 2020

[7] Talebi S, Eshraghi P. Nutrition in Phenylketonuria. Clin Nutr ESPEN. 2024 Oct 18:S2405- 4577(24)01336-6. doi: 10.1016/j.clnesp.2024.09.032. Epub ahead of print. PMID: 39427751

[8] MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); Phenylketonuria; [updated April 25, 2023. Available from: https://medlineplus.gov/genetics/condition/phenylketonuria/#resources.

Clinical rationale

Sepiapterin acts as a chaperone, stabilising the misfolded PAH enzyme. Sepiapterin is also a precursor to BH4, a cofactor crucial for PAH enzyme's function. It is proposed that sepiapterin is able to effectively reduce blood Phe levels by enhancing the conformational stability of misfolded PAH enzyme and increasing the intracellular concentrations of BH4.

Regulatory status

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes. Sephience was granted orphan status on 28 May 2025.

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies.

In April 2025 the European Medicines Agency adopted a positive opinion recommending marketing authorisation of Sephience for the indication of:

> *Sephience is indicated for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients with phenylketonuria (PKU).*

The Sponsor submitted similar applications in Canada, the US and Switzerland in June and July 2024.

The Sponsor stated that no similar application has been rejected, withdrawn or deferred in any region or country.

Sepiapterin was granted Orphan Drug Designation for the treatment of hyperphenylalaninemia in the US on 4 March 2021, the EU on 20 May 2021, and Switzerland on 15 May 2024.

Priority review status was granted in Canada on 2 May 2024 (Priority Evaluation), and Switzerland on 5 June 2024 (Fast Track Authorisation Procedure).

Registration timeline

Table 1 captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 1: Timeline for Sephience, submission PM-2024-02536-1-3.

Description	Date
Designation (Orphan)	28 May 2025
Submission dossier accepted and first round evaluation commenced	31 July 2024
Evaluation completed (End of round 2)	17 April 2025
Advisory committee meeting	June 2025
Registration decision (Outcome)	14 July 2025

Description	Date
Registration in the ARTG completed	17 July 2025
Number of working days from submission dossier acceptance to registration decision*	195

*Statutory timeframe for standard submissions is 255 working days

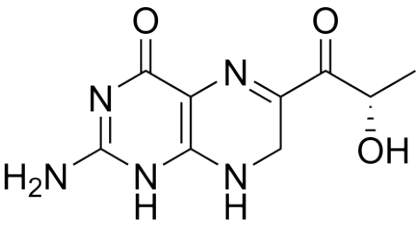
Assessment overview

Quality evaluation summary

Sepiapterin is both a natural product and synthetic small molecule of the pterin subclass of the pteridine class. In vivo, it is metabolised to form tetrahydrobiopterin, which is a cofactor required for breakdown to phenylalanine and metabolism of phenylalanine, tyrosine and tryptophan to precursors of dopamine and serotonin.

The drug substance, sepiapterin (Figure 1) is manufactured by chemical synthesis. The proposed specification was developed in-house and adequately controls the identity, potency, purity, and chemical and physical properties of the drug substance relevant to the dose form, with the exception of control of particle size distribution which requires further tightening.

Figure 1. Chemical structure of sepiapterin:



The synthetic impurities are controlled to either ICH Q3A[9] or where higher were adequately qualified.

The analytical methods used to analyse the product were adequately described and validated.

Risk evaluations on the potential presence of nitrosamines and elemental impurities were performed. No significant risk was identified.

The stability data supports a retest period of 24 months when stored at 5 °C.

The proposed drug product is a yellow to orange powder sealed in a heat-sealed aluminium sachet. Strengths are differentiated by sachet labelling and by the size of the sachet (50 x 72 mm for 250 mg strength, 60 x 90 mm for 1000 mg strength). The formulation of each strength differs only in the quantity of product filled in each sachet. The formulation includes the drug substance, and a number of excipients commonly used for their described purposes as diluent, disintegrant, suspending agent, sweetener and lubricant respectively. The excipients isomalt, mannitol and sucralose are present in the formulation in quantities which require declaration of their presence on the product labelling as per Therapeutic Goods Order 91.

The manufacturing process is typical for the dosage form and is appropriately developed and controlled.

[9] ICH Q3A (R2) Impurities in new drug substances - Scientific guideline. Available at https://www.ema.europa.eu/en/ich-q3a-r2-impurities-new-drug-substances-scientific-guideline

The product can be mixed in water, apple juice or a small amount of soft foods such as apple sauce or jams prior to administration, and the compatibility of the product with these vehicles has been acceptably demonstrated.

The drug product specifications adequately control the quality of the drug product at release and throughout the shelf-life.

The impurities are controlled according to ICH Q3B[10], or where higher, were adequately qualified.

The analytical methods used to analyse the product were adequately described and validated.

Risk evaluations on the potential presence of nitrosamines and elemental impurities were performed. No significant risk was identified.

A shelf life of 24 months when stored below 25 °C is supported.

Registration of Sephience is recommended from a quality perspective.

Nonclinical evaluation summary

The submitted nonclinical dossier was of high quality, with the package of studies conducted in accordance with ICH M3 (R2).[11] All pivotal safety-related studies were GLP-compliant.

In vitro, sepiapterin stabilised and increased activity of recombinant proteins harbouring common clinical PKU mutations at micromolar concentrations. In vivo, sepiapterin was rapidly converted to BH4, the active PAH chaperone, supporting the proposed clinical indication.

No clinically relevant inhibition was seen on a set of potential off-target sites including receptors, ion channels, enzymes and transporters. No investigation of other proteins known to be activated by BH4 (e.g. nitric oxide synthase) was made. However, toxicity studies did not uncover any unique toxicities or raise specific concerns about off-target effects of sepiapterin.

Safety pharmacology studies (incorporated into repeat dose toxicity studies) assessed effects on cardiovascular, respiratory, and central nervous systems. No adverse effects were seen on CNS or respiratory function in rats. No significant inhibition of hERG K+ channel tail current was observed at clinically relevant sepiapterin concentrations, however hERG current data for BH4 was unreliable. Since no sepiapterin-related cardiovascular effects were observed in repeat-dose toxicity studies in marmosets, sepiapterin is not predicted to prolong the QT interval in patients.

Overall, the pharmacokinetic profile in animals was qualitatively similar to that of humans. Sepiapterin was rapidly absorbed and converted to BH4, with a similar T_{max} in all species. BH4 half-life values were similar in rats, dogs, monkeys and humans. Plasma protein binding of sepiapterin and BH4 was low in humans but was not determined in any other species. Tissue distribution of sepiapterin was wide but penetration into brain and spinal cord was very limited. Sepiapterin was extensively metabolised, with qualitatively similar profiles in animals and humans. Drug-related material was excreted via faeces and urine, with faeces as the predominant route of excretion in both animals and humans. Biliary excretion was shown in rats.

Sepiapterin is not expected to alter the exposure of co-administered drugs that are CYP450 substrates or inhibitors. Sepiapterin and BH4 are substrates of BCRP, but co-administered

[10] ICH Q3B (R2) Impurities in new drug products - Scientific guideline. Available at ICH Q3B (R2) Impurities in new drug products - Scientific guideline | European Medicines Agency (EMA)

[11] ICH M3 (R2) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals - Scientific guideline. Available at https://www.ema.europa.eu/en/ich-m3-r2-non-clinical-safety-studies-conduct-human-clinical-trials-pharmaceuticals-scientific-guideline

inhibitors/inducers of BCRP are not expected to notably alter exposure to sepiapterin. In vitro sepiapterin inhibited OATP1B3 and BH4 inhibited OCT1 at clinically relevant concentrations. Caution may be needed in co-administering drugs that are known to be substrates of these transporters. Sepiapterin is a substrate of efflux transporter BCRP and ENT2 and BH4 is a substrate of efflux transporters BCRP and P-gp and renal transporterMATE2-K in vitro. However, drug interactions are not expected for these transporters at clinically relevant concentrations.

Repeat-dose toxicity studies by the oral route were conducted in mice (4 weeks) rats (up to 6 months), and marmoset monkeys (up to 9 months). Maximum exposures (AUC) were moderate in rats and low to moderate in marmosets. The major target organs for toxicity were the kidney (tubular degeneration, crystal deposit, fibrosis, associated with increased kidney weight, serum urea and creatinine) and GI tract (reversible soft / creamy luminal material in the stomach, duodenum, jejunum, ileum, cecum; no microscopic correlate).

Sepiapterin was not mutagenic in the bacterial mutation assay but was positive in the in vitro chromosomal aberration assay. However, sepiapterin was negative in micronucleus and Comet assays in rats. A weight of evidence approach considering all genotoxicity studies suggests a low risk of genotoxicity for sepiapterin, with the negative results in in vivo studies considered more reliable than the findings in in vitro studies.

No carcinogenicity studies were submitted, which is considered acceptable. Using a weight of evidence approach, the carcinogenic potential of sepiapterin is humans is considered low.

Fertility and early embryonic development were unaffected in male and female rats treated with sepiapterin. There were no treatment-related effects on embryofetal development in rats and rabbits or pre/postnatal development in rats at moderate exposure levels.

No adverse effects were observed in repeat-dose toxicity studies in juvenile rats.

Sepiapterin, did not show in vitro activity on receptors known to be associated with drug abuse. In addition, sepiapterin did not show any CNS activities that would be indicative of abuse liability.

The proposed limit for eight impurities in the drug substance and product have been adequately qualified by submitted toxicity data.

There are no nonclinical objections to the registration of sepiapterin for the proposed indication.

Clinical evaluation summary

Summary of clinical studies

The clinical efficacy and safety of sepiapterin for PKU was supported by a pivotal phase 3 study MD-003-PKU, and two supportive studies Study PKU-002 and Study MD-004-PKU. In total 188 subjects with PKU were treated. While this is a relatively small number for an entire clinical program it is acknowledged that PKU is a rare disorder.

Pharmacokinetics

Sepiapterin is orally absorbed, with a saturable process in the dose range 20 mg/kg to 60 mg/kg. This was demonstrated by dose proportionality between 2.5 mg/kg and 20 mg/kg, but not between 20 mg/kg and 60 mg/kg. Sepiapterin is rapidly metabolised to BH4 which is then metabolised and/or recycled by endogenous pathways. Unabsorbed sepiapterin is metabolised by gut microflora.

The T_{max} for sepiapterin was 1 to 2 hours across the dose range 2.5 mg/kg to 80 mg/kg. C_{max} increased in a less than dose-proportional manner, but AUC_{last} was approximately dose-proportional (slope [90% CI] was 1 [0.71 to 1.14]).

In Study MD-005, bioavailability was increased by a high fat meal for both the 20 mg/kg and 60 mg/kg dose levels. For the 20 mg/kg dose level, the geometric mean ratio (90% CI) Fed/Fasted for $AUC_{0\text{-}24h}$ was 163.23 (109.51 to 243.32) for sepiapterin and 250.94 (221.42 to 284.40) for BH4. For the 60 mg/kg dose level, the geometric mean ratio (geometric mean ratio; 90% CI) Fed/Fasted for $AUC_{0\text{-}24h}$ was 196.62 (124.18 to 311.33) for sepiapterin and 283.84 (251.29 to 320.62) for BH4. Hence, a high fat meal increased exposure to sepiapterin by approximately 60% to 100% and to BH4 by approximately 150% to 200%. In comparing the results of Part A and Part B, a low-fat meal increased exposure to sepiapterin by approximately 70% to 150% and to BH4 by approximately 60% to 70%.

In population PK analysis 2021-022, the typical estimates were 6.36 L for apparent central volume of distribution and 1.21 L for apparent volume of peripheral distribution.

Sepiapterin is metabolised by sepiapterin reductase/carbonyl reductase and dihydrofolate reductase in a 2-step unidirectional process to form pharmacologically active metabolite BH4. BH4 is further metabolised non-enzymatically or enzymatically mediated by aromatic amino acid hydroxylases, such as PAH, tyrosine hydroxylase and tryptophan hydroxylase, and pterin-4α-carbinolamine dehydratase, dihydropteridine reductase, xanthine oxidase and nitric oxide synthase in various tissues.

In population analysis 2021-022, there was linear clearance. The typical estimate for apparent systemic clearance was 1.90 L/h.

There are potential pharmacogenetic effects that have not been explored. In Study MD-005, bioequivalence was not demonstrated for either the 20 mg/kg or 60 mg/kg dose levels for the Phase 1/2 and Phase 3 formulations. However, the pivotal Phase III study was conducted using the formulation intended for marketing. The PK data obtained from the early development formulation are applicable to the marketed formulation.

Pharmacodynamics

Sepiapterin acts as a dual pharmacological chaperone (sepiapterin and BH4) to improve the activity of the defective phenylalanine hydroxylase (PAH) enzyme, achieving a high concentration of BH4 intracellularly. Sepiapterin is a natural precursor of the enzymatic cofactor BH4, a critical co-factor for PAH. By enhancing the conformational stability of misfolded PAH enzyme and increasing the intracellular concentrations of BH4, sepiapterin is able to effectively reduce blood Phe concentrations.

The primary outcome of the pivotal study is a PD outcome i.e. blood Phe level. Therefore, the PD effect is overall well characterised.

Efficacy

Dosage selection for the pivotal study

Study PKU-002 was a phase 2, randomised , multicenter, double-crossover, open label, active-controlled, study in adult subjects with PKU. 24 subjects were randomised in 6 sequence groups of 4 subjects per group. Each sequence group was randomized to receive sepiapterin 60 mg/kg/day, sepiapterin 20 mg/kg/day, and sapropterin 20 mg/kg/day, in random order over a period of 7 days, with a 7-day washout period between each treatment sequence. The

primary objective was to assess preliminary efficacy of sepiapterin in reducing blood Phe levels at Day 3, 5 and 7 versus Day 1 for each period of treatment.

This study was a proof-of-concept study and thus no formal sample size calculation was performed. Study PKU-002 was not powered to show statistically significant differences in blood Phe concentrations between the treatment groups.

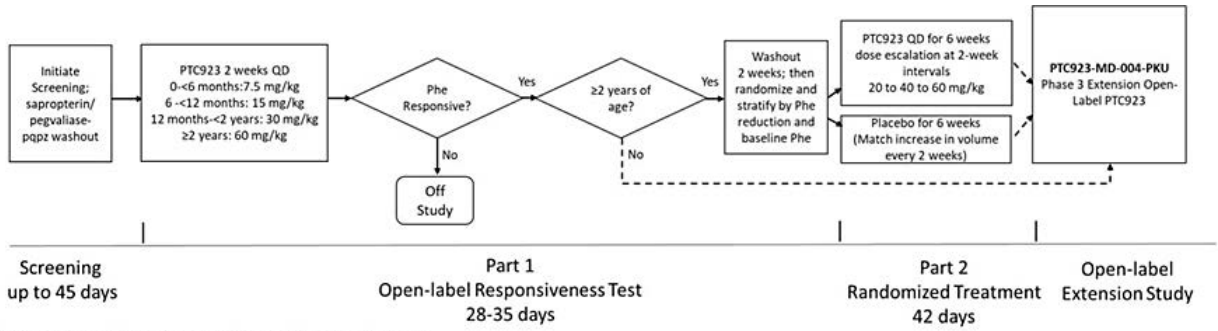
The study results showed that treatment with sepiapterin 20 mg/kg and 60 mg/kg/day resulted in a dose-dependent decrease in blood Phe concentration relative to baseline. The LS mean (SE) change in Phe concentration from baseline was -146.88 (41.76) for sepiapterin 20 mg/kg and -206.37 (41.77) for sepiapterin 60 mg/kg, thus favouring the 60 mg/kg dose. Pairwise comparisons of LSM blood Phe concentration reductions for all treatments favoured sepiapterin 60 mg/kg/day.

Pivotal Study PTC923-MD-003-PKU (Study MD-003-PKU)

Study MD-003-PKU was a Phase 3, double-blind, placebo-controlled, randomised, efficacy study of sepiapterin versus placebo in participants with PKU of all ages. The primary objective was to evaluate the efficacy of sepiapterin in reducing blood phenylalanine (Phe) levels in participants with PKU as measured by mean change in blood Phe levels from baseline to Weeks 5 and 6.

The study was designed with a responsiveness test (Part 1), followed by randomisation and a double-blind dose escalation phase, followed by an open-label follow-on study (Study PTC923-MD-004-PKU). The study design is summarised in Figure 1.

Figure 1. Study PTC923-MD-004-PKU Design



Abbreviations: Phe, phenylalanine; PTC923, sepiapterin

Key inclusion criteria

- Male or female subjects of any age
- 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 three most recent Phe levels from the subject's medical history (inclusive of the Screening value)
- Clinical diagnosis of PKU with HPA documented by past medical history of at least two blood Phe measurements ≥600 µmol/L
- Women of childbearing potential must have a negative pregnancy test at Screening and agree to abstinence or the use of at least one highly effective form of contraception
- Willing to continue current diet unchanged while participating in the study

Key exclusion criteria

- Inability to tolerate oral medication

- 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
- History of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy
- History of allergies or adverse reactions to synthetic BH4 or sepiapterin
- Any clinically significant laboratory abnormality as determined by the investigator. In general, each laboratory value from Screening and baseline chemistry and haematology panels should fall within the limits of the normal laboratory reference range, unless deemed not clinically significant by the investigator
- A female who is pregnant or breastfeeding, or considering pregnancy
- Serious neuropsychiatric illness (e.g., 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.
- 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
- Any abnormal physical examination and/or laboratory findings indicative of signs or symptoms of renal disease, including calculated GFR <60 mL/min/1.73m^2. 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
- Requirement for concomitant treatment with any drug known to inhibit folate synthesis (e.g., methotrexate)
- 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
- Concomitant treatment with BH4 supplementation (e.g., sapropterin dihydrochloride, KUVAN) or pegvaliase-pqpz (PALYNZIQ)
- Unwillingness to washout from BH4 supplementation (e.g., sapropterin dihydrochloride, KUVAN) or pegvaliase-pqpz (PALYNZIQ).

Study treatments

The intervention period was preceded by an open-label responsiveness test (Part 1), during which participants received sepiapterin (7.5 mg/kg for participants 0 to <6 months of age, 15 mg/kg for participants 6 to <12 months of age, 30 mg/kg for participants 12 months to <2 years of age, and 60 mg/kg for participants ≥2 years of age) for 14 days starting on Day 1. Participants who experienced a ≥15% reduction in blood Phe were classified as responsive and randomised to Part 2.

The treatment arms for Part 2 were:

- Sepiapterin 20 mg/kg for Weeks 1 and 2, 40 mg/kg for Weeks 3 and 4, and 60 mg/kg for Weeks 5 and 6
- Placebo

The total duration of treatment during Part 2 was 6 weeks.

Participants who were taking BH4 supplementation or pegvaliase-pqpz completed a washout period prior to the study. Concomitant use of BH4 supplementation, pegvaliase-pqpz, or any drug known to inhibit folate synthesis was not permitted.

Endpoints

The primary efficacy outcome measure was the mean change in blood Phe levels from baseline to Weeks 5 and 6 (average over a 2-week period) in the Part 2 double-blind phase.

The secondary efficacy outcome measures were:

- Proportion of participants with baseline Phe levels ≥600 µmol/L who achieve Phe levels <600 µmol/L at the end of the double-blind treatment period
- Proportion of participants with baseline Phe levels ≥360 µmol/L who achieve Phe levels <360 µmol/L at the end of the double-blind treatment period
- Mean change and percent change from baseline in blood Phe levels at each dose level

Randomisation, blinding and statistical methods

The study was double-blind. Participants were randomised centrally, and randomisation was stratified by response in Part 1 (mean % reduction in Phe of ≥15% to <30% and mean % reduction ≥30%) and baseline blood Phe <600 µmol/L and ≥600 µmol/L.

For the primary endpoint with a sample size of 80 participants ≥2 years of age for the stratum of participants with mean percent reduction in blood Phe levels of ≥30% during Part 1, the power to detect a difference in reduction in blood Phe between sepiapterin and placebo was >95%, assuming a treatment difference of 250 µmol/L and a within-treatment-group SD of 250 µmol/L, with a 2-sided α of 0.05.

For the primary endpoint for all participants in Part 2, the power to detect a difference in reduction in blood Phe between sepiapterin and placebo was >95%, assuming a treatment difference of 200 µmol/L, a within-treatment-group SD of 250 µmol/L, and a total sample size of 106, with a 2-sided α of 0.05. This sample size assumed approximately 60% of participants ≥2 years of age enrolled in Part 1 experienced a ≥15% reduction in Phe levels.

The primary efficacy endpoint was first analysed for the population of patients with ≥30% reduction in Phe during Part 1, and if significant at the p <0.05 level then the entire population was analysed. A mixed model repeated measures was used for hypothesis testing.

Participant flow

There were 157 participants included in Part 1 who received sepiapterin. Of these, 114 (73.1%) were responsive. Two of these participants were <2 years age and continued directly into the long-term safety study. A further three withdrew prior to randomisation. One participant who was a non-responder was included in Part 2. Hence, 110 participants were included in Part 2 (56 randomised to sepiapterin and 54 to placebo).

Baseline data

The median age at baseline was 15.0 years for subjects in Part 1 (range 1 – 61 years). The median age at randomisation and treatment for subjects in Part 2 was 13.0 years for the sepiapterin arm and 15.0 years for the placebo arm.

The number of subjects ≥1 year to <2 years in Part 1 was 3. In part 2 the number of subjects ≥1 year to <2 years was 0 in the sepiapterin arm and 0 in the placebo arm. The number of subjects ≥2 years to <6 years in Part 1 was 5. In part 2 the number of subjects ≥2 years to <6 years was 7

in the sepiapterin arm and 3 in the placebo arm. The number of subjects ≥6 year to <12 years in Part 1 was 11. In part 2 the number of subjects ≥6 year to <12 years was 17 in the sepiapterin arm and 12 in the placebo arm. The number of subjects ≥12 year to <18 years in Part 1 was 10. In part 2 the number of subjects ≥12 year to <18 years was 14 in the sepiapterin arm and 19 in the placebo arm. The number of subjects ≥18 years in Part 1 was 18. In part 2 the number of subjects ≥18 years was 18 in the sepiapterin arm and 20 in the placebo arm.

The majority of patients (76.6% in part 1 and 65.5% in part 2) were diagnosed at birth with PKU. 36.2% of patients in part 1 had classical PKU, and 17.3% of patients in part 2 had classical PKU (14.3% in the sepiapterin group versus 20.4% in the placebo group).

Disease characteristics for participants who did not progress beyond Part 1 were generally similar to those of participants in Part 2.

Results for the primary efficacy outcome

For Part 1 of the full analysis set (FAS) studying Phe reduction from baseline ≥30% over 2 weeks, sepiapterin was superior to placebo. The least squares (LS) mean (95% CI) change from baseline to Weeks 5 and 6 in the sepiapterin group was -415.75 (-463.52 to -367.97) µmol/L and in the placebo group was -19.88 (-67.97 to 28.21) µmol/L; difference, sepiapterin – placebo, -395.87 (-463.07 to -328.66) µmol/L, p <0.0001.

In part 2, sepiapterin was superior to placebo (Tables 2 and 3). The LS mean (95% CI) change from baseline to Weeks 5 and 6 in the sepiapterin group was -289.59 (-352.00 to - 227.18) µmol/L and in the placebo group was 65.31 (0.07 to 130.54) µmol/L; difference, sepiapterin – placebo, -354.90 (-427.14 to -282.66) µmol/L, p <0.0001.

Table 2. Mean Change in Blood Phe Levels (µmol/L) From Baseline to Week 5 and Week 6 in Part 2 (Full Analysis Set with Phe Reduction from Baseline ≥30% During Part 1)

	Sepiapterin (N=49)	Placebo (N=49)	Difference Sepiapterin vs Placebo	P Value
Baseline				
n	49	49		
Mean (SD)	646.11 (253.007)	654.04 (261.542)		
Weeks 5 and 6				
n	49	49		
Mean (SD)	236.04 (174.942)	637.85 (259.886)		
Mean change from baseline (SD)	-410.07 (204.442)	-16.19 (198.642)		
LS mean estimate for the mean change from baseline				
LS mean (SE)	-415.75 (24.066)	-19.88 (24.223)	-395.87 (33.848)	<0.0001
95% CI	(-463.52, -367.97)	(-67.97, 28.21)	(-463.07, -328.66)	

Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed model for repeated measures; Phe, phenylalanine; SD, standard deviation, SE, standard error.

Note: Baseline is the average of Day-1 and Day 1 blood Phe levels in Part 2.

LS means, SEs, CIs, and p values are based on the MMRM model on change from baseline in blood Phe with treatment, baseline Phe stratum (<600 or ≥600 µmol/L), visit, and treatment-by-visit interaction; baseline blood Phe as fixed effects; and a random participant effect with an unstructured covariance matrix.

Table 3. Mean Change in Blood Phe Levels (µmol/L) From Baseline to Weeks 5 and 6 in Part 2 (Full Analysis Set)

	Sepiapterin (N=56)	Placebo (N=54)	Difference Sepiapterin vs Placebo	P Value
Baseline				
N	56	54		
Mean (SD)	645.59 (246.085)	667.81 (264.574)		
Weeks 5 and 6				
N	56	54		
Mean (SD)	280.74 (236.964)	641.54 (270.157)		
Mean change from baseline (SD)	-364.84 (244.997)	-26.27 (199.384)		
LS mean estimate for the mean change from baseline				
LS mean (SE)	-289.59 (31.528)	65.31 (32.958)	-354.90 (36.435)	<0.0001
95% CI	(-352.00, -227.18)	(0.07, 130.54)	(-427.14, -282.66)	

Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed model for repeated measures; Phe, phenylalanine; SD, standard deviation; SE, standard error.

Note: Baseline is the average of Day-1 and Day 1 blood Phe levels in Part 2.

LS means, SEs, CIs, and p values are based on the MMRM model on change from baseline in blood Phe with treatment, baseline Phe stratum (<600 or ≥600 µmol/L), Phe reduction (>15% to <30% or >30%), visit, and treatment-by-visit interaction; baseline blood Phe as fixed effects; and a random participant effect with an unstructured covariance matrix.

There were no subgroup effects. In participants who were non-responsive to BH4 therapy, the difference (95% CI), sepiapterin – placebo, was -185.01 (-345.93 to -24.09) µmol/L, p= 0.0259.

Results for other efficacy outcomes

- The proportion of participants with baseline Phe concentration ≥600 µmol/L who achieved Phe concentration <600 µmol/L (full analysis set with Phe reduction from baseline ≥30% during Part 1) was 26 (92.9%) in the sepiapterin group and nine (30.0%) in the placebo, OR (95% CI), sepiapterin/placebo, 30.33 (5.30 to 294.24), p<0.0001.
- The proportion of participants with baseline Phe concentration ≥600 µmol/L who achieved Phe concentration <600 µmol/L (full analysis set) was 26 (81.3%) in the sepiapterin group and ten (30.3%) in the placebo, OR (95% CI), sepiapterin/placebo, 10.68 (2.76 to 41.27), p <0.0001.
- The proportion of participants with baseline Phe concentration ≥360 µmol/L who achieved Phe concentration <360 µmol/L (full analysis set with Phe reduction from baseline ≥30% during Part 1) was 37 (84.1%) in the sepiapterin group and four (9.3%) in the placebo, OR (95% CI), sepiapterin/placebo, 51.54 (12.28 to 254.34), p<0.0001.
- The proportion of participants with baseline Phe concentration ≥360 µmol/L who achieved Phe concentration <360 µmol/L (full analysis set) was 39 (78.0%) in the sepiapterin group and five (10.4%) in the placebo, OR (95% CI), sepiapterin/placebo, 25.26 (7.71 to 82.74), p <0.0001.
- The proportion of participants with baseline Phe concentration ≥120 µmol/L who achieved Phe concentration <120 µmol/L (full analysis set with Phe reduction from baseline ≥30% during Part 1) was 11 (22.4%) in the sepiapterin group and none (0%) in the placebo, OR not evaluable, p = 0.0004.
- Phe concentrations decreased to Weeks 3 and 4, and then stabilised to Weeks 5 and 6, indicating no increase in effect from the 40 mg/kg dose level to the 60 mg/kg dose level. For the full analysis set with Phe reduction from baseline ≥30% during Part 1, the difference (95% CI), sepiapterin – placebo, for Weeks 1 and 2 was -289.89 (-356.29 to -223.50) µmol/L, for Weeks 3 and 4 was -375.47 (-435.88 to -315.06) µmol/L and for Weeks 5 and 6 was -395.47 (-463.07 to -328.66) µmol/L. The findings were similar for the full analysis set.

Other efficacy studies

Study PTC923-PKU-002 (Study PKU-002)

Study PKU-002 was a Phase 2, open-label. randomised, active controlled proof of concept study in PKU patients. The study included patients ≥18 years and ≤60 years of age with clinical diagnosis of PKU and with HPA documented by past medical history of at least one blood Phe measurement ≥360 µmol/L, and with a blood Phe concentration ≥450 µmol/L anytime during screening, or a blood Phe concentration ≥450 µmol/L when averaging the three most recent Phe concentrations from the patient's medical history (inclusive of the screening value).

All PAH mutations were permitted into the study. Genotyping was not required. However, patients with classical PKU (i.e., Phe concentrations ≥1200 µmol/L and or historical evidence of Phe concentrations ≥1200 µmol/L in their medical history) were capped per protocol at 20% of the total population, assuming 30 patients were enrolled. The study treatments were

1. Sepiapterin 20 mg/kg/day
2. Sepiapterin 60 mg/kg/day
3. Sapropterin dihydrochloride (Kuvan) 20 mg/kg/day.

The treatments were administered in random order. Each treatment period was 7 days and there was a 7-day washout period between treatments. Patients were instructed to continue their usual diet without modification and to keep a 3-day diet record during each treatment and washout period. A dietician monitored each patient's diet to calculate Phe consumption and had regular contact with patients.

The outcome measure was blood Phe concentrations measured by plasma and by dried blood sampling. Plasma samples were collected on Days -7 and -1 of the pre-study period and Days 1 and 7 of the treatment period. Dried blood samples were collected on Days -7, -5, -3 and -1 of the pre-study period and Days 1, 3, 5 and 7 of the treatment period.

Study participants

There were 24 patients included in the study. All patients completed the study treatments and the study. There were 16 (66.7%) females and eight (33.3%) males. The median (range) age was 26.5 (18 to 43) years. Median (range) weight was 66.0 (49 to 118) kg.

Twenty-two (91.7%) of the 24 patients received at least one concomitant medication, the most common of which pertained to general nutrients (14 [58.3%] patients), including amino acids, carbohydrates, minerals, and vitamins.

Study results

The decrease in dried blood Phe concentration was greatest for the sepiapterin 60 mg/kg dose level: LS mean (SE) change from baseline -146.88 (41.76) µmol/L for sepiapterin 20 mg/kg, -206.37 (41.77) µmol/L for sepiapterin 60 mg/kg and -91.46 (41.74) µmol/L for sapropterin 20 mg/kg. The difference between sepiapterin 60 mg/kg and sapropterin 20 mg/kg was statistically significant: LS mean (SE) -114.91 (38.98) µmol/L, p = 0.0098. There was no significant difference between sepiapterin 20 mg/kg and sapropterin 20 mg/kg.

The % change from baseline in plasma Phe was greatest in the sepiapterin 60 mg/kg group LS mean (SD) % change from baseline 2.0 (105.59) % for sepiapterin 20 mg/kg, -33.2 (37.30) % for sepiapterin 60 mg/kg and -21.9 (38.37) % for sapropterin 20 mg/kg. The difference in plasma concentrations between sepiapterin 60 mg/kg and sapropterin 20 mg/kg was statistically significant: LS mean (SE) -131.67 (57.22) µmol/L, p = 0.0484. The difference between sepiapterin 60 mg/kg and sepiapterin 20 mg/kg was statistically significant: LS mean (SE)

161.15 (57.22) µmol/L, p = 0.0073. There was no significant difference between sepiapterin 20 mg/kg and sapropterin 20 mg/kg.

Dried blood sampling Phe concentrations decreased by Day 3 in all treatment groups and remained relatively stable until Day 7. The reduction in blood Phe concentrations measured as an absolute mean change from baseline increased with increasing baseline disease severity.

Overall, 66.7%, 58.3%, and 54.2% of patients receiving sepiapterin 20 mg/kg/day, sepiapterin 60 mg/kg/day, or sapropterin 20 mg/kg/day, respectively, had a weekly mean dried blood sample Phe reduction of at least 10%. Overall, 50.0% of patients receiving sepiapterin 20 mg/kg/day or sepiapterin 60 mg/kg/day had a weekly mean dried blood sample Phe reduction of at least 20%, compared with 41.7% of patients receiving sapropterin 20 mg/kg/day. Overall, 33.3% of patients receiving sepiapterin 20 mg/kg/day, 41.7% of patients receiving sepiapterin 60 mg/kg/day, and 33.3% of patients receiving sapropterin 20 mg/kg/day had a weekly mean dried blood sample Phe reduction of at least 30%.

The proportion of patients with either normalised plasma concentrations of Phe or concentrations in the acceptable treatment range at Day 7 was 10 (41.7%) for sepiapterin 20 mg/kg, 12 (50.0%) for sepiapterin 60 mg/kg and 10 (41.7%) for sapropterin 20 mg/kg.

There was no significant difference between the treatments in the classical PKU subpopulation, but this only included 11 patients.

Study PTC923-MD-004-PKU (Study MD-004-PKU)

Study MD-004-PKU was an open-label extension study to Study MD-003-PKU. The study is ongoing and an interim report was provided. The study commenced on 14th February 2022. The study treatments were sepiapterin administered daily with food:

- 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/day
- 12 months to <2 years of age: up to 30 mg/kg/day
- ≥2 years of age: up to 60 mg/kg/day

Treatment was intended to be for at least 12 months.

The primary efficacy outcome measure was the change from baseline in dietary Phe/protein consumption measured during the Dietary Phe Tolerance Assessment period. Dietary Phe tolerance is evaluated at Baseline and every 2 weeks over the course of the 26-week assessment period. Maintenance of Blood Phe levels was also measured and reported.

QOL measures (Phenylketonuria Quality of Life [PKU-QOL] score and EQ-5D) were collected but are not reported in the interim report.

The safety outcome measures were AEs, clinical laboratory tests, vital signs, and physical examinations.

The study included subjects who had completed Study MD-003-PKU but could include additional subjects is they had responded with a ≥15% reduction in Phe in a sepiapterin responsiveness study. Subjects were excluded from the study if they were taking an antifolate drug, pegvaliase-pqpz, or BH4 supplementation (i.e., sapropterin dihydrochloride).

The study has enrolled 106 subjects, including two non-feeder study subjects who had not been dosed at the time of the data cutoff. Hence 104 subjects are included in the analysis. Median (range) screening Phe concentration was 434.50 (44.2 to 1630.0) µmol/L. There were 18

(17.3%) subjects with classical PKU and 86 (82.7%) without classical PKU. Median (range) prescribed daily protein was 44.35 (1.6 to 122.2) g.

Study result

Daily use of sepiapterin permitted an approximately 3.3-fold increase in mean daily Phe consumption (24.4 mg/kg/day at baseline versus 79.3 mg/kg/day at Week 26), with an increase in blood Phe levels that remained largely within tolerance limits. The LS mean (95% CI) change from baseline to Week 26 was 54.563 (44.223 to 64.903) g. There were no subgroup effects. Plasma concentrations of BH4 were not influenced by age. Overall, plasma Phe concentrations over time were maintained from Study MD-003-PKU. Blood tyrosine concentrations were stable over time.

Safety

There were no pivotal studies that assessed safety as the sole primary outcome. Evaluable safety and tolerability data were derived from several studies: Study MD-005, Study MD- 008-HV, Study MD-007-HV, Study DDI-101-HV and Study PKU-001.

The safety data is based on 388 subjects, including studies in PKU, volunteer studies and two studies for other indications. In clinical trials, 181 patients with PKU have been treated with sepiapterin. There were 102 patients treated for >26 weeks and 16 treated for >52 weeks. Total exposure was 78.94 person-years. There were 93 (51.4%) males and 88 (48.6%) females. There were 80 (44.20%) patients treated with 20 mg/kg, three (1.66%) with 30 mg/kg, 56 (30.94%) with 40 mg/kg, and 179 (98.90%) with 60 mg/kg. There were 166 (91.71%) White patients.

The Integrated Summary of Safety included only the data from Study MD-003-PKU and Study MD-004-PKU.

Treatment emergent adverse events

By age group, there were no treatment related treatment emergent adverse events (TEAEs) in participants aged <2 years, nine in four (26.7%) participants aged 2 to <6 years, 18 in 10 (25.0%) participants aged 6 to <12 years, 22 in 11 (25.6%) participants.

In Study MD-003-PKU in Part 1, treatment related TEAEs were reported in 28 (17.8%) participants. The most frequently reported treatment related TEAEs were diarrhoea in six (3.9%) participants, faeces discoloured in four (2.6%), vomiting in three (1.9%), upper abdominal pain in three (1.9%) and nausea in three (1.9%). In Part 2, treatment related TEAEs were reported in six (10.7%) participants in the sepiapterin group and six (11.1%) in the placebo. These were predominantly gastrointestinal disorders.

In Study PKU-002 treatment related TEAEs were reported in no patients during sepiapterin 20 mg/kg/day, three (12.5%) during sepiapterin 60 mg/kg/day and none during sapropterin 20 mg/kg/day.

In Study MD-004-PKU there were 47 treatment related TEAEs reported in 19 (18.3%) participants. The most commonly reported TEAEs were headache in six (5.8%), diarrhoea in four (3.8%) and faeces discoloured in three (2.9%).

By age group, discontinuation due to TEAE was reported in no participants aged <2 years, one (6.7%) participant aged 2 to <6 years, none aged 6 to <12 years, none aged 12 to <18 years, and none in participants aged ≥18 years.

Serious adverse events

By age group, there were no serious adverse events (SAE) in participants aged <2 years, participants aged 2 to <6 years, participants aged 6 to <12 years, or participants aged 12 to <18 years. There was one treatment emergent SAE in a subject aged ≥18 years.

In Study MD-003-PKU, and supporting study and Study PKU-002 there were no deaths. In Study MD-004-PKU there was one SAE reported in one (1.0%) participant (asthmatic crisis).

Adverse events of special interest

Studies were not conducted in special populations. There is insufficient information in children below 2 years, pregnancy and lactation.

There were three discontinuations due to TEAE in the development program. In Study MD-003-PKU in Part 1, discontinuation due to TEAEs was reported in two (1.3%) participants (anxiety, vomiting) and in Study MD-004-PKU discontinuation due to AE was reported for one (1.0%) participant (constipation/flatulence/disturbance in attention/headache). In Study MD-004-PKU, one participant had elevations in leukocyte and platelet counts that were not clinically significant. There were no clinically significant abnormalities in clinical laboratory tests. There was no significant increase in QTc with sepiapterin treatment.

Risk management plan

PTC Therapeutics Australia Pty Ltd submitted EU-RMP version 0.1 (dated 13 March 2024; DLP 22 September 2023) and ASA (Australia specific annex) version 0.1 (dated 3 June 2024) in support of this application. The Sponsor also provided an updated EU RMP version 0.2 (dated 11 December 2024; DLP 2 September 2024) and an ASA version 0.2 (dated 5 February 2025). The summary of safety concerns in the ASA aligns with the draft EU-RMP. The summary of safety concerns is acceptable from an RMP perspective.

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 4:

Table 4: Summary of safety concerns for Sephience

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	None	–	–	–	–
Missing information	Long-term use	✓	✓*	✓	–
	Use during pregnancy and lactation	✓	–	✓	–

*Phase 3 Open Label Study PTC923-MD-004-PKU

Routine and additional pharmacovigilance activities are proposed. The additional pharmacovigilance activity is a Phase 3 open label study (PTC923-MD-004-PKU) which will

provide information regarding the long-term safety of sepiapterin. The pharmacovigilance plan is acceptable from an RMP perspective.

Only routine risk minimisation activities are proposed which is adequate to manage the safety concerns. The Sponsor has confirmed that the Instructions for Use document will be included in the product packaging. The risk minimisation plan is acceptable.

Risk-benefit analysis

Indication

The Sponsor is proposing a broad indication for sepiapterin for the treatment of hyperphenylalaninaemia in paediatric and adult patients with phenylketonuria.

Sepiapterin offers an alternative to Pegvaliase in patients <16 years of age and in patients who do not respond to sapropterin. The pivotal and supportive studies have attempted to include patients with PKU across all age groups.

It is noted that the data on efficacy and safety in subjects less than 2 years of age is deficient, as only a total of three subjects under 2 years old were recruited and none were included in the placebo-controlled arm. Additionally, participants who did not respond to sepiapterin in the responsiveness testing phase were not randomised. This raises potential issues regarding the generalisability of this enriched patient population who were sepiapterin responders. However, the Sponsor has noted that that some non-responders showed reduction in mean blood Phe levels >15% in weeks three to four, so the effect may be delayed.

Efficacy

Data from the part 2 of PTC923-MD-003-PKU showed a significant reduction in blood Phe levels after 6 weeks versus placebo in subjects aged over 2 years who responded to sepiapterin during the 2-week treatment period of part 1. The efficacy of sepiapterin was evident from the statistically significant differences between the LS mean (95% CI) change from baseline to Weeks 5 and 6 between the sepiapterin and placebo groups in favour of sepiapterin.

It is also demonstrated that efficacy did not depend on baseline Phe concentration, and a small phase 2 supportive study demonstrated higher efficacy of sepiapterin over sapropterin.

Safety

The safety profile of sepiapterin is favourable, with no deaths or TEAEs related or possibly related to study treatment reported.

Advisory committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the Sponsor's response to these documents, advised the following in response to the Delegate's specific request for advice:

1. ***What is the committee's views on the suitability of including patients under 2 years old for the indication of sepiapterin?***

The ACM recommended limiting the indication to the treatment of hyperphenylalaninemia in paediatric patients aged two years and older, as well as adults with phenylketonuria (PKU). This advice was based on the limited efficacy and safety data available for children under two years, as only two subjects were enrolled in Part I of the pivotal Phase III study (PTC923-MD-003-

PKU). However, patients aged less than 2 years were enrolled in the open label study, PTC923MD-004-PKU. The ACM noted that there is usually higher compliance with dietary control for patients under 2 years of age.

2. ***What is the ACM's views regarding the indication inclusive of all patients with PKU, whether known to be responders or non-responders to sepiapterin?***

The ACM agreed that patients should undergo responsiveness testing to ensure they receive meaningful clinical benefits.

The ACM noted that the most severe form is classic PKU while less severe forms include mild and moderate PKU. Approximately 80% of Australian PKU patients have classic PKU. This patient group was a minority (35 of 156 patients) in study PTC923- MD-003-PKU, and only 46% of this cohort demonstrated a >30% response.

For unresponsive individuals, continued exposure presents unnecessary risks without therapeutic advantage. The ACM acknowledged that PKU is genetically heterogenous with over 1000 genetic variants with varying degrees of residual enzyme activity.

Therefore, this approach aligns with current clinical practice, reinforcing existing treatment protocols.

3. ***Should the PI include specification of testing for drug responsiveness and discontinuation guidance, or should this be left to the discretion of the treating physician?***

The ACM agreed that the PI should include specifications for drug responsiveness testing and guidance on treatment discontinuation to standardise the national approach and ensure equitable access for patients across all clinical settings.

Advisory committee conclusion

The ACM considered this product to have an overall positive benefit-risk profile with modifications to the wording of the indication:

> *SEPHIENCE is indicated for the treatment of hyperphenylalaninaemia (HPA) in paediatric patients 2 years and older and adult patients with phenylketonuria (PKU) who are proven to be responsive to SEPHIENCE.*

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Sephience (sepiapterin) for the following indication:

> *SEPHIENCE is indicated for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients with phenylketonuria (PKU).*

Specific conditions of registration

Sephience (sepiapterin) is to be included in the Black Triangle Scheme. The PI and CMI for Sephience must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.

The Sephience EU-Risk Management Plan (RMP) (version 0.2, dated 11 December 2024; DLP 2 September 2024), with Australia-Specific Annex (ASA) (version 0.2, dated 5 February 2025), included with submission PM-2024-02536-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the Sponsor wishes, the six-monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must be submitted within ninety calendar days of the data lock point for that report.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

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