EU RISK MANAGEMENT PLAN

SEPIAPTERIN

RMP version to be assessed as part of this application:

RMP version number:	Version 1.0
Data lock point for this RMP:	02 September 2024
Date of final sign-off:	01 May 2025

Rationale for submitting an updated RMP: To make updates to the Missing information of Use during pregnancy and lactation as requested by the Agency in the latest assessment within procedure EMEA/H/C/006331.

Summary of significant changes in this RMP:

Added ‘restricted medical prescription' for sepiapterin mentioned in the SmPC as ‘other routine risk minimisation measure beyond the Product information’ to the Missing information of Use during pregnancy and lactation (Table 11 and Table 12);

Added Pregnancy and Lactation Form as another routine pharmacovigilance activity to the Missing information of Use during pregnancy and lactation (Table 12 and full copy in Annex 4); Updated Missing information of Long-term use to Long-term safety in the list of safety concerns, as requested. Updates corresponding to aforementioned changes in report body and Part VI, Summary of the Risk Management Plan.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Version number:	Not applicable
Approved with procedure:	Not applicable
Date of approval (opinion date):	Not applicable

QPPV name: Lara Sutton

QPPV oversight declaration:

The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialised Term	Explanation
ABC	ATP-binding cassette
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
ATC	Anatomical Therapeutic Chemical (code)
BCRP	Breast cancer resistance protein
BH_4	Tetrahydrobiopterin
BQL	Below the quantifiable limit
BSEP	Bile salt export pump
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
cPKU	Classical phenylketonuria
CSR	Clinical study report
CV	Cardiovascular
CYP	Cytochrome P450
DDI	Drug-drug interaction
DHFR	Dihydrofolate reductase
DTT	Dithiothreitol
ECG	Electrocardiogram
EEA	European Economic Area
EFD	Embryo-foetal developmental
ENT1	Equilibrative nucleoside transporter 1
ENT2	Equilibrative nucleoside transporter 2
EOS	End of Study
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life - 5 Dimensions
ETV	Early Termination Visit
EU	European Union
FOB	Functional observation battery
GD	Gestational day
GERD	Gastroesophageal reflux disease
GLP	Good Laboratory Practice
hERG	Human ether-à-go-go-related gene
HPA	Hyperphenylalaninemia
INN	International Nonproprietary Names
MAH	Marketing authorisation holder
MATE	Multidrug and toxin extrusion
MDR1	Multidrug resistance protein 1
NCS	Not clinically significant
NO	Nitric oxide
NOAEL	No-observed-adverse-effect level
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PAH	Phenylalanine hydroxylase
PBD	Primary BH_4 deficiency
PCD	Pterin-4α-carbinolamine dehydratase
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
Phe	Phenylalanine
PK	Pharmacokinetic(s)
PKU	Phenylketonuria
PKU-QOL	Phenylketonuria quality of life

Abbreviation or Specialised Term	Explanation
PL	Package leaflet
PND	Postnatal day
PSUR	Periodic safety update report
PT	Preferred term
QoL	Quality of life
QTcF	QT interval with Fridericia's correction
rAvPAL	Recombinant phenylalanine ammonia lyase
RMP	Risk Management Plan
SAE	Serious adverse event
SAWP	Scientific Advice Working Party
SmPC	Summary of product characteristics
SOC	System Organ Class
SR	Sepiapterin reductase
TEAE	Treatment-emergent adverse event
TK	Toxicokinetic
T_{max}	Time to maximal observed plasma concentration
Tyr	Tyrosine

PART I PRODUCT OVERVIEW

Table 1: Product Overview

Active substance (INN or common name)	Sepiapterin
Pharmacotherapeutic group (ATC Code)	Various alimentary tract and metabolism products A16AX28
Marketing Authorisation Holder	PTC Therapeutics International Limited
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Sephience™
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Pteridine derivative
	Summary of mode of action: Sepiapterin is a natural precursor of the enzymatic cofactor tetrahydrobiopterin (BH_4), a critical cofactor for phenylalanine hydroxylase (PAH) and acts as a dual pharmacological chaperone (sepiapterin and BH_4). By enhancing conformational stability of misfolded PAH enzyme and increasing the intracellular concentrations of BH_4, sepiapterin is able to effectively reduce blood phenylalanine levels.
	Important information about its composition: Sepiapterin is a new molecular entity and an exogenously synthesised, structurally equivalent version of biologically produced endogenous sepiapterin. Sepiapterin is converted to BH_4 via the pterin salvage pathway, mediated by sepiapterin reductase (SR) and dihydrofolate reductase (DHFR).
Hyperlink to the Product Information	Sepiapterin Product Information (Module 1.3.1)
Indication in the EEA	Current: Sepiapterin is indicated for the treatment of hyperphenylalaninemia (HPA) in adults and paediatric patients with phenylketonuria (PKU).
	Proposed: Not applicable
Dosage in the EEA	Current: Recommended dose of sepiapterin in patients older than 2 years of age is 60 mg/kg/day taken once daily. The maximum recommended dose is 60 mg/kg/day. The recommended dose (mg/kg/day) of sepiapterin in paediatric patients younger than 2 years of age is detailed in the table below:

Age	**Starting Dose: (mg/kg) of Sepiapterin Per Day**
0 to <6 months	7.5 mg/kg/day
6 to <12 months	15 mg/kg/day
12 months to <2 years	30 mg/kg/day
≥2 years	60 mg/kg/day*

*Maximum daily dose ≥2 years

	Proposed: Not applicable
Pharmaceutical form and strengths	Current: Oral Powder in sachet (yellow to orange) Strengths: 250 and 1000 mg
	Proposed: Not applicable

Active substance (INN or common name)	Sepiapterin
Will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC, Anatomical Therapeutic Chemical; BH_4: tetrahydrobiopterin; EEA, European Economic Area; EU, European Union; INN, International Nonproprietary Names; PAH, phenylalanine hydroxylase; RMP, Risk Management Plan.

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Sepiapterin is indicated for the treatment of hyperphenylalaninemia (HPA) in adults and paediatric patients with phenylketonuria (PKU).

Phenylketonuria (PKU) is a rare, serious, autosomal-recessive inborn error of metabolism that is characterised by a deficiency in phenylalanine hydroxylase (PAH), which metabolises phenylalanine (Phe) (Scriver and Kaufman 2001). Gene mutations of PAH result in decreased catalytic activity and subsequently HPA (Al Hafid and Christodoulou 2015).

Prevalence

The prevalence of PKU varies widely among ethnicities and geographic regions, affecting approximately 1 in 24000 individuals worldwide (Hillert 2020). In Europe, the mean prevalence is approximately 1:10000 newborns (van Wegberg 2017). Prevalence was particularly high in Italy (1:4000), Ireland (1:4545), and Turkey (1:6667), while Northern Europe has the lowest PKU rates in Europe, particularly in Finland (1:112000) (Hillert 2020).

Worldwide, the PKU prevalence was highest in European and certain Middle Eastern populations including Iran and Jordan (both 1:5000) (Hillert 2020). The lowest PKU prevalence was reported in Asian countries such as Thailand (1:227273), Japan (1:125000), Philippines (1:116006), and Singapore (1:83333), with the exception of China (1:15924), which is comparable to Europe (Hillert 2020).

The prevalence of HPA is calculated to be between 0.09/10000 and 2.55/10000 in Europe and varies depending on the geographical region and population (Hillert 2020, Elhawary 2022), with PKU representing 98% of all HPA reported (Ho and Christodoulou 2014). Taking a conservative approach, with a prevalence of 2.55 per 10000, this results in an estimated 113917 individuals in the European Economic Area living with HPA.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

Phenylketonuria is the most common autosomal-recessive Mendelian phenotype of amino acid metabolism (Hillert 2020), affecting both genders. To inherit this condition, both parents are carriers of the mutated gene. With the near universal adoption of newborn screening, PKU is diagnosed at birth and has been described in all ethnic groups, with differences in prevalence tending to be highest in certain European countries such as Italy and Ireland and lowest in Asian countries (Hillert 2020), as detailed above.

Most cases of HPA are caused by pathogenetic mutations of the PAH gene (PKU and variants) located on human chromosome 12 (Woo 1983). A small number of HPA cases are caused by defects in the BH_4 metabolism and DnaJ heat shock protein family (Hsp40) member C12 (DNAJC12) deficiency (Chen 2023). There are >3300 bi-allelic variants of the PAH gene (BioPKU.org 2023), each of which exhibits a unique phenotype as a result of differences in the amount of enzyme produced and/or enzyme activity. Phenylalanine hydroxylase phenotype is utilised in the classification of PKU disease severity (Blau 2010, Li 2018, Hillert 2020).

The main existing treatment options

The European guidelines for the diagnosis and treatment of PKU recommend treatment of patients with untreated blood Phe concentrations between 360 and 600 µmol/L during the first 12 years of age; patients ≥12 years old with untreated Phe levels <600 µmol/L do not require treatment, only follow up is recommended, and all patients with untreated blood Phe concentrations >600 µmol/L should be treated (van Wegberg 2017).

If left untreated, PKU results in global developmental delay or severe irreversible intellectual disability, as well as growth failure, hypopigmentation, motor deficits, ataxia, and seizures (Charrière 2023).

Currently, there is no cure for PKU and patients are placed on a restricted diet that consists of natural protein restriction and the consumption of specifically designed Phe-free amino acid supplements. Phenylketonuria requires this lifetime restriction of dietary Phe commencing within 10 days of birth to mitigate against severe and irreversible neurological damage and dysfunction (Blau 2010, van Spronsen 2017, van Wegberg 2017). Dietary management is comprised of three aspects: natural protein restriction, Phe-free-L-amino acid supplements, and low-protein food (van Wegberg 2017). The PKU diet remains very challenging for patients and their families, due to cost and impact on quality of life (QoL), and despite optimal dietary management, outcomes remain suboptimal (Ashe 2019). Most patients with PKU do not achieve a sustained reduction in blood Phe levels to within the recommended range (120 to 600 µmol/L) using diet alone to manage the condition effectively (van Wegberg 2017).

To date, two products have been approved for the treatment of HPA in patients with PKU based on a reduction in blood Phe concentration.

Kuvan (sapropterin dihydrochloride) (marketing authorisation holder [MAH]: BioMarin International Limited) was authorised in the European Union (EU) on 02 December 2008 (Kuvan SmPC). Kuvan is indicated for the treatment of HPA in adults and paediatric patients with PKU or BH_4 deficiency who have been shown to be responsive to such treatment. On 16 February 2022, Sapropterin Dipharma (sapropterin dihydrochloride) (MAH: Dipharma Arzneimittel GmbH) was authorised for the same indications (Sapropterin Dipharma SmPC).

Sapropterin is a synthetic version of the naturally occurring 6R-tetrahydrobiopterin (6R-BH_4), which is a cofactor of the hydroxylases for Phe, tyrosine (Tyr), and tryptophan. The rationale for administration of sapropterin to patients with BH_4-responsive PKU is to enhance the activity of the defective PAH and thereby increase or restore the oxidative metabolism of Phe sufficient to reduce or maintain blood Phe levels, prevent or decrease further Phe accumulation, and increase tolerance to Phe intake in the diet. For patients with BH_4 deficiency, Kuvan administration aims to replace the deficient levels of BH_4, thereby restoring the activity of PAH.

The major limitation of treatment with sapropterin is poor bioavailability. Sapropterin is a lipophobic molecule that is unstable in vivo. Sapropterin administration results in a pronounced increase in plasma BH_2 with a moderate increase in intracellular BH_4. Sapropterin is clinically effective in a minority of subjects with PKU with effectiveness defined as blood Phe reduction ≥20 to 30%, and while this permits some relaxation of the Phe-restricted diet for patients who respond to this therapy, most need to continue with some degree of dietary restriction to provide adequate control of blood Phe to protect the central nervous system (CNS) (Bratkovic 2022). Furthermore, sapropterin has limited efficacy in classical PKU (cPKU), given that patients with little or no residual PAH activity do not respond to exogenous BH_4, thus rendering the optimal target blood level in untreated adults of

<600 µmol/L difficult to achieve. From a treatment access perspective, sapropterin is still unavailable in some European countries (van Wegberg 2017).

The second approved treatment is Palynziq (pegvaliase-pqpz) (MAH: BioMarin International Limited), authorised in the EU on 03 May 2019 (Palynziq SmPC). Palynziq is indicated for the treatment of patients with PKU aged 16 years and older who have inadequate blood Phe control (blood Phe levels greater than 600 µmol/L) despite prior management with available treatment options. From a treatment access perspective, Palynziq is not available in most European countries.

Pegvaliase-pgpz is a PEGylated recombinant phenylalanine ammonia lyase (rAvPAL) enzyme that converts Phe to ammonia and trans-cinnamic acid that are primarily eliminated by liver metabolism. Pegvaliase is derived from the cyanobacterium *Anabaena variabilis* expressed in *Escherichia coli*. During manufacture, the rAvPAL protein is purified and subsequently PEGylated with 20 kDa linear NHS methoxypolyethylene glycol (NHS-PEG), forming the active substance, pegvaliase (rAvPAL-PEG). The total molecular weight of pegvaliase is ~1000 kDa. The purpose of the PEGylation of rAvPAL is to reduce immune recognition of the rAvPAL bacterial protein and increase the half-life.

Pegvaliase is considered as second-line therapy and only for those with uncontrolled blood Phe on existing treatment; it is not authorised for use in patients <16 years of age. Another limitation is its subcutaneous formulation that requires lengthy dose titration (Lah 2022). The time taken to achieve reductions in blood Phe is extensive with only 54% and 44% of patients reaching blood Phe levels of ≤600 and ≤360 µmol/L after 12 months of treatment in Study 301, respectively (Palynziq SmPC). Serious adverse reactions are associated with pegvaliase, in particular acute systemic hypersensitivity reactions. Additional risk minimisation measures including a guide for healthcare professionals, a guide for patients and trained observers, and a patient alert card are required to highlight the need for premedication, patient monitoring, training, and availability of adrenaline injection devices to minimise and manage this risk (Palynziq Product Information Annex II).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Phenylketonuria is usually diagnosed at birth, in countries where routine newborn screening is available, and requires the lifetime restriction of dietary Phe commencing within 10 days of birth to mitigate against severe and irreversible neurological damage and dysfunction (Blau 2010, van Spronsen 2017, van Wegberg 2017).

Newborns with PKU initially do not have any symptoms but without treatment babies usually develop signs of PKU within a few months (Mayo Clinic 2022). The initial signs and symptoms of untreated PKU can be mild or severe and may include: a musty odour in the breath, skin, or urine caused by too much Phe in the body; neurological problems that may include seizures; skin rashes such as eczema; lighter skin, hair, and eye colour than family members because Phe cannot transform into melanin; microcephaly; hyperactivity; intellectual disability; delayed development; behavioural, emotional, and social problems; and mental health disorders (Mayo Clinic 2022).

Phenylketonuria is historically classified into three groups based on the metabolic phenotypic expression of pretreatment blood Phe concentrations and daily dietary Phe tolerance (Camp 2014, Hillert 2020):

- Classical PKU defined as having pretreatment blood Phe concentration of >1200 µmol/L

- Mild PKU defined as having pretreatment blood Phe concentrations of 600 to 1200 µmol/L
- Mild HPA defined as having pretreatment blood Phe concentrations of 120 to 600 µmol/L

A direct association has been documented between blood Phe levels obtained on an unrestricted diet and the development of severe intellectual disability (Waisbren 2007). Deficits in Phe metabolism and the chronic accumulation of Phe in the brain lead to a number of deleterious downstream effects, including cognitive deficits and neuropsychological dysfunction (Feillet 2010). High levels of Phe can result in significant cognitive impairment, including cognitive reasoning, visual-spatial attention speed, sustained attention, and visuo-motor control (Kaufman 1989, Romani 2022). If left untreated, severe and irreversible intellectual disability can occur (Scriver and Kaufman 2001, Waisbren 2007).

The cognitive effect of PKU may reflect the impact of Phe on the brain. Decreased PAH activity results in both HPA and hypotyrosinemia. Furthermore, high Phe levels restrict the transport of Tyr and tryptophan across the blood-brain barrier, leading to a decreased concentration of dopamine and serotonin (Feillet 2010).

Additional impact of elevated Phe levels in the brain includes the creation of a hypomonoaminergic state, reduced glutaminergic neurotransmission leading to reduced synaptic plasticity, and impaired myelination (Ashe 2019). Other effects include alterations in the methylation pattern of genes, formation of amyloid-like Phe aggregates, oxidative stress, and cardiovascular (CV) and renal effects (Kaufman 1989, Pietz 1999, Burlina 2000, Blau 2010, Pilotto 2019, Hillert 2020).

Phenylketonuria patients also experience diminished QoL, growth, nutrition, and bone pathology. Notably, accruing evidence suggests that patients who can consume more natural dietary protein, due to either less severe PAH genotypes or pharmaceutical interventions, may have improved outcomes in growth, QoL, and risk factors for certain chronic diseases (ie, osteoporosis) (McWhorter 2022).

While PKU does not directly impact life expectancy, the comorbidities associated with PKU discussed below are recognised to affect patient's QoL, as related to psychosocial, mental, and physical health.

Important comorbidities

As PKU patients age they often experience multiple comorbidities across several organ systems compared with the general population. These abnormalities are attributed to both HPA and the low-protein, Phe-restricted diet.

Neuropsychiatric symptoms associated with PKU exceed general population estimates for inattention, hyperactivity, depression, and anxiety, with high Phe associated with an increased prevalence of neuropsychiatric symptoms and executive functioning deficits, whereas low Phe is associated with improved neurological performance (Bilder 2016).

With the introduction of the low Phe diet in the early 1960s, it became clear that these patients also suffered from a wide array of comorbidities affecting multiple organ systems beyond the established neurological deficits (National PKU Alliance). A large United States insurance claim-based observational study evaluating the comorbidities of 3691 PKU patients and 18455 matched controls from 1998 to 2014 identified renal insufficiency with hypertension and obesity as the two most common comorbidities (Burton 2018). These are followed in decreasing order of prevalence by renal insufficiency without hypertension, gastritis and oesophagitis, renal calculus, alopecia and baldness, oesophageal disorders,

osteoporosis, gastroesophageal reflux disease (GERD), urticaria, anaemia, asthma, gallbladder diseases (gallstones, cholecystitis), dermatitis and eczema, and allergic and chronic rhinitis (Burton 2018).

A more recent retrospective observational study used health insurance claims data from the French Système National des Données de Santé (SNDS) database from 2006 to 2018 to identify 3549 patients with PKU (both classic PKU and other causes of HPA) and matched these patients with 17170 controls by age, sex, and region (Charrière 2023). Of these 3549 PKU patients, 2175 were at least 16 years old and suffered significantly more than controls from specific comorbidities of interest including osteoporosis, hypertension, hypercholesterolemia, diabetes, obesity, ischaemic heart diseases, and depression.

PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

Sepiapterin is a new molecular entity, an exogenously synthesised, structurally equivalent version of biologically produced endogenous sepiapterin, and is intended to facilitate a reduction in elevated blood Phe concentration in patients with PKU. Endogenous sepiapterin serves as a substrate for de novo synthesis of tetrahydrobiopterin (BH_4) via the pterin salvage pathway (Mayer and Werner 1995) making sepiapterin a naturally occurring precursor for BH_4.

The comprehensive nonclinical programme comprised pharmacology, safety pharmacology, pharmacokinetic (PK), absorption, distribution, metabolism, and excretion (ADME) studies of sepiapterin and its major metabolite BH_4 and toxicology studies according to the recommendations set forth in ICH M3 (R2) Guidance, Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (ICH 2010). All nonclinical toxicology and safety pharmacology studies were conducted in compliance with Good Laboratory Practice (GLP) regulations, as appropriate. Extensive in vitro and in vivo studies were conducted to address any secondary off-target pharmacodynamic (PD), PK, ADME, and PK drug-drug interaction (DDI) properties of sepiapterin.

As the intended route of administration for sepiapterin in humans is oral, animal toxicology studies were performed using the oral route of administration. In humans, orally administered sepiapterin is quickly absorbed and rapidly metabolised to BH_4, resulting in significant and rapid increases in BH_4 in systemic circulation (Smith 2019b). PK data show that sepiapterin administered via the oral route is converted to BH_4 in all species evaluated, including mouse, rat, rabbit, marmoset monkey, cynomolgus monkey, and dog.

Rats and marmoset monkeys were selected as the toxicology species because, similar to humans, absorption of sepiapterin was fast, and the conversion from sepiapterin to BH_4 was rapid and extensive. The nonclinical programme for sepiapterin included pivotal, GLP-compliant repeat-dose toxicity studies in rats and marmoset monkeys up to 6-month and 9-month duration, respectively, with safety pharmacology endpoints to assess the effects of sepiapterin on CV (marmoset monkeys only), CNS (rats only), and respiratory systems (rats only). A GLP- compliant human ether-à-go-go-related gene (hERG) assay was conducted. In addition, as part of toxicology studies using sepiapterin, toxicokinetic (TK) assessment of sepiapterin and BH_4 in adult, neonatal and pregnant rats, marmoset monkeys, and pregnant rabbits was performed.

A battery of GLP-compliant genotoxicity studies including mutagenicity in bacteria (Ames), chromosomal damage in a mammalian system (in vitro), and a combination bone marrow micronucleus and liver comet study in rats, have been completed with sepiapterin. A 26-week transgenic mouse carcinogenicity study has been conducted with sepiapterin,

Reproductive toxicity studies including fertility and early embryonic development in rats, embryo-foetal developmental (EFD) studies in pregnant rats and rabbits and pre- and post-natal development study in rats have been completed. Juvenile animal toxicity study in rats have been completed.

An in vitro phototoxicity study has been completed with sepiapterin.

The key safety findings from nonclinical studies and relevance to human usage are presented in Table 2 below.

Table 2: Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Toxicity	
Acute or repeat-dose toxicity studies No single-dose toxicity studies were conducted with sepiapterin. The safety of sepiapterin was evaluated following daily oral administration for 14 days, 13 weeks, or 26 weeks to Sprague Dawley rats (Study CNSA-TOX-001-2017, Study CNSA-TOX-001-2018, Study PTC923-2020-003) and 14 days, 13 weeks, or 39 weeks (9 months) to marmoset monkeys (Study CNSA-TOX-002-2017, Study CNSA-TOX-002-2018, Study PTC923-2020-004). Upon oral administration of sepiapterin in the repeat-dose animal toxicology studies, absorption of sepiapterin was fast, and the conversion from sepiapterin to BH_4 was rapid and extensive. In the systemic circulation, sepiapterin was generally BQL in rats or less than 5% of the BH_4 values in marmoset monkeys. Exposure to BH_4 in rats and marmoset monkeys was sufficient to allow for meaningful assessment of potential toxicities. Generally, there was no gender difference or accumulation of BH_4. The only target organ identified in the 13- and 26-week studies was the kidney in rats. In the 26-week chronic toxicity study in rats, microscopic kidney findings at ≥100 mg/kg/day included areas of renal tubular degeneration/regeneration, interstitial inflammation, and fibrosis indicative of cell injury and subsequent repair. Additional kidney changes included deposition of tubular crystals within the distal papillary collecting tubules and ducts, with an associated mild tubular epithelial cell hyperplasia (simple hyperplasia). The hyperplasia was considered secondary to a reactive/adaptive response to the presence of sepiapterin-related inflammation and crystals in the kidney. The absence of papillary tubular hyperplastic lesions and crystal deposition in the recovery animals supports the reactive/adaptive nature of this finding and indicates that the hyperplasia was fully reversible and not preneoplastic in this study. Following the 4-week recovery period, microscopic changes related to the administration of sepiapterin persisted in the kidney of 1 of 5 female animals at 100 mg/kg/day. However, crystals and tubular hyperplasia were not observed in this animal, which was suggestive of partial recovery Furthermore, sepiapterin-related changes were not observed in the kidneys of males at 100 and 200 mg/k/day or in females at 200 mg/kg/day, which was indicative of full recovery.	From the nonclinical studies, the only target organ identified in the 13- and 26-week studies in Sprague Dawley rats was the kidney. All findings were partially or fully reversible during the recovery phases. There were no changes in the kidneys in the 13-week or 9-month studies in marmoset monkeys. These renal findings were reversible and can be minimised by taking precautions and monitoring in the clinic. Sepiapterin has not been shown to cause renal toxicity in the clinical development programme. In the Pooled PKU Studies (Studies 003 and 004) (Module SIII), of the 157 subjects treated with sepiapterin, 2 (1.3%) subjects experienced 3 TEAEs of chromaturia and 1 (0.6%) subject experienced 1 proteinuria TEAE under the SOC Renal and urinary disorders (ISS Safety Analysis Set, Table 1.3.1.2). All these TEAEs were of Grade 1 severity (ISS Safety Analysis Set, Table 1.3.1.5) and nonserious (ISS Safety Analysis Set, Table 1.3.1.11). Only the chromaturia TEAEs were regarded as treatment-related (ISS Safety Analysis Set Table 1.3.1.7). Two TEAEs of chromaturia resolved and 1 TEAE of chromaturia and 1 of proteinuria were ongoing (Study 003 CSR, Listing 16.2.7.1). In the Pooled PKU Studies, of the 54 subjects in the placebo group no Renal and urinary disorders TEAEs were reported (ISS Safety Analysis Set, Table 1.3.1.2). No other TEAEs were reported in the Renal and urinary disorders SOC and there were no Investigations SOC TEAEs suggestive of renal effects reported. There were no clinically significant renal laboratory values of note in either Part 1 or Part 2 of Study 003 (Study 003 CSR, Section 12.4.2.2) or in Study 004 (Study 004 CSR, Section 12.4.2.3). In Study PKU-002 no significant renal findings were identified (PKU-002 CSR, Section 12.2.2).

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
There were no findings in the kidney or any other organs in marmoset monkeys following chronic administration (up to 9 months) of sepiapterin at doses up to 300 mg/kg/day, which corresponded to BH_4 $AUC_{0\text{-}24h}$ values of 19550 h•ng/mL (approximately 1.5-fold higher than exposures in rats with kidney findings).	
Reproductive/developmental toxicity Sepiapterin had no maternal or paternal toxicity or effects on male or female mating or fertility parameters or any effects on any reproductive parameters in Sprague Dawley rats at doses up to 300 mg/kg/day (Study PTC923-2022-028). There were no adverse effects noted following administration of up to 1000 mg/kg/day sepiapterin in the embryo-foetal development studies in pregnant rats (Study PTC923-2021-005, Study PTC923-2021-023) and rabbits (Study PTC923-2021-006, Study PTC923-2021-024). However, in pregnant rabbits, there were nonadverse, transient mean maternal body weight loss and decreased mean food consumption at the beginning of dosing at 1000 mg/kg/day (GD 7 to 10). A pre- and post-natal development study in rats, demonstrated no sepiapterin-related maternal effects in the F0 generation females or growth and development during the preweaning or postweaning periods or sexual maturation, or neurobehavioural or reproductive function in the F1 generation males and females at doses up to 300 mg/kg/day (highest dose assessed).(Study PTC923-2023-048). There were no toxicities in any of the reproductive organs in the toxicity studies up to 26 weeks in rats (Study CNSA-TOX-001-2017, Study CNSA-TOX-001-2018, Study PTC923-2020-003) and up to 39 weeks in marmoset monkeys (Study CNSA-TOX-002-2017, Study CNSA-TOX-002-2018, Study PTC-923-2020-004).	Animal studies do not indicate direct or indirect harm with respect to pregnancy, early embryonic development, embryo-foetal development, pre- and post-natal development. Inclusion criteria for Study 003 and Study 004 state that females must be either postmenopausal for ≥1 year or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 6 months or, if of childbearing potential and not abstinent, willing to use a highly effective method of contraception throughout the study such as 1 of the following: • Hormonal contraception (stable dose for 3 months) • Intrauterine device/intrauterine hormone-releasing system, plus barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom). Females who are abstinent were not required to use a contraceptive method unless they became sexually active. Exclusion criteria include any female subject who is pregnant or considering pregnancy (Module SIV.1). There has been one pregnancy reported in the clinical development programme. The subject was enrolled in Study 003. The subject received sepiapterin 60 mg/kg for 15 days during Part 1 of the study. Thirty days after starting study drug, the subject's repeat urine pregnancy test and serum pregnancy test confirmed the pregnancy. The subject was withdrawn from the study due to pregnancy and did not enter Part 2 or the open-label extension period of the study. The outcome of the pregnancy was normal. Section 4.6 of the SmPC informs healthcare professionals that although animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, as a precautionary measure, it is preferable to avoid use of sepiapterin during pregnancy.
Juvenile toxicity studies in a 10-week juvenile toxicity (PND4 through PND70) study in rats, doses of 0, 5/30, 10/100 or 30/300 mg/kg/day demonstrated no sepiapterin-related mortalities, clinical signs, effects on body weight or body weight gains or effects on food consumption. There were no sepiapterin-related effects on sexual maturation, motor activity, acoustic startle or learning and memory were observed. There	The safety of sepiapterin has been evaluated in paediatrics with over half the subjects with PKU treated with sepiapterin <18 years of age (Module SIII, Table 4). There was no substantive difference in the TEAE profile or incidence of Grade 3 or higher TEAEs between age groups (<2 years, 2 to <6 years, 6 to <12 years, 12 to <18 years, and ≥18 years) and between sepiapterin or placebo group (Module

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
were no sepiapterin-related effects on clinical pathology, bone measurements, bone densitometry, organ weights or necroscopic findings. As higher BH_4 baseline and $AUC_{0\text{-}24h}$ values on PND9 were noted in neonatal rats as compared with adult rats (Study PTC923-2020-006), dosing was initiated at a ~10-fold lower dose from PND4 through PND28 and then increased to higher doses between PND29 and PND70 to allow for exposures in neonates equivalent to adult rats. The NOAEL was 30/300 mg/kg/day (Study PTC923-2023-045).	2.7.4, Section 5.1.1). There were no treatment-related serious TEAEs in any age group.
Genotoxicity Sepiapterin was evaluated in a battery of GLP-compliant in vitro and in vivo genotoxicity studies. In vitro genotoxicity studies including bacterial reverse mutation test (ie, Ames assay) (Study CNSA-TOX-003-2017) and mammalian chromosomal aberration test in cultured human lymphocytes (Study CNSA-TOX-004-2017) were conducted. Sepiapterin was not mutagenic in the Ames assay. Sepiapterin induced structural chromosomal aberrations following continuous treatment in human lymphocytes without a liver metabolising system (S9 mix). However, it did not cause chromosome aberrations in the presence of S9 mix. Due to the results in the in vitro chromosomal aberration assay, two in vivo mammalian toxicity evaluations (micronucleus and comet assays) were conducted in male rats to assess micronuclei formation and DNA damage (Study CNSA-TOX-005-2017). At doses up to 2000 mg/kg/day, there was no increase in the frequency of micronucleated polychromatic erythrocytes and no dose-dependent increase in DNA damage in the liver. Results from both in vivo assays met the criteria for a negative response with the demonstration of exposure to both sepiapterin and its metabolite, BH_4. Based on the negative results in the in vivo assays, sepiapterin appears to present minimal genotoxic risk.	Sepiapterin is unlikely to be genotoxic in humans based on nonclinical studies. The SmPC section 5.3 informs healthcare professionals that sepiapterin was considered not genotoxic after evaluation in a battery of GLP-compliant genotoxicity studies.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Carcinogenicity A 26-week transgenic mouse carcinogenicity study has been conducted with sepiapterin, and there were no effects on survival or no carcinogenic effects at dose levels up to 300 mg/kg/day in CByB6F1-Tg(HRAS)2Jic hemizygous male mice and up to 1000 mg/kg/day in CByB6F1-Tg(HRAS)2Jic hemizygous female mice. There were also no non-neoplastic histopathology findings in sepiapterin-treated mice. These results are in concordance with the conclusions of the Weight of Evidence assessment for carcinogenicity (Per the Scientific Advice provided by the CHMP - EMEA/H/SA/4715/1/2020/III) that carcinogenicity risks for sepiapterin are low.	Sepiapterin is not expected to be carcinogenic in humans because in vivo, sepiapterin is rapidly metabolised to BH_4 and the lack of carcinogenic potential of BH_4 has been well characterised. In January 2021, as part of Scientific Advice (EMEA/H/SA/4715/1/2020/III), the SAWP and the CHMP agreed that a weight-of-evidence–based assessment of sepiapterin, referencing data from sapropterin, would be sufficient to justify a waiver of carcinogenicity studies. The SmPC section 5.3 informs healthcare professionals that 26-week carcinogenicity study in transgenic mice has been conducted with sepiapterin.
Safety pharmacology	
Cardiovascular system, including potential effect on the QT interval and nervous system Cardiovascular safety pharmacology was assessed through in vitro and in vivo GLP-compliant studies, including assays evaluating the potential for hERG channel current effects. Sepiapterin had no discernible effects at the maximum concentration tested in the hERG assay (Study CNSA-PHARM-001-2017), and the IC_{50} was therefore concluded to be greater than 30 µM (approximately 7000 ng/mL). In the in vitro hERG assay for the metabolite BH_4 (Study PTC923-2023-056), BH_4 did not inhibit hERG tail current at the achieved concentration of 866 µM (272 µg/mL). No sepiapterin-related cardiovascular effects were observed in marmoset monkeys in 14-day, 3-month, and 9-month repeat-dose studies testing sepiapterin doses up to 1000, 300, and 300 mg/kg/day, respectively (Study CNSA-TOX-002-2017, Study CNSA-TOX-002-2018, Study PTC923-2020-004). Respiratory and CNS functions were assessed in studies in Sprague Dawley rats testing sepiapterin doses up to 1000 mg/kg (14-day study; Study CNSA-TOX-001-2017) and 300 mg/kg (13-week study; Study CNSA-TOX-001-2018). Analysis of post-first daily dose respiratory results was performed using percent changes from baseline and did not reveal an effect of sepiapterin on	These nonclinical safety studies suggest that sepiapterin is unlikely to have CV, CNS or respiratory safety pharmacology liabilities in humans. In the Pooled PKU Studies, there were no TEAEs reported under the Cardiac disorders SOC in subjects treated with sepiapterin or placebo (ISS Safety Analysis Set, Table 1.3.1.2). One (0.6%) subject treated with sepiapterin experienced 1 TEAE of ECG QT prolonged under the Investigations SOC (ISS Safety Analysis Set, Table 1.3.1.2). The event was nonserious (ISS Safety Analysis Set, Table 1.3.1.11), of Grade 1 severity (ISS Safety Analysis Set, Table 1.3.1.5), considered as unlikely to be related to treatment (ISS Safety Analysis Set, Table 1.3.1.7) and was ongoing at study completion (Study 003 CSR, Listing 16.2.7.1). No pooled analyses were performed on ECGs. In Study 003, the overall interpretation of ECGs was normal for most (>70%) subjects at baseline and at all subsequent time points. All abnormal results were NCS, and the proportion of abnormal NCS results was similar between sepiapterin and placebo groups at baseline (21.4% vs. 20.4%) and Part 2 Day 42 (25.6% of both groups). No subject in Study 003 had a maximum QTcF value >480 milliseconds. The percentage of

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
respiratory parameters. There were no sepiapterin-related quantitative or qualitative FOB changes observed, indicating no effect on CNS function.	subjects with a >30-millisecond increase from baseline QTcF was similar in Part 1 and Part 2. No subjects in any group had a >60-millisecond increase from baseline QTcF (Study 003 CSR, Section 12.5.2 Table 32). In Study 004, overall interpretation of ECGs was normal for most subjects at baseline. Although occasional ECG abnormalities were observed, none was considered clinically significant (Study 004 CSR, Section 12.6.2 Table 11). There were no TEAEs related to ECG findings or any other cardiac disorders. No subject had a maximum QTcF value >450 msec. No subjects in any group had a >30-msec increase from baseline QTcF. In Study PKU-002 changes in ECG parameters over the study were generally small and comparable across treatment groups (Study PKU-002 CSR, Section 12.5.2 Table 23). There were no TEAEs related to ECG findings or other cardiac disorders. A concentration-QT analysis was used to investigate the relationship between observed plasma concentrations of BH_4, as well as sepiapterin, and QTc and ΔQTc based on data collected in healthy subjects and patients with PKU after oral administration of sepiapterin and to assess the QT effect of BH_4 in four studies (PTC923-2023-062 study report). No significant changes in heart rate or time lag between BH_4 plasma concentration and ΔQTc were observed. Furthermore, there is a negligible trend of QTc change with BH4 or sepiapterin concentrations. Based on the C-QTc model, the upper bounds of the 90% CI for the predicted ΔQTcF at the C_{max} for the therapeutic dose (60 mg/kg orally) with and without relevant intrinsic and extrinsic factors were below the regulatory threshold of 10 ms, indicating that BH_4, and consequently sepiapterin, does not prolong the QTc interval. In the Pooled PKU Studies, the most common TEAE by PT under the Nervous system disorders SOC, was headache. Of the 157 subjects treated with sepiapterin, 20 (12.7%) subjects experienced 30 headache TEAEs (ISS Safety Analysis Set, Table 1.3.1.2), with 6 (3.8%) subjects having TEAEs considered to be treatment-related (ISS Safety Analysis Set, Table 1.3.1.7). All were nonserious (ISS Safety Analysis Set, Table 1.3.1.11), with 15 Grade 1 severity TEAEs reported in 15 (9.6%) subjects and 5 Grade 2 severity TEAEs reported in 5 (3.2%) subjects (ISS Safety Analysis Set, Table 1.3.1.5). Of the 54 subjects in the placebo group, 1 (1.9%) subject experienced 1 headache TEAE (ISS Safety Analysis Set, Table 1.3.1.2) which was nonserious (ISS Safety Analysis Set, Table 1.3.1.11), Grade 1 severity (ISS Safety Analysis

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
	Set, Table 1.3.1.5) and not related to treatment (ISS Safety Analysis Set, Table 1.3.1.7). The second most frequently reported Nervous system disorder TEAE was dizziness. Six (3.8%) subjects, treated with sepiapterin, experienced 8 TEAEs of dizziness (ISS Safety Analysis Set, Table 1.3.1.2). All were nonserious (ISS Safety Analysis Set, Table 1.3.1.11) with 4 Grade 1 severity TEAEs occurring in 4 (2.5%) subjects and 2 Grade 2 severity TEAEs occurring in 2 (1.3%) subjects (ISS Safety Analysis Set, Table 1.3.1.5). The dizziness TEAEs were considered related to treatment in 4 (2.5%) subjects (ISS Safety Analysis Set, Table 1.3.1.7). Of the 54 subjects in the placebo group, 6 (3.8%) subjects experienced 8 TEAEs of dizziness (ISS Safety Analysis Set, Table 1.3.1.2). All were nonserious (ISS Safety Analysis Set, Table 1.3.1.11) with 4 Grade 1 severity TEAEs reported in 4 (2.5%) subjects and 2 Grade 2 severity TEAEs reported in 2 (1.3%) subjects (ISS Safety Analysis Set, Table 1.3.1.5). The majority of the TEAEs of headache and dizziness all resolved (Study 003 CSR, Listing 16.2.7.1). In Study PKU-002 the most frequently reported TEAE in subjects treated with sepiapterin was headache (6/24, 25%); dizziness was observed in 1 (4.2%) subject (PKU-002 CSR, Section 12.2.2 Table 20). Headache is listed as a very common (≥1/10) adverse reaction in the SmPC section 4.8. In terms of respiratory AEs, the most common TEAE by PT under the Respiratory, thoracic and mediastinal disorders SOC was cough. Of the 157 subjects treated with sepiapterin in the Pooled PKU Studies, 13 (8.3%) subjects experienced 16 TEAEs of cough (ISS Safety Analysis Set, Table 1.3.1.2), with none considered to be treatment-related (ISS Safety Analysis Set, Table 1.3.1.7). All were nonserious (ISS Safety Analysis Set, Table 1.3.1.11), with Grade 1 events occurring in12 (7.6%) subjects and 1 (0.6%) subject experienced a Grade 2 TEAE (ISS Safety Analysis Set, Table 1.3.1.5). Of the 54 subjects in the placebo group, 1 (1.9%) subject experienced 1 cough TEAE (ISS Safety Analysis Set, Table 1.3.1.2), which was nonserious (ISS Safety Analysis Set, Table 1.3.1.11), of Grade 1 severity (ISS Safety Analysis Set, Table 1.3.1.5) and not related to treatment (ISS Safety Analysis Set, Table 1.3.1.7). The second most frequently reported respiratory TEAE was oropharyngeal pain. Eleven (7.0%) subjects, treated with sepiapterin, experienced 12 TEAEs of oropharyngeal pain (ISS Safety Analysis Set, Table 1.3.1.2). All were nonserious (ISS Safety Analysis Set, Table 1.3.1.11) with Grade 1 events occurring in 9

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
	(5.7%) subjects and Grade 2 events occurring in 2 (1.3%) subjects (ISS Safety Analysis Set, Table 1.3.1.5). None were considered to be treatment-related (ISS Safety Analysis Set, Table 1.3.1.7). Of the 54 subjects in the placebo group, 1 (1.9%) subject experienced 1 TEAE of oropharyngeal pain (ISS Safety Analysis Set, Table 1.3.1.2), which was nonserious (ISS Safety Analysis Set, Table 1.3.1.11), of Grade 1 severity (ISS Safety Analysis Set, Table 1.3.1.5) and not related (ISS Safety Analysis Set, Table 1.3.1.7). The majority of respiratory TEAEs all resolved (Study 003 CSR, Listing 16.2.7.1). The only AE of note was a Grade 3 TEAE of asthmatic crisis that occurred in a subject with underlying severe non-allergic non-eosinophilic asthma treated with sepiapterin, which was reported as an SAE as it required hospitalisation. This SAE was considered not to be related to sepiapterin by the investigator, but to the subject's underlying asthma. In Study PKU-002 the only reported TEAE in the Respiratory, thoracic and mediastinal disorders SOC in subjects treated with sepiapterin, was oropharyngeal pain (1/24, 4.2%) (PKU-002 CSR, Section 12.2.2 Table 20). The majority of CV, CNS, and respiratory AEs observed in the clinical studies were nonserious, transient and mild in severity and are therefore not safety concerns for sepiapterin. In study PTC923-TQT-102-HV, cardiodynamic evaluation demonstrated that sepiapterin (60 mg/kg and 120 mg/kg) did not have a clinically relevant effect on either HR or cardiac conduction (ie, PR and QRS intervals) and there were no TEAEs reported under the Cardiac disorders SOC in any of the treatment arms.
Mechanisms for drug interactions Pharmacokinetic (PK) drug-drug interactions PK drug-drug interaction studies indicate that sepiapterin and BH_4 are unlikely to be either perpetrators or victims of cytochrome P450 (CYP) enzyme related DDIs. Sepiapterin showed no or very limited apparent inhibition of CYP isozymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 (Study XS-0004-DV-BB). There was no induction of human CYP1A2, 2B6, and 3A4 based on enzyme activity and mRNA expression (Study XS-0004-DV-DB). It is unlikely that sepiapterin will be a perpetrator of drug-drug interactions for CYP-mediated metabolism. Sepiapterin is metabolised by SR and DHFR in a 2-step reduction to form BH_4. The BH_4 is oxidised during catalytic aromatic acid oxidation and regenerated by PCD and DHPR. It is unlikely that sepiapterin or BH_4 metabolism will be CYP-mediated.	Drug-drug interaction studies showed no clinically meaningful interactions. Sepiapterin did not show signs of potential CYP-mediated metabolic drug-drug interactions during in vitro testing. Metabolism of sepiapterin and its major metabolite BH_4 is not mediated by CYP enzymes. The SmPC section 4.5 informs healthcare professionals that in vitro drug-drug interaction studies indicate the sepiapterin and BH_4 are unlikely to be perpetrators of CYP-mediated metabolism. It also informs them that in vitro, sepiapterin did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4, nor induce CYP1A2, CYP2B6, or CYP3A4. An in vitro study showed that both sepiapterin and BH_4 are inhibitors of BCRP. However, a clinical study in healthy volunteers (Study PTC923-DDI-101-HV) indicated that sepiapterin

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Studies were conducted to evaluate sepiapterin and BH_4 as an inhibitor and substrate of human efflux transporters (ie, ABC transporters) BCRP, BSEP, and MDR1 (also called P-gp), and uptake transporters ENT1, ENT2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2 (Study PTC923-2020-002, Study PTC923-2021-012, Study PTC923-2021-013). Sepiapterin is a substrate of efflux transporter BCRP, but not a substrate of MDR1. At high concentration (3000 µM), sepiapterin is likely a substrate of uptake transporter ENT2. However, it is deemed not clinically relevant considering sepiapterin Cmax (2.82 ng/mL, eq 11.9 nM) at therapeutic dose 60 mg/kg. Sepiapterin is unlikely a substrate of all other uptake transporters studied (ENT1, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT, and OCT2). Sepiapterin is a weak inhibitor of efflux transporter BCRP (IC_{50} 647.7 µM) but does not inhibit efflux transporters MDR1 and BSEP. Sepiapterin does not inhibit uptake transporters MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT, and OCT2). At high concentration (3000 µM), sepiapterin weakly inhibits uptake transporter ENT1 (50%) and ENT2 (70%). BH_4 was both a substrate and an inhibitor of efflux transporters BCRP and MDR1. The IC_{50} values were 778.4 and 992.9 µM for BCRP and MDR1, respectively. BH_4 did not inhibit BSEP efflux transporter at concentration up to 250 µM. BH_4 did not inhibit uptake transporters ENT1, ENT2, MATE1, MATE2-K, OAT1, OAT3, and OCTP1B3. BH_4 weakly inhibited OCT1 (32% at 1500 µM) and OCT2 (23% at 150 µM) in the presence of stabilising agent 0.1% DTT. BH_4 was a substrate of efflux transporter BCRP and MDR1, and uptake transporter MATE2-K, but was unlikely to be a substrate of MATE1, OAT1, OATP1B1, OATP1B3, OCT1, and OCT2. BH_4 was not a substrate of uptake transporters ENT1, ENT2, and OAT3 when assays were conducted in the presence of stabilizing reagent 0.1% dithiothreitol. At high concentration (1000 µM), BH_4 stimulated mildly OATP1B1 mediated uptake of control substrate Estradiol-17-β-glucuronide (31%). Study PTC923-DDI-101-HV evaluated the potential BCRP) mediated DDIs of sepiapterin with BCRP inhibitor and substrate in healthy subjects. A small increase (~24%) of sepiapterin and metabolite BH_4 plasma exposures was observed when sepiapterin (20 mg/kg) was coadministered orally with the BCRP inhibitor curcumin (2 g). However, the magnitude is not considered to be clinically relevant and no dose adjustment of sepiapterin is warranted. Oral coadministration of sepiapterin with the BCRP	does not affect BCRP substrate rosuvastatin exposure. The SmPC section 4.5 informs healthcare professionals that in healthy subjects, administration of a single dose of sepiapterin at the maximum therapeutic dose of 60 mg/kg had no effect on the pharmacokinetics of a single dose of rosuvastatin (BCRP substrate) administered concomitantly. In vitro study results indicating that both sepiapterin and BH4 are substrates of BCRP. Clinical investigation in healthy volunteers (Study PTC923-DDI-101-HV) indicates that oral coadministration of BCRP inhibitor curcumin (2 g) does not lead to a clinically relevant increase in exposures to sepiapterin and BH_4 and no dose adjustment is warranted. BH_4 is a cofactor for NO synthetase. There is a potential risk of drug-drug interactions with inhibitors of DHFR (eg, trimethoprim, methotrexate, pemetrexed, pralatrexate and trimetrexate) that may be clinically significant based on known pharmacodynamics (Module SVII.1.1). The SmPC section 5.2 informs healthcare professionals that sepiapterin is metabolised by SR/carbonyl reductase and DHFR in a two-step unidirectionally process to form BH_4. The metabolism of BH_4 is presumed to follow the same pathway as endogenous BH_4 entering the regeneration cycle, oxidised to 4α-hydroxy-tetrahydrobiopterin during the aromatic amino acid hydroxylation and regenerated to form BH_4 by PCD and DHPR. The SmPC sections 4.4 and 4.5 also advise healthcare professionals to monitor patients when coadministering sepiapterin and medications known to be inhibitors of DHFR. Coadministering sepiapterin with inhibitors of DHFR (eg, trimethoprim, methotrexate, pemetrexed, pralatrexate and trimetrexate) may require more frequent monitoring of blood Phe levels because these drugs can decrease BH_4 levels by inhibiting the enzyme DHFR. Caution is recommended when using such medicinal products while taking sepiapterin. The potential of drug interactions in the presence of SR has not been investigated clinically. Caution should be exercised when sepiapterin is coadministered with SR inhibitors, such as sulfasalazine or sulfamethoxazole (Module 2.7.4, Section 5.3).

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
substrate rosuvastatin (10 mg) did not impact the PK of rosuvastatin. Potential Non-CYP enzyme mediated drug interactions Exogenous supplied sepiapterin is rapidly converted to BH_4 in a 2-step unidirectional enzymatic mediated process by SR and DHFR (Werner 2011, Smith 2019a). Inhibition of SR (eg, sulfasalazine and sulfamethoxazole) and DHFR (eg, methotrexate, pemetrexed, pralatrexate and trimetrexate) on the exposures to sepiapterin and BH4, as well as the safety have not been investigated clinically. Pharmacodynamic (PD) drug interactions The secondary PD assays conducted with sepiapterin indicated no off-target effects. No PD drug interaction studies have been conducted (Module 2.6.2, Section 5).	
Other toxicity-related information or data	
Drug Dependence Assessment Review of relevant data outlining potential drug dependence of sepiapterin was conducted. Specifically, the mechanism of action, effects of sepiapterin and BH_4 on neurotransmitters associated with drug dependence (eg, dopamine and serotonin), nonclinical safety data from sepiapterin, activity of sepiapterin at possible secondary neurotransmitter targets related to drug dependence, relevant literature, chemistry and manufacture, and publicly available drug class-relevant data (Kuvan) were reviewed. Based on the weight of evidence, the abuse potential of sepiapterin appears extremely low. Kuvan, a currently marketed drug indicated for treatment of PKU, in the same class as sepiapterin (BH_4 modulator), has not shown any indications of dependence following over a decade of marketing and use. Therefore, PTC Therapeutics concludes there is no scientific justification for additional studies to measure abuse liability or schedule sepiapterin as a controlled substance. **Phototoxicity** An in vitro phototoxicity study (Study PTC923-2021-010) conducted in BALB/c 3T3 mouse fibroblasts to assess phototoxic potential demonstrated that sepiapterin had no phototoxic potential.	The abuse potential of sepiapterin in humans appears highly unlikely (Module SVI). As of 02 September 2024, from the Pooled PKU Studies (Study 003 and Study 004) no subjects experienced TEAEs related to photosensitivity or phototoxicity. (ISS Safety Analysis Set, Table 1.3.1.2).

Abbreviations: AE, adverse event; ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; BQL, below the quantifiable limit; BSEP, bile salt export pump; CHMP, Committee for Medicinal Products for Human Use; CNS, central nervous system, CYP, cytochrome P450; DHFR, dihydrofolate reductase; DHPR, dihydropteridine reductase; DTT, dithiothreitol; ECG, electrocardiogram; ENT, equilibrative nucleoside transporter; FOB, functional observation battery; GD, gestational day; GLP, Good Laboratory Practice; hERG, human ether-à-go-go-related gene; MATE, multidrug and toxin extrusion; MDR1, multidrug resistance protein 1; NCS, not clinically significant; NO, nitric oxide; NOAEL, no-observed-adverse-effect level; OATP, organic anion transporting polypeptide; PCD, pterin-4α-carbinolamine dehydratase; PD, pharmacodynamic; P-gp, P-glycoprotein; OAT, organic anion transporter; OCT, organic cation transporter;

Phe, phenylalanine; PKU, phenylketonuria; PND, postnatal day; PT, preferred term; QTcF, QT interval with Fridericia's correction; SAE, serious adverse event; SAWP, Scientific Advice Working Party; SmPC, summary of product characteristics; SOC, System Organ Class; SR, sepiapterin reductase; TEAE, treatment-emergent adverse event.

Conclusions from the nonclinical development programme

Data from nonclinical studies demonstrate a nonclinical safety profile supportive of the use of sepiapterin at the highest proposed dose of 60 mg/kg/day based on age for treatment of patients with PKU.

Nonclinical studies described in the literature support the mechanism of action of sepiapterin.

Secondary PD assessments performed in vitro showed that it is unlikely that sepiapterin would have any clinically meaningful off-target interactions. Sepiapterin has shown no adverse effects on CNS, respiratory, and CV function in nonclinical safety pharmacology studies. Sepiapterin had no discernible effects in the hERG channel study at the maximum concentration tested.

Sepiapterin belongs to a class of compounds with pharmacological activity that is not associated with drug dependence.

The PK (ADME) properties of sepiapterin have been assessed in multiple species (mice, rats, rabbits, dogs, marmoset monkeys, and cynomolgus monkeys). Following oral administration, sepiapterin was quickly absorbed (time to maximal observed concentration [T_{max}] generally ≤2 hours) and rapidly converted to BH_4 in all species studied.

Sepiapterin did not show signs of potential cytochrome P450 (CYP)-mediated metabolic DDIs during in vitro testing. The metabolism of sepiapterin and its major metabolite BH_4 is not mediated by CYP enzymes. In vitro, sepiapterin is a substrate and an inhibitor of efflux transporter BCRP, but not a substrate nor an inhibitor of multidrug resistance protein 1 (MDR1; also called P-glycoprotein [P-gp]); BH_4 is a substrate and an inhibitor of BCRP and a substrate and an inhibitor of MDR1. Clinical study in adult healthy volunteers demonstrated that sepiapterin at the oral dose 60 mg/kg did not inhibit BCRP substrate rosuvastatin and coadministration sepiapterin with BCRP inhibitor curcumin only slightly increased the major metabolite BH_4 C_{max} and $AUC_{0\text{-}24h}$ (~24%) and this increase was considered not clinically relevant.

Rats and marmoset monkeys were selected as the toxicology species for studies of sepiapterin because, similar to humans, absorption of sepiapterin in these species was fast, and the conversion from sepiapterin to BH_4 was rapid and extensive. In the systemic circulation, levels of sepiapterin were less than 5% of the BH_4 values in rats and marmoset monkeys.

The only target organ identified in the 13- and 26-week studies in Sprague Dawley rats was the kidney at doses ≥100 mg/kg/day. All findings were partially or fully reversible during the recovery phases. No sepiapterin-related renal changes were observed in either the 13-week (300 mg/kg/day) or 9-month (300 mg/kg/day) studies in marmoset monkeys.

Sepiapterin was not genotoxic in the in vitro bacterial mutation assay or in the in vivo micronucleus and comet assays in rats. A 26-week transgenic mouse carcinogenicity study has been conducted with sepiapterin, and there were no effects on survival or no carcinogenic effects at dose levels up to 300 mg/kg/day in CByB6F1-Tg(HRAS)2Jic hemizygous male mice and up to 1000 mg/kg/day in CByB6F1-Tg(HRAS)2Jic hemizygous female mice. There were also no non-neoplastic histopathology findings in sepiapterin-treated mice.

There were no adverse effects noted in the reproductive and developmental toxicology studies performed with sepiapterin. Sepiapterin had no maternal or paternal toxicity or effects

on male or female mating or fertility parameters or any effects on any reproductive parameters in Sprague Dawley rats at doses up to 300 mg/kg/day (highest tested dose). No maternal or EFD toxicity was observed in pregnant rat and rabbit studies at doses up to 1000 mg/day. However, in pregnant rabbits, there were nonadverse, transient mean maternal body weight loss and decreased mean food consumption at the beginning of dosing (gestational day [GD] 7 to 10) at 1000 mg/kg/day, the highest tested dose. In the pre-and post-natal development study in rats, maternal doses of sepiapterin up to 300 mg/kg/day (highest tested dose) were well tolerated in the F0 generation females and did not affect growth or development of the F1 generation rats during the preweaning or postweaning periods. There were no effects on reflex and physical development evaluations, sexual maturation, or neurobehavioural or reproductive function in the F1 generation rats. No toxicities were observed in any of the reproductive organs in the chronic studies up to 26 weeks in rats and 39 weeks in marmoset monkeys. There were no adverse effects noted in the juvenile toxicity studies at doses up to 30/300 mg/kg/day from postnatal day (PND) 4 through PND70.

Sepiapterin did not demonstrate any phototoxic potential.

There is a potential risk of DDIs with inhibitors of DHFR (eg, trimethoprim, methotrexate, pemetrexed, pralatrexate, and trimetrexate) based on known pharmacodynamics. However, the effect has not been investigated clinically (Module SVII.1.1).

There were no safety concerns identified from nonclinical findings.

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

Pooled exposure data supporting authorisation for sepiapterin is provided from 5 clinical studies in subjects with PKU:

- PTC923-MD-003-PKU - A completed, pivotal, Phase 3, placebo-controlled efficacy and safety study (Study 003)
- PTC923-MD-004-PKU - An ongoing, Phase 3, long-term, open-label, efficacy and safety study (Study 004)
- PKU-002 - A completed, Phase 2, head-to-head comparator study of sepiapterin and sapropterin
- PTC923-PKU-301 - An ongoing , Phase 3, randomized, crossover, open-label, active-controlled study of sepiapterin versus sapropterin in participants with phenylketonuria ≥2 years of age
- PTC923-PKU-401 - An ongoing, Phase 3b open-label study of long-term neurocognitive outcomes in children with phenylketonuria treated with sepiapterin

Additional completed studies in the clinical development programme include 2 studies in indications other than PKU and 6 Phase 1 clinical pharmacology studies in human volunteers:

- Phase 2, randomised, double-blind, placebo-controlled study in females with moderate to severe diabetic gastroparesis (GAS-001)
- Phase 1/2, randomised, open-label, intra-subject dose escalation study in primary BH_4 deficiency (PBD) (-PBD-001)
- First-in-human, single and multiple ascending doses, PK/PD, and food effect study (PKU-001)
- Bioavailability and food effect study (PTC923-MD-005-HV)
- Japanese ethno-bridging study (PTC923-MD-007-HV)
- Absorption, metabolism, and excretion study (PTC923-MD-008-HV)
- DDI study (PTC923-DDI-101-HV)
- TQT study (PTC923-TQT-102-HV)

As of 02 September 2024, a total of 533 subjects have been exposed to sepiapterin in the completed and ongoing clinical studies. This includes 279 subjects with PKU, 10 subjects with moderate to severe diabetic gastroparesis, 8 subjects with primary BH_4 deficiency, and 236 healthy volunteers (Module 2.7.4, Section 1.2). Exposure to sepiapterin across all clinical studies consists of 80.83 patient-years, including 78.84 patient-years of exposure in subjects with PKU.

Clinical trial exposure data are presented for all subjects with PKU treated with sepiapterin in Study 003, Study 004, Study PKU-002 , PTC923-PKU-301, and PTC923-PKU-401 by duration of exposure (Table 3), age group and sex (Table 4), dose (Table 5), racial group (Table 6) and ethnicity group (Table 7).

Table 3: Duration of Exposure in Subjects Treated With Sepiapterin in PKU Studies

Duration of Exposure[a]	Number of Subjects Treated With Sepiapterin	Person-Years[b]
≤1 Week	45 (15.96%)	2.97
>1 to ≤2 Weeks	69 (24.47%)	2.64
>2 to ≤12 Weeks	26 (9.22%)	3.15
>12 to ≤26 Weeks	14 (4.96%)	4.99
>26 to ≤52 Weeks	33 (11.70%)	22.04
>52 Weeks	95 (33.69%)	159.78
Total	282	195.58

Abbreviations: PKU, phenylketonuria
Note: PKU Studies = Study 003, Study 004, Study PKU-002, PTC923-PKU-301, PTC923-PKU-401.
[a] Duration of exposure (in weeks) = (Date of the last study drug intake – Date of the first study drug intake + 1) / 7
[b] Person-years of exposure = Number of days of all subjects in each group on study drug / 365.25.
Source: RMP Table T_01 (clinical cutoff date: 02 September 2024)

Table 4: Exposure by Age Group and Sex in Subjects Treated With Sepiapterin in PKU Studies

Age Group	Number of Subjects Treated With Sepiapterin		Person-Years[a]	
	Male	Female	Male	Female
<2 Years	8 (5.63%)	7 (5.00%)	3.25	4.29
2 to <6 Years	13 (9.15%)	14 (10.00%)	15.7	6.45
6 to <12 Years	30 (21.13%)	27 (19.29%)	24.16	23.25
12 to <18 Years	46 (32.39%)	29 (20.71%)	32.22	20.65
≥18 Years	45 (31.69%)	63 (45.00%)	27.95	37.67
Total	142	140	103.27	92.31

Abbreviations: PKU, phenylketonuria
Note: PKU Studies = Study 003, Study 004, Study PKU-002, PTC923-PKU-301, PTC923-PKU-401
[a] Person-years of exposure = Number of days of all subjects in each group on study drug / 365.25.
Source: RMP Table T_02 (clinical cutoff date: 02 September 2024)

Table 5: Exposure by Dose in Subjects Treated With Sepiapterin in PKU Studies

Dose Level	Number of Subjects Treated With Sepiapterin	Person-Years[a]
7.5 mg/kg	4 (1.42%)	0.44
20 mg/kg	80 (28.37%)	2.60
30 mg/kg	12 (4.26%)	4.35
40 mg/kg	56 (19.86%)	2.15
60 mg/kg	271 (96.10%)	185.14
Total	282	195.58

Abbreviations: PKU, phenylketonuria
Note: PKU Studies = Study 003, Study 004, Study PKU-002, PTC923-PKU-301, PTC923-PKU-401.A single subject can be dosed at more than 1 dose level. Therefore, percentages may add up to more than 100% in each group.
[a] Person-years of exposure = Number of days of all subjects in each group on study drug / 365.25.
Source: RMP Table T_03 (clinical cutoff date: 02 September 2024)

Table 6: Exposure by Racial Group in Subjects Treated With Sepiapterin in PKU Studies

Racial Group	Number of Subjects Treated With Sepiapterin	Person-Years[a]
White	244 (86.52%)	175.41
Asian	15 (5.32%)	6.14
Other	23 (8.16%)	14.03
Total	282	195.58

Abbreviations: PKU, phenylketonuria
PKU Studies = Study 003, Study 004, Study PKU-002, PTC923-PKU-301, PTC923-PKU-401.
[a] Person-years of exposure = Number of days of all subjects in each group on study drug / 365.25.
Source: RMP Table T_04 (clinical cutoff date: 02 September 2024)

Table 7: Exposure by Ethnicity Group in Subjects Treated With Sepiapterin in PKU Studies

Ethnicity	Number of Subjects Treated With Sepiapterin	Person-Years[a]
Hispanic or Latino	30 (10.64%)	30.82
Not Hispanic or Latino	247 (87.59%)	162.15
Not Reported	3 (1.06%)	0.74
Unknown	2 (0.71%)	1.86
Total	282	195.58

Abbreviations: PKU, phenylketonuria
PKU Studies = Studies 003, Study 004, Study PKU-002, PTC923-PKU-301, PTC923-PKU-401.
[a] Person-years of exposure = Number of days of all subjects in each group on study drug / 365.25.
Source: RMP Table T_05 (clinical cutoff date: 02 September 2024)

Safety-related data presented in this Risk Management Plan (RMP) are based on Pooled pivotal PKU Studies (Study 003 and Study 004), with supportive data from Study PKU-002.

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion criteria from pivotal Phase 3 Study 003 that are not discussed further as they are common to most clinical trials to ensure standardisation of the trial population:

- The individual, in the opinion of the investigator, is unwilling or unable to adhere to the requirements of the study
- Inability to tolerate oral medication
- History of allergies or adverse reactions to BH_4 or related compounds, or to any excipients in the study drug formulation
- Current participation in any other investigational drug study or use of any investigational agent within 30 days prior to Screening
- 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
- 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
- Major surgery within the prior 90 days

The remaining exclusion criteria from Study 003 are discussed below and may be grouped together:

A female who is pregnant or breastfeeding, or considering pregnancy

Reason for exclusion:

While animal studies do not indicate direct or indirect harm with respect to pregnancy, early embryonic development, embryo-foetal development, pre and postnatal development (Module SIII), females who were pregnant or considering pregnancy were excluded from clinical trial participation as a safety precaution for safety reasons. Females of childbearing potential who were not abstinent and males (if sexually active and nonsterile) with female partners of childbearing potential were required to use effective contraception during Study 003. Likewise, females who were breastfeeding were excluded as precautionary measure.

Is it considered to be included as missing information? Yes

Rationale:

As described in Module SI, PKU is a rare, serious, autosomal-recessive inborn error of metabolism that is characterised by a deficiency in PAH, which metabolises Phe (Scriver and Kaufman 2001). It is a lifelong condition that is present from birth.

Up to 02 September 2024, there has been limited exposure of sepiapterin during pregnancy in the clinical development programme, with only one pregnancy reported in a 20-year-old female in study 003 who did not use any method of contraception and was exposed to sepiapterin for approximately 4 weeks until pregnancy was detected. The patient

subsequently discontinued sepiapterin and gave birth at term by Caesarean section to a normal male baby who was fed with standard infant formula.(Module SII, Module SIV.3). There has been no exposure during lactation in the clinical development programme (Module SIV.3).

As a rare condition, it is expected exposure to sepiapterin during pregnancy and lactation will be limited. Considering the size of the patient population, no additional pharmacovigilance activities are planned. Any cases of pregnancy or lactation that are reported during the postmarketing period will be followed up using routine pharmacovigilance activities to evaluate the outcome of sepiapterin exposure. As part of these routine pharmacovigilance activities the Sponsor uses the Pregnancy and Lactation Form for collection of further details on the progress and outcome of the pregnancy or lactation.

The SmPC, section 4.6, advises healthcare professionals that animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. However, as a precautionary measure, it is preferable to avoid use of sepiapterin during pregnancy. With regards to breastfeeding, healthcare professionals are informed that it is unknown whether sepiapterin metabolites are excreted in human milk and that the risk to the newborn/infant cannot be excluded, therefore a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from sepiapterin therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Patients are advised in the package leaflet (PL) to ask their doctor or pharmacist for advice before taking sepiapterin if they are pregnant or breastfeeding, think they may be pregnant or are planning to have a baby. The PL advises patients that, as a precaution, it is preferable to avoid use of sepiapterin if they are pregnant or breastfeeding.

Gastrointestinal disease (such as irritable bowel syndrome, inflammatory bowel disease, chronic gastritis, 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

Reason for exclusion:

Sepiapterin is orally administered and quickly absorbed, reaching maximum plasma concentration at around 3 to 5 hours (T_{max}). Patients with gastrointestinal disease (such as irritable bowel syndrome, inflammatory bowel disease, chronic gastritis, peptic ulcer disease, etc) that could affect the absorption of study drug, were excluded from clinical trial participation, at the investigator's discretion.

It is important to note that the above exclusion criteria of preexisting gastrointestinal conditions included a wide spectrum of severity and type of disease (acute versus chronic). Of these, selected patients were screened and enrolled (at the investigator's assessment that the absorption of sepiapterin would likely not be impacted), and these patients were ultimately deemed responsive to sepiapterin.

Patients with a history of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy, were additionally excluded from clinical trial participation as their inclusion could have affected the absorption, and therefore the efficacy assessment of sepiapterin.

Is it considered to be included as missing information? No

Rationale:

In these patients, the absorption of sepiapterin could be affected, and therefore sepiapterin may not reach the intended maximum plasma concentration. BH_4 levels will decrease with decreased absorption of sepiapterin, and therefore may have some reduction in the efficacy of sepiapterin. Sepiapterin can cause gastrointestinal effects (Module SVII.1.1).

In the Pooled PKU Studies (Study 003 and Study 004) the most common treatment-related TEAEs by System Organ Class (SOC) in subjects who received any dose of sepiapterin were Gastrointestinal disorders (20.4%) (ISS Safety Analysis Set, Table 1.3.1.7).

Gastrointestinal effects are an identified risk of sepiapterin as they were observed in the clinical development programme. As discussed in Module SVII.1.1, all the TEAEs observed were nonserious, with the majority mild in severity and resolved, and can be managed in clinical practice using standard of care. The SmPC advises healthcare professionals that diarrhoea (very common), faeces discoloured (common) and abdominal pain (common) are adverse reactions of sepiapterin.

In clinical practice use of sepiapterin in patients with gastrointestinal disease or with a history of gastric surgery may still be of benefit to patients, despite lower predicted gastrointestinal absorption of the drug. For those patients with these conditions, the safety profile is not expected to differ substantially than in patients without these conditions.

Clinical diagnosis of a primary BH_4 deficiency (PBD)

Reason for exclusion:

Patients with a clinical diagnosis of a PBD were excluded from clinical trial participation as their inclusion could have affected the efficacy and safety assessment of sepiapterin.

Following oral administration, sepiapterin is rapidly converted intracellularly to BH_4 (Smith 2019a), the natural cofactor of PAH, and is intended to (i) restore BH_4 to physiological levels in patients who lack endogenous BH_4, (ii) increase BH_4 levels in patients who have lower than normal physiological levels of BH_4, and/or (iii) enhance the chaperone effect on PAH in PAH-deficient patients by providing pharmacological levels of BH_4 while also directly enhancing the thermal stability of PAH.

Is it considered to be included as missing information? No

Rationale:

The safety of sepiapterin in patients with PBD was evaluated in a separate Phase 1/2, multicentre, randomised, open-label, intra-subject dose escalation study, Study PBD-001. All 8 subjects aged 2.2 to 20 years of age included in the study had a confirmed diagnosis of PBD. PK data from the study provided preliminary evidence of efficacy of sepiapterin in male and female subjects ≥2 years of age with PBD (Study PBD-001 CSR, Section 13).

In this study while TEAEs occurred in 7 of the 8 subjects (87.5%), there were no severe TEAEs or serious adverse events (SAEs) (Study PBD-001 CSR, Section 13). The most frequently reported TEAEs were vomiting, fatigue, and decreased appetite (3 of 8 subjects; 37.5% each), and psychomotor hyperactivity (2 of 8 subjects; 25.0%). There was no evidence of a dose-related effect in the frequency of these events and no subject withdrew due to a TEAE. Changes in laboratory parameters or vital signs were minimal.

Use of sepiapterin in patients with PBD is not missing information as sepiapterin is not currently indicated for use in this population. From the limited data available, there are no safety concerns in this population.

Concomitant treatment with any drug known to inhibit folate synthesis (eg, methotrexate)

Reason for exclusion:

The metabolic pathway of sepiapterin is well understood. Sepiapterin is rapidly converted to BH_4 in vivo by a two-step reduction via sepiapterin reductase (SR) and dihydrofolate reductase (DHFR) in the pterin salvage pathway. Conversion/formation of BH_4 following sepiapterin oral administration may be subject to inhibition of DHFR due to inhibitors such as methotrexate (Module 2.7.2, Section 3.3.3.1.2). Use of DHFR inhibitors was therefore prohibited as their inclusion could have affected the conversion of sepiapterin to BH_4, and therefore the efficacy and safety assessment of sepiapterin.

Is it considered to be included as missing information? No

Rationale:

No in vitro metabolism studies have been conducted; however, the theoretical probability exists that conversion of BH_4 following sepiapterin oral administration may be subject to inhibition of DHFR due to inhibitors such as methotrexate (Sawabe 2004).

Although concomitant administration of DHFR inhibitors has not been studied, such medicinal products may interfere with sepiapterin and BH_4 metabolism (Module 2.7.4, Section 6.4).

As a precautionary measure, Section 4.5 of the SmPC warns healthcare professionals that there is a potential risk of DDIs with inhibitors of DHFR (eg, trimethoprim, methotrexate, pemetrexed, pralatrexate and trimetrexate) and that caution is recommended when using such medicinal products while taking sepiapterin.

Drug-drug interactions will be monitored in clinical practice. The potential risk of DDIs with inhibitors of DHFR is discussed further in Module SVII.1.1.

Concomitant treatment with Palynziq (pegvaliase-pqpz) or Kuvan (sapropterin dihydrochloride)

Unwillingness to washout of Kuvan (sapropterin dihydrochloride) treatment

Reason for exclusion:

As discussed in Module SI, two products have been approved for the treatment of HPA in patients with PKU based on a reduction in blood Phe concentration. Kuvan (sapropterin dihydrochloride) is indicated for the treatment of HPA in adults and paediatric patients with PKU or BH4 deficiency who have been shown to be responsive to such treatment (Kuvan SmPC). Palynziq (pegvaliase-pqpz**)** is indicated for the treatment of patients with PKU aged 16 years and older who have inadequate blood Phe control (blood Phe levels greater than 600 µmol/L) despite prior management with available treatment options (Palynziq SmPC). Patients taking either of these medications, or unwilling to washout of Kuvan, were excluded from clinical trial participation as their inclusion could have affected the efficacy and safety assessment of sepiapterin.

Is it considered to be included as missing information? No

Rationale:

It is not expected that use of sepiapterin with either sapropterin or pegvaliase will occur.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 8: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Although use of a highly effective method of contraception was a requirement, and female patients who were pregnant or considering pregnancy was an exclusion criterion in the clinical study programme for sepiapterin, there has been one pregnancy reported in Study 003 (Module SIV.1). The subject received sepiapterin 60 mg/kg during Part 1 of the study which was stopped after approximately 2 weeks due to a positive urine pregnancy test. Gestation time of the pregnancy was subsequently established as approximately 4 weeks. The subject was withdrawn from the study due to pregnancy. At 39 weeks, 6 days, the patient gave birth by Caesarean section to a healthy male baby: weight 3260 g, height 52 cm, and head circumference 33 cm. The baby's Apgar score was 7 at 1 minute and 9 at 5 minutes. Mild jaundice resolved after phototherapy for 24 h. Postnatally, the baby progressed well and was being fed with infant formula.
Breastfeeding women	Not included in the clinical development programme.
Patients with relevant comorbidities: Patients with hepatic impairment	Sepiapterin has not been studied in patients with hepatic impairment.
Patients with renal impairment	Sepiapterin has not been studied in patients with renal impairment.
Patients with cardiovascular impairment	There is limited exposure in patients with cardiovascular impairment. There was 1 (2.1%) subject in Part 1 of Study 003 with a medical history of heart murmur under the Investigations SOC (Study 003 CSR, Table 14.1.8.1, Listing 16.2.4.6). Additionally, there was 1 (0.6%) subject in Part 2 of Study 003 with a medical history of tachycardia and palpitations (under the Cardiac disorders SOC) (Study 003 CSR, Table 14.1.8.1, Listing 16.2.4.6). This subject received placebo in Part 2 of Study 003.
Immunocompromised patients	Sepiapterin has not been studied in immunocompromised patients.

Type of Special Population	Exposure
Patients with a disease severity different from inclusion criteria in clinical trials	In Study 003, subjects with any phenylalanine hydroxylase mutation were permitted to screen and enrol into the study. However, subjects with classical PKU (ie, blood Phe birth levels ≥1200 µmol/L and/or historical evidence of Phe concentrations ≥1200 µmol/L in their medical history) were to be capped at 20% of the total study population. In Part 2 of Study 003, PKU disease characteristics were generally similar between the sepiapterin and placebo groups. More than half (65.5%) of the 110 subjects had PKU diagnosed at birth, and the majority (82.7%) had "biochemically defined" nonclassical PKU (Study 003 CSR, Table 14.1.6.1).
Population with relevant different ethnic origin	From the pooled exposure data (Module SIII, Table 7), the main ethnic groups for subjects with PKU treated with sepiapterin was: Not Hispanic or Latino (247 of 282), with smaller numbers of subjects characterized as Hispanic or Latino (30 of 282), Not Reported (3 of 282), and unknown (2 of 282).
Subpopulations carrying relevant genetic polymorphisms	Subjects with any phenylalanine hydroxylase mutation were permitted to screen and enrol into Study 003. Genotyping was not required for inclusion/exclusion; however, all subjects in Study 003 underwent genotyping unless documented in their medical history and this data was collected for analysis.
Use in paediatric patients	From the pooled exposure data (Module SIII, Table 4), 174 subjects with PKU treated with sepiapterin were <18 years of age. The number of paediatric subjects with PKU treated with sepiapterin were as follows: <2 years: 15 of 174 2 to <6 years: 27 of 174 6 to <12 years: 57 of 174 12 to <18 years: 75 of 174 Study PKU-002 did not include paediatric subjects. The inclusion criteria specified patients ≥18 years and ≤60 years of age.

Abbreviations: Phe, phenylalanine; PKU, phenylketonuria; SOC, System Organ Class.

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

Sepiapterin is not authorised in any country at the time of the data lock point (02 September 2024) of this report.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Sepiapterin belongs to a class of compounds with pharmacological activity that is not associated with abuse liability (Module 2.6.6, Section 8.2.1). No CNS-relevant clinical observations have been recorded in any nonclinical safety pharmacology or toxicology study of sepiapterin in rats and marmoset monkeys. Specifically, there were no relevant clinical observations relevant to abuse liability or observations in neurobehavioural functional observation battery (FOB) or during active dosing or cessation of dosing that would be suggestive of CNS effects. It is unlikely that drug abusers would engage in complex manipulations of the formulation because the abuse potential of sepiapterin appears to be negligible. Continuous monitoring of safety data from clinical studies of sepiapterin in humans has not shown any indications of an increase or any new trends in TEAEs potentially related to abuse potential (Module 2.7.4, Section 5.6).

Based on the weight of evidence, the abuse potential of sepiapterin appears highly unlikely. The SmPC, section 4.9, informs healthcare professionals that the mode of action does not indicate sepiapterin has abuse potential or would evoke a withdrawal or rebound effect.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- None

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- None

Known risks that do not impact the risk-benefit profile:

- None

Other reasons for considering the risks not important:

- None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised):

- **Gastrointestinal effects**

Gastrointestinal effects are an identified risk of sepiapterin based on findings in the clinical development programme.

No significant gastrointestinal findings were reported in nonclinical studies (Module SII).

In the Pooled PKU Studies (Study 003 and Study 004) of the 222 subjects treated with sepiapterin, 96 (43.2%) subjects reported 202 TEAEs of Gastrointestinal disorder (ISS Safety Analysis Set, Table 1.3.1.2). The most common treatment-related TEAEs by preferred term (PT), were diarrhoea (8.6%), faeces discoloured (4.5%), nausea (2.7%), and abdominal pain upper (2.7%) (ISS Safety Analysis Set, Table 1.3.1.7). The majority of these events were mild in severity (ISS Safety Analysis Set, Table 1.3.1.5). No SAEs were reported in the Pooled PKU Studies (ISS Safety Analysis Set, Table 1.3.1.11).

Diarrhoea:

In the Pooled PKU Studies, diarrhoea was the most common TEAE by PT under the Gastrointestinal disorders SOC. Of the 222 subjects treated with sepiapterin, 33 (14.9%) subjects experienced 38 diarrhoea TEAEs (ISS Safety Analysis Set, Table 1.3.1.2), with 21 TEAEs in 19 (8.6%) subjects considered to be treatment-related (ISS Safety Analysis Set, Table 1.3.1.7). All were nonserious (ISS Safety Analysis Set, Table 1.3.1.11) and the majority were mild in severity. The majority of first diarrhoea TEAEs occurred during the initial 12 weeks of exposure to sepiapterin (ISS Safety Analysis Set, Table 1.3.1.3.1). Of the 54 subjects in the placebo group, 1 (1.9%) subject experienced 1 TEAE of diarrhoea (ISS Safety Analysis Set, Table 1.3.1.2), which was nonserious (ISS Safety Analysis Set, Table 1.3.1.11), of Grade 2 severity (ISS Safety Analysis Set, Table 1.3.1.5) and not related to treatment (ISS Safety Analysis Set, Table 1.3.1.7). In Study 003, the majority of TEAEs of diarrhoea resolved; 2 subjects were reported to be recovering (Study 003, Listing 16.2.7.1).

In Study PKU-002, 1/24 (4.2%) subject experienced 1 TEAE of diarrhoea (Study PKU-002 CSR, Table 14.3.1.2).

Faeces discoloured:

In the Pooled PKU Studies, of the 222 subjects treated with sepiapterin, 19 (4.5%) subjects experienced 15 TEAEs of faeces discoloured (ISS Safety Analysis Set, Table 1.3.1.2), all of which were considered to be treatment-related (ISS Safety Analysis Set, Table 1.3.1.7). All were nonserious (ISS Safety Analysis Set, Table 1.3.1.11) and Grade 1 severity (ISS Safety Analysis Set, Table 1.3.1.5). All of the first TEAEs of faeces discoloured occurred during the initial 12 weeks of exposure to sepiapterin (ISS Safety Analysis Set, Table 1.3.1.3.1). Of the 54 subjects in the placebo group, none experienced a TEAE of faeces discoloured (ISS Safety Analysis Set, Table 1.3.1.2). In Study 003, the majority of TEAEs of faeces discoloured resolved; 2 subjects were reported to not have yet recovered (Study 003, Listing 16.2.7.1).

In Study PKU-002 no subjects experienced a TEAE of faeces discoloured (Study PKU-002 CSR, Table 14.3.1.2).

Vomiting:

In the Pooled PKU studies, of the 222 subjects treated with sepiapterin, 24 (10.8%) subjects experienced 32 TEAEs of vomiting, with 11 TEAEs experienced by 8 (3.6%) subjects considered related to treatment. All events were nonserious and the majority were mild in severity. The majority of first occurrences of vomiting were reported during the initial 12 weeks of exposure to sepiapterin. One subject in Study PTC923-MD-003-PKU Part 1 reported a mild in severity TEAE of vomiting and had study treatment withdrawn. The patient discontinued the study. The episode of vomiting resolved on the same day, was nonserious, and was considered possibly related to study treatment. Of the 54 subjects in the placebo group, 3 (5.6%) subjects experienced 3 TEAEs of vomiting that were nonserious and

mild in severity. One (1.9%) subject experienced 1 event of vomiting that was considered to be related to treatment.

Nausea:

In the Pooled PKU Studies, of the 222 subjects treated with sepiapterin, 12 (5.4%) subjects experienced 14 TEAEs of nausea (ISS Safety Analysis Set, Table 1.3.1.2), with 7 TEAEs in 6 (2.7%) subjects considered to be treatment-related (ISS Safety Analysis Set, Table 1.3.1.7). All were nonserious (ISS Safety Analysis Set, Table 1.3.1.11) and Grade 1 or 2 severity (ISS Safety Analysis Set, Table 1.3.1.5). The first occurrence of nausea TEAEs was variable, with the majority of the nausea TEAEs occurring during the initial 26 weeks of exposure to sepiapterin (ISS Safety Analysis Set, Table 1.3.1.3.1). Of the 54 subjects in the placebo group, 3 (5.6%) subjects experienced 3 TEAEs of nausea (ISS Safety Analysis Set, Table 1.3.1.2) of which 2 TEAEs in 2 (3.7%) subjects were considered treatment-related (ISS Safety Analysis Set, Table 1.3.1.7). All were nonserious (ISS Safety Analysis Set, Table 1.3.1.11) and Grade 1 severity TEAEs (ISS Safety Analysis Set, Table 1.3.1.5). In Study 003, the majority of the TEAEs of nausea resolved; one subject was reported to have not yet recovered (Study 003, Listing 16.2.7.1).

In Study PKU-002, 1/24 (4.2%) subject experienced a TEAE of nausea (Study PKU-002 CSR, Table 14.3.1.2).

Abdominal pain / abdominal pain upper:

In the Pooled PKU Studies, of the 222 subjects treated with sepiapterin, 10 (4.5%) subjects experienced 10 TEAEs of abdominal pain (ISS Safety Analysis Set, Table 1.3.1.2), with 4 TEAEs in 4 (1.8%) subjects considered to be treatment-related (ISS Safety Analysis Set, Table 1.3.1.7). All were nonserious (ISS Safety Analysis Set, Table 1.3.1.11) and Grade 1 severity TEAEs reported in 6 (2.7%) subjects and 3 Grade 2 severity TEAEs in 4 (1.8%) subjects (ISS Safety Analysis Set, Table 1.3.1.5). The majority of the first TEAEs of abdominal pain occurred between the initial 2 to 26 weeks of exposure to sepiapterin (ISS Safety Analysis Set, Table 1.3.1.3.1).

Of the 54 subjects in the placebo group, 1 (1.9%) subject experienced 1 TEAE of abdominal pain (ISS Safety Analysis Set, Table 1.3.1.2), which was nonserious (ISS Safety Analysis Set, Table 1.3.1.11), Grade 1 severity (ISS Safety Analysis Set, Table 1.3.1.5) and not considered treatment-related (ISS Safety Analysis Set, Table 1.3.1.7). In Study 003, all of the TEAEs of abdominal pain resolved (Study 003, Listing 16.2.7.1).

In the Pooled PKU Studies, of the 222 subjects treated with sepiapterin, 11 (5.0%) subjects experienced 17 TEAEs of abdominal pain upper (ISS Safety Analysis Set, Table 1.3.1.2), with 9 TEAEs in 6 (2.7%) subjects considered to be treatment-related (ISS Safety Analysis Set, Table 1.3.1.7). All were nonserious (ISS Safety Analysis Set, Table 1.3.1.11) and the majority were Grade 1 severity (ISS Safety Analysis Set, Table 1.3.1.5). The majority of the first TEAEs of abdominal pain upper occurred during the initial 12 weeks of exposure to sepiapterin (ISS Safety Analysis Set, Table 1.3.1.3.1). Of the 54 subjects in the placebo group, 1 (1.9%) subject experienced 1 TEAE of abdominal pain upper (ISS Safety Analysis Set, Table 1.3.1.2), which was nonserious (ISS Safety Analysis Set, Table 1.3.1.11), Grade 1 severity (ISS Safety Analysis Set, Table 1.3.1.5) and not considered treatment-related (ISS Safety Analysis Set, Table 1.3.1.7). In Study 003, all of the TEAEs of abdominal pain upper resolved (Study 003, Listing 16.2.7.1).

In Study PKU-002 no subject experienced a TEAE of abdominal pain or abdominal pain upper (Study PKU-002 CSR, Table 14.3.1.2).

Overall, in the Pooled PKU Studies, 3 subjects receiving a dose of 60 mg/kg sepiapterin, discontinued treatment due to 4 gastrointestinal TEAEs (ISS Safety Analysis Set, Table 1.3.2.2). One subject in Part 1 of Study 003, experienced mild vomiting that resolved the same day, was nonserious, and was considered possibly related to study treatment (Module 2.7.4, Section 2.1.4). The second subject, in Study 004, discontinued the study on Day 8 due to TEAEs of constipation and flatulence, both mild in severity; and disturbance in attention and headache, both moderate in severity. The third subject, in Study PTC923- MD- 004-PKU, discontinued from the study on Day 86 due to a TEAE of constipation, which was moderate in severity.

Gastrointestinal effects are frequently reported with sepiapterin use, with diarrhoea listed as a very common (≥1/10) adverse reaction and faeces discoloured and abdominal pain listed as common (≥1/100 to <1/10) adverse reactions in the SmPC section 4.8.

Gastrointestinal effects are not an important risk of sepiapterin as all the TEAEs observed were nonserious, with the majority mild in severity and resolved, and can be managed in clinical practice using standard of care.

Drug-drug interactions with inhibitors of dihydrofolate reductase (DHFR) (eg, trimethoprim, methotrexate, pemetrexed, pralatrexate, trimetrexate)

There is a potential risk of DDIs with inhibitors of DHFR (eg, trimethoprim, methotrexate, pemetrexed, pralatrexate and trimetrexate) based on known PD. Once dosed, sepiapterin is quickly converted during metabolism by SR and DHFR unidirectionally to BH_4. Increased BH_4 from sepiapterin administration is presumed to be oxidised during catalytic aromatic acid oxidation and regenerated by pterin-4α-carbinolamine dehydratase (PCD) and dihydropteridine reductase (DHPR) like endogenous BH_4. Conversion/formation of BH_4 following sepiapterin oral administration may be subject to inhibition of DHFR due to inhibitors such as methotrexate (Sawabe 2004). However, the impact and risk related to inhibition of DHFR has not been investigated clinically.

Drug-drug interactions with inhibitors of DHFR is not an important risk as it does not impact the risk/benefit balance of sepiapterin. Protocols for ongoing studies with sepiapterin contain exclusion criteria on concomitant treatment with any drug known to inhibit folate synthesis, and concomitant medication sections in protocols also stipulate that concomitant use of any drugs known to inhibit folate synthesis (eg, methotrexate, pemetrexed, trimetrexate) is not permitted.

The SmPC section 5.2 informs healthcare professionals that sepiapterin is metabolised by SR/carbonyl reductase and DHFR in a two-step unidirectionally process to form BH_4. The metabolism of BH_4 is presumed to follow the same pathway as endogenous BH_4 entering the regeneration cycle, oxidised to 4α-hydroxy-tetrahydrobiopterin during the aromatic amino acid hydroxylation and regenerated to form BH_4 by PCD and DHPR. The SmPC sections 4.4 and 4.5 also advises healthcare professionals to monitor patients when coadministering sepiapterin and medications known to be inhibitors of DHFR. Coadministering sepiapterin with inhibitors of DHFR (eg, trimethoprim, methotrexate, pemetrexed, pralatrexate and trimetrexate) may require more frequent monitoring of blood Phe levels because these drugs can decrease BH_4 levels by inhibiting the enzyme DHFR. Caution is recommended when using such medicinal products while taking sepiapterin.

SVII.1.2Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Missing information: Long-term safety

The long-term safety of sepiapterin in patients is an area of missing information based on insufficient data on long-term exposure in the clinical development programme.

As of 02 September 2024, 222 subjects from the Pooled PKU Studies (Study 003 and Study 004) have received a total of 191.63 patient-years of exposure to sepiapterin. The median duration of exposure for these 222 subjects with PKU treated with sepiapterin was 34.286 weeks (range: 0-104 weeks). Ninety-five (42.8%) subjects with PKU have been treated for ≥ 52 weeks and 10 (4.5%) have been treated for ≥ 104 weeks. As HPA due to PKU is a chronic condition, it is recognised that long-term efficacy and safety data of sepiapterin are limited.

Risk-benefit impact:

The benefit of sepiapterin as an effective treatment for HPA in adult and paediatric patients with PKU is considered to outweigh any risks associated with long-term safety, an area of missing information where data are limited but where the safety profile is expected to be the same as observed thus far in the clinical development programme.

Long-term safety will be further characterised in Study 004 (Part III.2).

Missing information: Use during pregnancy and lactation

Use of sepiapterin during pregnancy and lactation is an area of missing information based on insufficient data in these populations in the clinical development program.

As of 02 September 2024, one pregnancy was reported in Study 003 in a 20-year- old female who received sepiapterin 60 mg/kg during Part 1 of the study. Administration of sepiapterin was stopped after approximately 2 weeks due to a positive urine pregnancy test and gestation time was established as approximately 4 weeks. The subject was withdrawn from the study due to pregnancy. At 39 weeks, 6 days, the patient gave birth by Caesarean section to a healthy male baby: weight 3260 g, height 52 cm, and head circumference 33 cm. The baby's Apgar score was 7 at 1 minute and 9 at 5 minutes. Mild jaundice developed on the second day, which resolved after phototherapy for 24 h. Postnatally, the baby progressed well and was being fed with infant formula.

As of 02 September 2024, there has been no exposure during lactation in the clinical development programme for sepiapterin.

As a rare condition, it is expected that exposure to sepiapterin during pregnancy and lactation in patients with PKU will be limited. Any cases of pregnancy or lactation reported during the postmarketing period will be followed up using routine pharmacovigilance activities to evaluate the outcome of sepiapterin exposure. As part of these routine pharmacovigilance activities, further details on the progress and outcome of the pregnancy or lactation will be collected on the Pregnancy and Lactation Form.

The SmPC, section 4.6, advises healthcare professionals that animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. However, as a precautionary measure, it is preferable to avoid use of sepiapterin during pregnancy. With regards to breastfeeding, healthcare professionals are informed that there is insufficient data on the excretion of sepiapterin in human milk but, as a risk to the newborn cannot be excluded, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from sepiapterin therapy taking into account the benefit of breast feeding

for the child and the benefit of therapy for the woman. Patients are advised in the package leaflet (PL) to ask their doctor for advice before taking sepiapterin if they are pregnant or breastfeeding, think they may be pregnant or are planning to have a baby. The PL notes that, as a precaution, it is preferable to avoid use of sepiapterin during pregnancy or breastfeeding.

Risk-benefit impact

Considering the size of the patient population and the provision of the above routine risk minimisation measures in the SmPC and PL, administration of sepiapterin during pregnancy or lactation is anticipated to be avoided by PKU patients or carefully discussed with their doctor.

Continuous routine pharmacovigilance activities will ensure that any safety information received on exposure to sepiapterin during pregnancy and lactation will be analysed and reported as required, including via Periodic Safety Update Reports (PSURs).

These are considered adequate measures and any additional risk minimisation measures, or pharmacovigilance activities are not considered necessary for this missing information for sepiapterin.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

None

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

None

SVII.3.2 Presentation of the Missing Information

Missing information: Long-term safety

Evidence source:

As HPA due to PKU is a chronic condition, once responsiveness to sepiapterin is demonstrated, sepiapterin is intended for long-term use.

Up to 02 September 2024, the median duration of exposure for the 222 subjects with PKU treated with sepiapterin in the Pooled PKU Studies was 34.286 weeks (range: 0-104 weeks) Ninety-five (42.8%) subjects with PKU have been treated with sepiapterin for ≥ 52 weeks and 10 (4.5%) have been treated for ≥ 104 weeks. For a treatment that is expected to be administered chronically it is recognised that long-term efficacy and safety data are limited.

Population in need of further characterisation:

The long-term efficacy and safety of sepiapterin will be further characterised in ongoing Study 004 (Part III.2). The study is an ongoing, Phase 3, open label, long-term follow-up study to assess the long-term safety of sepiapterin 60 mg/kg/day, with a treatment duration of a maximum of 38 months. This study is designed to gather important long-term safety and Phe tolerance data for sepiapterin in subjects with PKU.

As of 02 September 2024, 169 subjects have been enrolled, and 95 of these subjects had received ≥ 12 months of treatment with sepiapterin. Additional subjects will be enrolling

from feeder study PTC923-PKU-301. PTC projects that when study PTC923-MD-004-PKU is complete, approximately 200 to 220 subjects will have received ≥ 12 months of treatment.

Missing information: Use during pregnancy and lactation

Evidence source:

Nonclinical data does not indicate direct or indirect harmful effects with respect to pregnancy or lactation and clinical data in limited with only 1 report of pregnancy with normal outcome reported in study 003. Although administration of sepiapterin is recommended to be avoided during pregnancy and lactation, this may inadvertently occur, and safety data is limited.

Population in need of further characterisation:

At study entry, women of childbearing potential must have a negative pregnancy test and agree to abstinence or the use of at least one highly effective form of contraception. Therefore, although not excluded, reporting or pregnancy and lactation cases is not anticipated from the clinical development program. Missing information for this patient population will be continuously screened from postmarketing reporting and any safety information received on exposure to sepiapterin during pregnancy or lactation (including via the Pregnancy and Lactation Form that will collect further details on the progress and outcome of all reported pregnancies or cases of lactation) will be analysed and reported as required, including via Periodic Safety Update Report (PSUR).

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table 9: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety
	Use during pregnancy and lactation

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for Missing information:

Not applicable

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable

III.2 Additional Pharmacovigilance Activities

PTC923-MD-004-PKU summary

Study short name and title:

PTC923-MD-004-PKU – A Phase 3 Open-label Study of PTC923 (Sepiapterin) in Phenylketonuria.

Rationale and study objectives:

PTC923-MD-004-PKU is an ongoing, long-term efficacy and safety study to evaluate the long-term safety of sepiapterin in subjects with PKU and to evaluate changes from baseline in dietary phenylalanine (Phe)/protein consumption.

Study design:

Study 004 is Phase 3 open-label study of sepiapterin 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 and a determination for sepiapterin responsiveness.

For all subjects, the treatment phase of the study consists of open-label treatment with sepiapterin 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 sepiapterin is authorised 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/day

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

All subjects will provide blood Phe samples at Month 1 Days 5, 10, 14, 19, 24, and 28. Blood Phe samples will be collected after fasting or no earlier than 3 hours postprandial at approximately the same time of day at each collection timepoint. During this period, all subjects will continue their usual diet and will maintain 3-day diet records once every 2 weeks.

For those subjects who qualify for 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 monthly to coincide with Week 4 of each month.

Interim analyses will be conducted for different regulatory submissions. Changes from baseline in mean daily dietary Phe/protein consumption will be analysed. Safety and tolerability will be primarily assessed by AEs, vital signs, physical examinations, and clinical laboratory tests (chemistry, haematology, and urinalysis). Blood Phe and Tyr concentrations over time will be analysed.

An Early Termination Visit (ETV)/End of Study (EOS) visit will be performed for all subjects who discontinue the study prematurely or for all remaining subjects at study conclusion. During the EOS, 3-day diet records will be collected, AEs, concomitant medications, and blood Phe and Tyr will be assessed. The Phenylketonuria - Quality of Life (PKU-QOL) (subset of subjects whose primary language is English [British or American], Turkish, Dutch, German, Spanish, Italian, Portuguese, or French only) and European Quality of Life - 5 Dimensions (EQ-5D) will be administered.

Changes from baseline in mean daily dietary Phe/protein consumption, and the changes from baseline in PKU-QOL and EQ-5D will be analysed. Safety and tolerability will be primarily assessed by AEs, vital signs, physical examinations, and clinical laboratory tests (chemistry, haematology, and urinalysis). Blood Phe and Tyr concentrations over time will be analysed.

Study population:

Approximately 200 male and female subjects of any age with a clinical diagnosis of PKU with HPA who meet the criteria for study participation.

Milestones:

First patient enrolled: 14 February 2022

Interim data cuts/CSRs: 22 September 2023; 02 September 2024.

Final CSR: September 2026

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 10: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
PTC923-MD-004-PKU A Phase 3 Open-label Study of PTC923 (Sepiapterin) in Phenylketonuria. Ongoing	PTC923-MD-004-PKU is an ongoing, long-term efficacy and safety study to evaluate the long-term safety of sepiapterin in subjects with phenylketonuria (PKU) and to evaluate changes from baseline in dietary phenylalanine (Phe)/protein consumption.	Long-term safety	First subject enrolled:	14 February 2022
			Interim data cut/CSR	22 September 2023 02 September 2024
			Final CSR	September 2026

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned or ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 11: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Long-term safety (Missing information)	Routine risk communication: *SmPC sections 4.4 and 4.8.* *PL section 2 and 4.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *SmPC section 4.2 (treatment must be initiated and supervised by a physician in the treatment of PKU - restricted medical prescription).* *PL section 3*
Use during pregnancy and lactation (Missing information)	Routine risk communication: *SmPC sections 4.6 and 5.3* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *SmPC section 4.2 (treatment must be initiated and supervised by a physician in the treatment of PKU - restricted medical prescription).*

Abbreviations: SmPC, summary of product characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 12: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Long-term safety (Missing information)	Routine risk minimisation measures: *SmPC sections 4.4 and 4.8* *PL section 2 and 4* Other routine risk minimisation measures beyond the Product Information: *SmPC section 4.2 (restricted medical prescription).* *PL section 3*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Study PTC923-MD-004-PKU*

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use during pregnancy and lactation (Missing information)	Routine risk communication *SmPC sections 4.6 and 5.3* *PL section 2* *SmPC section 4.2 (treatment must be initiated and supervised by a physician in the treatment of PKU - restricted medical prescription).*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Pregnancy and Lactation Form - will be sent to collect further details on pregnancy or lactation* Additional pharmacovigilance activities: *None*

Abbreviations: SmPC, summary of product characteristics.

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR SEPIAPTERIN

This is a summary of the RMP for sepiapterin. The RMP details important risks of sepiapterin, how these risks can be minimised, and how more information will be obtained about sepiapterin's risks and uncertainties (missing information).

Sepiapterin's summary of product characteristics (SmPC) and its PL give essential information to healthcare professionals and patients on how sepiapterin should be used.

This summary of the RMP for sepiapterin should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of sepiapterin's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Sepiapterin is a manmade version of a naturally occurring substance required to produce co-factor BH4. This is needed by certain enzymes (proteins) in the body to break down the amino acid phenylalanine into tyrosine.

Sepiapterin is used to treat hyperphenylalaninemia (high blood levels of phenylalanine) in patients of all ages with phenylketonuria (PKU). Our bodies break down the protein in foods into amino acids. PKU is an inherited disease where people cannot break down the amino acid phenylalanine, causing it to build up in the blood and brain, which can be harmful.

Sepiapterin helps the body break down phenylalanine, which allows it to reduce the harmful excess of phenylalanine in the blood. Sephience is taken by mouth.

Further information about the evaluation of sepiapterin's benefits can be found in sepiapterin's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of sepiapterin, together with measures to minimise such risks and the proposed studies for learning more about sepiapterin's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that

immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of sepiapterin is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of sepiapterin are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of sepiapterin. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term administration of the medicine).

Table 13: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety
	Use during pregnancy and lactation

II.B Summary of Important Risks

Missing Information: Long-Term Safety	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.4 and 4.8.* *PL Section 2 and 4* Other routine risk minimisation measures beyond the Product Information: *SmPC section 4.2 (restricted medical prescription)* *PL section 3* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Study PTC923-MD-004-PKU* See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Use during pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.6 and 5.3* *PL section 2* Other routine risk minimisation measures beyond the Product Information: *SmPC section 4.2 (restricted medical prescription)* *PL section 3*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None* See section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: SmPC, summary of product characteristics.

II.C Post-Authorisation Development Plan

II.C.1 Studies That Are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of sepiapterin.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name: PTC923-MD-004-PKU

A Phase 3 Open-label Study of PTC923 (Sepiapterin) in Phenylketonuria

Purpose of the study:

PTC923-MD-004-PKU is an ongoing, long-term efficacy and safety study to evaluate the long-term safety of sepiapterin in subjects with PKU and to evaluate changes from baseline in dietary Phe/protein consumption.

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

The Pregnancy and Lactation Form - will be sent by PTC Pharmacovigilance upon notification of any patient being exposed to sepiapterin while pregnant or breastfeeding.

PREGNANCY AND LACTATION REPORT FORM

Program / Study ID (if applicable):		**Please EMAIL the completed form to PTC Therapeutics Pharmacovigilance Department:** **Email:** Pharmacovigilance@ptcbio.com
Country:	Date of awareness: _____/_____/_____ DD MMM YYYY	

SECTION 1: REPORT INFORMATION

Information reported *(select all that apply)*	☐ Pregnancy (complete sections 1 – 6, and 8-13)	☐ Lactation exposure (complete sections 1- 2, and 7-13)

SECTION 2: PATIENT INFORMATION

☐ Pregnancy or Lactation in Patient **or** ☐ Pregnancy or Lactation in Patient's Partner
If pregnancy or Lactation in partner of patient indicate the partner details in Section 2.

Date of Birth / Age	**Height and Weight**
Date of Birth*: _____ DD/MMM/YYYY Age: _____ **Please do not provide patient's full / partial date of birth if not permitted by country data privacy regulations / laws*	Height: _____ ☐cm ☐inch Weight: _____ ☐kg ☐lbs

Concurrent medical conditions and relevant medical history (excluding pregnancies and deliveries). Include any risk factors and relevant family history (including malaria diagnosis).

Condition	**Start Date DD/MMM/YYYY**	**Stop Date DD/MMM/YYYY**	**Ongoing**
			☐
			☐
			☐
			☐
			☐

SECTION 3: PREGNANCY INFORMATION

☐ Patient exposed to product is Pregnant OR ☐ Partner of Patient exposed to product is Pregnant

☐ Pregnancy is ongoing ☐ Preterm termination (see Section 6) ☐ Delivered (see Section 6)

Pregnancy test type: ☐ urine ☐ blood ☐ other (please describe) _____

☐ **Unintended pregnancy**	☐ **Intended pregnancy**
Contraceptive method used: ☐ None ☐ Steroidal contraceptive (oral, implanted, transdermal, or injected) ☐ Barrier methods (e.g. diaphragm, condoms, etc.) ☐ Sterilization ☐ Other (please specify): _____	More information: ☐ Naturally occurred ☐ Medically induced (e.g. insemination, In Vitro Fertilization, please specify): _____

PREGNANCY AND LACTATION REPORT FORM

Last menstruation date:	Date pregnancy was diagnosed:	Estimated due date:
_____ DD/MMM/YYYY	_____ DD/MMM/YYYY	_____ DD/MMM/YYYY
Gestation time on day of diagnosis of pregnancy _____ week, _____ day (1-7) **Method of assessment of gestation time (e.g. ultrasound) with date of assessment** Method: _____ Date: _____ DD/MMM/YYYY		**Number of foetuses:** _____ **Pregnancy weight gain:** _____ ☐kg ☐lbs

SECTION 4: PREGNANCY HISTORY

Number of previous pregnancies: _____ Number of live births: _____

Pregnancy number	Year	Outcome or event [1. Live birth with healthy baby, 2. Spontaneous abortion, 3. Elective abortion (specify context), 4. Stillbirth, 5. Congenital anomaly (please specify), 6. Ectopic pregnancy, 7. Molar pregnancy, 8. Other (please specify)]
		Specify the number of the appropriate outcome or event: _____ Narrative: _____
		Specify the number of the appropriate outcome or event: _____ Narrative: _____
		Specify the number of the appropriate outcome or event: _____ Narrative: _____

Remarks and notes (please include here any previous pregnancy complications not mentioned above, with any history of subfertility and its treatment, if any):

SECTION 5: PRENATAL AND PREGNANCY TESTING

☐ None

Type	Date *(DD/MMM/YYYY)*	Result	Narrative & Remarks
☐ Amniocentesis		☐ Normal ☐ Abnormal	
☐ Alpha Foetal Protein		☐ Normal ☐ Abnormal	
☐ Chorionic Villi Sampling		☐ Normal ☐ Abnormal	
☐ Foetal Stress Test		☐ Normal ☐ Abnormal	
☐ Ultrasound		☐ Normal ☐ Abnormal	

☐ Serology tests (rubella, toxoplasmosis, etc.)		☐ Normal ☐ Abnormal	
☐ Genetic screening		☐ Normal ☐ Abnormal	
☐ Other _____		☐ Normal ☐ Abnormal	

SECTION 6: PREGNANCY OUTCOME (fill only if pregnancy is not ongoing)

☐ **Preterm termination**

Type	**Date** (DD/MMM/YYYY)	**Remarks** (indication, lab results, etc.)
Spontaneous abortion		
Elective abortion (specify indication)		
Intrauterine death (>20 weeks gestation)		
Other (e.g. maternal death, etc.)		

☐ **Delivery**

Child information	**Sex**	**Delivery mode**	**Delivery Date**	**Delivery outcome**
1. Initials: _____ Weight: _____ ☐ g Height: _____ ☐ cm Apgar-score (1minute): _____ Apgar-score (5 minute): _____	☐ Male ☐ Female ☐ UNK	☐ Spontaneous vaginal ☐ Caesarean section – elective ☐ Caesarean section – emergency Reason: _____ ☐ Assisted vaginal (forceps, vacuum, etc.)	_____ DD/MMM/YYYY Week of gestation: _____	☐ Healthy ☐ Stillbirth ☐ Neonate death ☐ Major congenital anomaly ☐ Minor congenital anomaly
2. Initials: _____ Weight: _____ ☐ g Height: _____ ☐ cm Apgar-score: _____	☐ Male ☐ Female ☐ UNK	☐ Spontaneous vaginal ☐ Caesarean section – elective ☐ Caesarean section – emergency Reason: _____ ☐ Assisted Vaginal (forceps, vacuum, etc.)	_____ DD/MMM/YYYY Week of gestation: _____	☐ Healthy ☐ Stillbirth ☐ Neonate death ☐ Major congenital anomaly ☐ Minor congenital anomaly

☐ **Unknown**

Remarks regarding pregnancy outcome (please specify here any malformations observed, any specific conditions at birth, measurements taken e.g. head circumference, stating child number in case of twins/triplets):

SECTION 7: LACTATION EXPOSURE (BREASTFEEDING)

Start date of Breastfeeding:	**Stop date of Breastfeeding** **OR** **Breastfeeding ongoing** ☐
_____ DD/MMM/YYYY	_____ DD/MMM/YYYY

PREGNANCY AND LACTATION REPORT FORM

Remarks and notes (summarise any issues or concerns noted during lactation if any):

SECTION 8: SUSPECT PRODUCT INFORMATION

Name of Drug	Dosing details	**Start Date** *DD/MMM/YYYY* **Stop Date** *DD/MMM/YYYY*	**Estimated Time of exposure** *(select all that apply)*
	Unit dose, frequency and route: **Indication:**	_____ or week _____ or trimester _____ _____ or week _____ or trimester _____ ongoing ☐	☐ Before conception ☐ At conception ☐ During pregnancy ☐ Labour and delivery ☐ During lactation
Lot number and expiration date, if known **Lot number:** _____ **Expiration date:** ____/____/____ DD/MMM/YYYY			

SECTION 9: CONCOMITANT DRUG EXPOSURE

Product name Medication(s) generic name and brand name	**Dosing details** *(unit dose, frequency and route)*	**Indication**	**Start Date** *DD/MMM/YYYY*	**Stop Date** *DD/MMM/YYYY*	**Estimated Time of exposure**
			_____ or week _____ or trimester _____	_____ or week _____ or trimester _____ ongoing ☐	☐ Before conception ☐ At conception ☐ During pregnancy ☐Labour and delivery ☐ During lactation
			_____ or week _____ or trimester _____	_____ or week _____ or trimester _____ ongoing ☐	☐ Before conception ☐ At conception ☐ During pregnancy ☐ Labour and delivery ☐ During lactation
			_____ or week _____ or trimester _____	_____ or week _____ or trimester _____ ongoing ☐	☐ Before conception ☐ At conception ☐ During pregnancy ☐ Labour and delivery ☐ During lactation

SECTION 10: COMPLICATIONS DURING PREGNANCY, LABOR OR DELIVERY *(not described above)*

PREGNANCY AND LACTATION REPORT FORM

Write down any complications experienced by the mother and/or newborn with dates:

SECTION 11: ADDITIONAL INFORMATION

Write here any additional information you think is relevant (e.g. recreational drug use e.g. tobacco, alcohol, illicit drugs; history of congenital abnormality; more information on risk factors and family history e.g. psychomotor retardation in the family; consanguinity between parents; etc.). In case of any abnormal pregnancy outcomes or complications experienced during pregnancy or lactation, or foetal abnormalities, please specify relationship to suspect drug, other drugs:

SECTION 12: HEALTHCARE PROVIDER INFORMATION

Name:	
Title / Role:	
Address:	
Phone:	Email:
Permission to Contact HealthCare Provider: ☐ Yes ☐ No	

SECTION 13: REPORTER INFORMATION

Name:	
Address:	
Phone:	Email:
Title/position of person completing form:	
Permission to Contact Reporter ☐ Yes ☐ No	
Date reported: *DD/MMM/YYYY*	

Please send completed form to ***pharmacovigilance@ptcbio.com***

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable

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Pharmacovigilance Approval	[redacted] Pharmacovigilance Approval I approve the document(s) 01-May-2025 17:59:23 GMT+0000

Clinical Approval	[redacted] Clinical Approval I approve the document(s) 01-May-2025 18:19:41 GMT+0000

Pharmacovigilance Approval	[redacted] Pharmacovigilance Approval I approve the document(s) 01-May-2025 18:25:39 GMT+0000

Regulatory Approval	[redacted] Regulatory Approval I approve the document(s) 01-May-2025 19:00:29 GMT+0000

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