Clinical trial results:
A Phase 3 Study of PTC923 in Subjects With Phenylketonuria
Summary

EudraCT number	2021-000474-29
Trial protocol	DE ES PT DK NL IT
Global end of trial date	03 May 2023

Results information

Result version number	v1
This version publication date	19 November 2023
First version publication date	19 November 2023

Trial information

Trial identification

Sponsor protocol code	PTC923-MD-003-PKU

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05099640
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PTC Therapeutics, Inc.
Sponsor organisation address	100 Corporate Court, South Plainfield, United States, NJ 07080
Public contact	Medical Information, PTC Therapeutics, Inc., +011 44 1-866-562-4620, medinfo@ptcbio.com
Scientific contact	Medical Information, PTC Therapeutics International Limited, +353 19068700, medinfo@ptcbio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this trial is to evaluate the efficacy of PTC923 in reducing blood phenylalanine (Phe) levels in participants with phenylketonuria as measured by mean change in blood Phe levels from baseline to Weeks 5 and 6 (that is, the average of each respective treatment dose 2-week period of double-blind treatment).

Protection of trial subjects:

This trial was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of Good Clinical Practices (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 25
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	United States: 20
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Georgia: 16
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Turkey: 21
Country: Number of subjects enrolled	Australia: 15
Worldwide total number of subjects	157
EEA total number of subjects	34

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	3
Children (2-11 years)	55
Adolescents (12-17 years)	43
Adults (18-64 years)	56
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 2 parts: Part 1: Open-label and Part 2: Placebo-controlled Randomized Treatment. In Part 1, 157 participants received sepiapterin. In Part 2, 56 participants received sepiapterin and 54 participants received placebo.

Pre-assignment

Screening details:

Participants (≥2 years of age) who experienced a ≥15% reduction in blood Phe levels (responder) continued into Part 2. Non-responders did not continue to Part 2. Out of 111 participants who completed Part 1, 110 participants were eligible to progress to Part 2.

Period 1

Period 1 title	Part 1: Open-label (14 Days)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part 1: Sepiapterin

Arm description:

Participants received sepiapterin 30 milligrams (mg)/kilogram (kg) (participants 12 months to <2 years of age) or 60 mg/kg (participants ≥2 years of age) orally once daily for 14 days.

Arm type	Experimental
Investigational medicinal product name	Sepiapterin
Investigational medicinal product code	PTC923
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

Sepiapterin was administered per schedule specified in the arm description.

Number of subjects in period 1	Part 1: Sepiapterin
Started	157
Received at least 1 dose of study drug	157
Completed	111
Not completed	46
Consent withdrawn by subject	1
Participant decision	3
Adverse event, non-fatal	1
Non-responsive for sepiapterin	39
Other than specified	2

Period 2

Period 2 title	Part 2: Randomized Treatment (6 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 2: Sepiapterin

Arm description:

Participants received sepiapterin 20 mg/kg daily for Weeks 1 and 2, then sepiapterin 40 mg/kg daily for Weeks 3 and 4, then sepiapterin 60 mg/kg daily for Weeks 5 and 6.

Arm type	Experimental
Investigational medicinal product name	Sepiapterin
Investigational medicinal product code	PTC923
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

Sepiapterin was administered per schedule specified in the arm description.

Arm title	Part 2: Placebo

Arm description:

Participants received equivalent quantities of placebo to match the 20 to 40 to 60 mg/kg dose escalation of the sepiapterin treatment arm.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to sepiapterin was administered per schedule specified in the arm description.

Number of subjects in period 2[1]	Part 2: Sepiapterin	Part 2: Placebo
Started	56	54
Received at least 1 dose of study drug	56	54
Completed	55	54
Not completed	1	0
Participant decision	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: In Part 2, 56 participants were randomized to receive sepiapterin and 54 participants were randomized to receive placebo.

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Sepiapterin
Reporting group description:	
Participants received sepiapterin 30 milligrams (mg)/kilogram (kg) (participants 12 months to <2 years of age) or 60 mg/kg (participants ≥2 years of age) orally once daily for 14 days.	

Reporting group values	Part 1: Sepiapterin	Total	
Number of subjects	157	157	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	17.7		
standard deviation	± 12.24	-	
Sex: Female, Male Units: participants			
Female	72	72	
Male	85	85	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	25	25	
Not Hispanic or Latino	129	129	
Unknown or Not Reported	3	3	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	8	8	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	142	142	
More than one race	0	0	
Unknown or Not Reported	7	7	
Blood Phe Level in Classical PKU Participants			
Classical PKU participants: Participants with severe forms of PKU, typically very high blood Phe levels (>1200 µmol/L). Here, 'N' = 17 for Part 1 (Participants who Participated in Part 1 Only): Sepiapterin; 8 for Part 2: Sepiapterin; and 11 for Part 2: Placebo.			
Units: µmol/L			
arithmetic mean			
standard deviation	±	-	
Blood Phenylketonuria (Phe) Level Units: micromoles (µmol)/liter (L)			
arithmetic mean			
standard deviation	±	-	

Subject analysis sets	
Subject analysis set title	Part 1 (Participants Participated in Part 1 Only): Sepiapterin
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received sepiapterin 30 mg/kg (participants 12 months to <2 years of age) or 60 mg/kg (participants ≥2 years of age) orally once daily for 14 days.	
Subject analysis set title	Part 2: Sepiapterin
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received sepiapterin 20 mg/kg daily for Weeks 1 and 2, then sepiapterin 40 mg/kg daily for Weeks 3 and 4, then sepiapterin 60 mg/kg daily for Weeks 5 and 6.	
Subject analysis set title	Part 2: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received equivalent quantities of placebo to match the 20 to 40 to 60 mg/kg dose escalation of the sepiapterin treatment arm.	

Reporting group values	Part 1 (Participants Participated in Part 1 Only): Sepiapterin	Part 2: Sepiapterin	Part 2: Placebo
Number of subjects	47	56	54
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	18.4	16.5	18.4
standard deviation	± 15.07	± 11.12	± 10.65
Sex: Female, Male Units: participants			
Female	19	26	27
Male	28	30	27
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	8	12
Not Hispanic or Latino	40	47	42
Unknown or Not Reported	2	1	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	3	3	2
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	41	52	49
More than one race	0	0	0
Unknown or Not Reported	3	1	3
Blood Phe Level in Classical PKU Participants			
Classical PKU participants: Participants with severe forms of PKU, typically very high blood Phe levels (>1200 µmol/L). Here, 'N' = 17 for Part 1 (Participants who Participated in Part 1 Only): Sepiapterin; 8 for Part 2: Sepiapterin; and 11 for Part 2: Placebo.			
Units: µmol/L			

arithmetic mean	1495.8	737.56	812.14
standard deviation	± 641.18	± 277.279	± 295.239
Blood Phenylketonuria (Phe) Level Units: micromoles (µmol)/liter (L)			
arithmetic mean	651.16	645.59	667.81
standard deviation	± 333.439	± 246.085	± 264.574

End points

End points reporting groups

Reporting group title	Part 1: Sepiapterin
Reporting group description:	
Participants received sepiapterin 30 milligrams (mg)/kilogram (kg) (participants 12 months to <2 years of age) or 60 mg/kg (participants ≥2 years of age) orally once daily for 14 days.	
Reporting group title	Part 2: Sepiapterin
Reporting group description:	
Participants received sepiapterin 20 mg/kg daily for Weeks 1 and 2, then sepiapterin 40 mg/kg daily for Weeks 3 and 4, then sepiapterin 60 mg/kg daily for Weeks 5 and 6.	
Reporting group title	Part 2: Placebo
Reporting group description:	
Participants received equivalent quantities of placebo to match the 20 to 40 to 60 mg/kg dose escalation of the sepiapterin treatment arm.	
Subject analysis set title	Part 1 (Participants Participated in Part 1 Only): Sepiapterin
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received sepiapterin 30 mg/kg (participants 12 months to <2 years of age) or 60 mg/kg (participants ≥2 years of age) orally once daily for 14 days.	
Subject analysis set title	Part 2: Sepiapterin
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received sepiapterin 20 mg/kg daily for Weeks 1 and 2, then sepiapterin 40 mg/kg daily for Weeks 3 and 4, then sepiapterin 60 mg/kg daily for Weeks 5 and 6.	
Subject analysis set title	Part 2: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received equivalent quantities of placebo to match the 20 to 40 to 60 mg/kg dose escalation of the sepiapterin treatment arm.	

Primary: Mean Change From Baseline in Blood Phenylketonuria (Phe) Level to Weeks 5 and 6 (Averaged Over a 2-week Period) in the Part 2 Double-blind Phase

End point title	Mean Change From Baseline in Blood Phenylketonuria (Phe) Level to Weeks 5 and 6 (Averaged Over a 2-week Period) in the Part 2 Double-blind Phase
End point description:	
Baseline was defined as the average of Day -1 and Day 1 predose blood Phe levels in Part 2, and mean level at Weeks 5 and 6 was calculated as the average of blood Phe levels collected during the Week 5-6 analysis visit window. Least square (LS) mean and standard error (SE) were calculated using mixed model repeated measures (MMRM) method. Full Analysis Set (FAS) included all participants who were randomized and received at least 1 dose of double-blind study drug in Part 2. Non-responders in Part 1 did not continue to Part 2 and were not included in the analysis. Here, 'Overall number of participants analyzed' = participants of FAS with Phe reduction from Baseline ≥30% during Part 1, who continued in Part 2.	
End point type	Primary
End point timeframe:	
Baseline, Weeks 5 and 6 (average of the 2-week period)	

End point values	Part 2: Sepiapterin	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: µmol/L				
least squares mean (standard error)	-415.75 (± 24.066)	-19.88 (± 24.223)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 2: Sepiapterin v Part 2: Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-395.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-463.07
upper limit	-328.66
Variability estimate	Standard error of the mean
Dispersion value	33.848

Primary: Percent Change From Baseline in Blood Phe Level to Weeks 5 and 6 (Averaged Over a 2-week Period) in the Part 2 Double-blind Phase

End point title	Percent Change From Baseline in Blood Phe Level to Weeks 5 and 6 (Averaged Over a 2-week Period) in the Part 2 Double-blind Phase

End point description:

Baseline was defined as the average of Day -1 and Day 1 predose blood Phe levels in Part 2, and mean level at Weeks 5 and 6 was calculated as the average of blood Phe levels collected during the Week 5-6 analysis visit window. LS mean and SE were calculated using MMRM method. FAS included all participants who were randomized and received at least 1 dose of double-blind study drug in Part 2. Non-responders in Part 1 did not continue to Part 2 and were not included in the analysis. Here, 'Overall number of participants analyzed' = participants of FAS with Phe reduction from Baseline ≥30% during Part 1, who continued in Part 2.

End point type	Primary

End point timeframe:

Baseline, Weeks 5 and 6 (average of the 2-week period)

End point values	Part 2: Sepiapterin	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: percent change				
least squares mean (standard error)	-63.40 (± 3.537)	0.82 (± 3.561)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 2: Sepiapterin v Part 2: Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-64.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-74.09
upper limit	-54.35
Variability estimate	Standard error of the mean
Dispersion value	4.973

Secondary: Percentage of Participants With Baseline Phe Levels ≥600 µmol/L who Achieved Phe Levels <600 µmol/L in the Part 2 Double-blind Phase

End point title	Percentage of Participants With Baseline Phe Levels ≥600 µmol/L who Achieved Phe Levels <600 µmol/L in the Part 2 Double-blind Phase

End point description:

Baseline was defined as the average of Day -1 and Day 1 predose blood Phe levels in Part 2, and mean level at Weeks 5 and 6 was calculated as the average of blood Phe levels collected during the Week 5-6 analysis visit window. FAS included all participants who were randomized and received at least 1 dose of double-blind study drug in Part 2. Non-responders in Part 1 did not continue to Part 2 and were not included in the analysis. Here, 'Overall number of participants analyzed' = participants of FAS with Phe reduction from baseline ≥30% during Part 1 and had Part 2 baseline Phe levels ≥600 µmol/L.

End point type	Secondary

End point timeframe:

Weeks 5 and 6 (average of the 2-week period)

End point values	Part 2: Sepiapterin	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	30		
Units: percentage of participants				
number (confidence interval 95%)	92.9 (76.50 to 99.12)	30.0 (14.73 to 49.40)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 2: Sepiapterin v Part 2: Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	30.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.3
upper limit	294.24

Secondary: Percentage of Participants With Baseline Phe Levels ≥360 µmol/L who Achieved Phe Levels <360 µmol/L in the Part 2 Double-blind Phase

End point title	Percentage of Participants With Baseline Phe Levels ≥360 µmol/L who Achieved Phe Levels <360 µmol/L in the Part 2 Double-blind Phase

End point description:

Baseline was defined as the average of Day -1 and Day 1 predose blood Phe levels in Part 2, and mean level at Weeks 5 and 6 was calculated as the average of blood Phe levels collected during the Week 5-6 analysis visit window. FAS included all participants who were randomized and received at least 1 dose of double-blind study drug in Part 2. Non-responders in Part 1 did not continue to Part 2 and were not included in the analysis. Here, 'Overall number of participants analyzed' = participants of FAS with Phe reduction from baseline ≥30% during Part 1 and Part 2 baseline Phe levels ≥360 µmol/L.

End point type	Secondary

End point timeframe:

Weeks 5 and 6 (average of the 2-week period)

End point values	Part 2: Sepiapterin	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: percentage of participants				
number (confidence interval 95%)	84.1 (69.93 to 93.36)	9.3 (2.59 to 22.14)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 2: Sepiapterin v Part 2: Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	51.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.28
upper limit	245.34

Secondary: Mean Change From Baseline in Blood Phe Level at Each 2-Week Period (Averaged Over Each 2-Week Period) in the Part 2 Double-blind Phase

End point title	Mean Change From Baseline in Blood Phe Level at Each 2-Week Period (Averaged Over Each 2-Week Period) in the Part 2 Double-blind Phase

End point description:

Baseline was defined as the average of Day -1 and Day 1 predose blood Phe levels in Part 2, and mean levels at Weeks 1 and 2, Weeks 3 and 4, and Weeks 5 and 6 were calculated as the average of blood Phe levels collected during the Week 1-2, Week 3-4, and Week 5-6 analysis visit windows, respectively. FAS included all participants who were randomized and received at least 1 dose of double-blind study drug in Part 2. Non-responders in Part 1 did not continue to Part 2 and were not included in the analysis. Here, 'Overall number of participants analyzed' = participants of FAS with Phe reduction from Baseline ≥30% during Part 1 and continued in Part 2. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1 and 2, Weeks 3 and 4, and Weeks 5 and 6 (average of each 2-week period)

End point values	Part 2: Sepiapterin	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: µmol/L				
arithmetic mean (standard deviation)				
Weeks 1 and 2 (n = 49, 49)	-341.18 (± 226.178)	-53.27 (± 174.461)		
Weeks 3 and 4 (n = 49, 48)	-406.88 (± 199.259)	-30.43 (± 203.425)		
Weeks 5 and 6 (n = 49, 49)	-410.07 (± 204.442)	-16.19 (± 198.642)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 (Weeks 1 and 2)
Comparison groups	Part 2: Sepiapterin v Part 2: Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-289.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-356.29
upper limit	-223.5
Variability estimate	Standard error of the mean
Dispersion value	33.44

Statistical analysis title	Statistical Analysis 3 (Weeks 5 and 6)
Comparison groups	Part 2: Sepiapterin v Part 2: Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-395.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-463.07
upper limit	-328.66
Variability estimate	Standard error of the mean
Dispersion value	33.848

Statistical analysis title	Statistical Analysis 2 (Weeks 3 and 4)
Comparison groups	Part 2: Sepiapterin v Part 2: Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-375.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-435.88
upper limit	-315.06
Variability estimate	Standard error of the mean
Dispersion value	30.424

Secondary: Percent Change From Baseline in Blood Phe Level at Each 2-Week Period (Averaged Over Each 2-Week Period) in the Part 2 Double-blind Phase

End point title	Percent Change From Baseline in Blood Phe Level at Each 2-Week Period (Averaged Over Each 2-Week Period) in the Part 2 Double-blind Phase

End point description:

Baseline was defined as the average of Day -1 and Day 1 predose blood Phe levels in Part 2, and mean levels at Weeks 1 and 2, Weeks 3 and 4, and Weeks 5 and 6 were calculated as the average of blood Phe levels collected during the Week 1-2, Week 3-4, and Week 5-6 analysis visit windows, respectively. FAS included all participants who were randomized and received at least 1 dose of double-blind study drug in Part 2. Non-responders in Part 1 did not continue to Part 2 and were not included in the analysis. Here, 'Overall number of participants analyzed' = participants of FAS with Phe reduction from Baseline ≥30% during Part 1 and continued in Part 2. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1 and 2, Weeks 3 and 4, and Weeks 5 and 6 (average of each 2-week period)

End point values	Part 2: Sepiapterin	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: percent change				
least squares mean (standard error)				
Weeks 1 and 2 (n=49,49)	-48.55 (± 4.265)	-6.04 (± 4.285)		
Weeks 3 and 4 (n=49,48)	-62.46 (± 3.220)	-1.43 (± 3.257)		
Weeks 5 and 6 (n=49,49)	-63.40 (± 3.537)	0.82 (± 3.561)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 (Weeks 1 and 2)
Comparison groups	Part 2: Sepiapterin v Part 2: Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-42.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.45
upper limit	-30.59
Variability estimate	Standard error of the mean
Dispersion value	6.008

Statistical analysis title	Statistical Analysis 3 (Weeks 5 and 6)
Comparison groups	Part 2: Sepiapterin v Part 2: Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-64.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-74.09
upper limit	-54.35
Variability estimate	Standard error of the mean
Dispersion value	4.973

Statistical analysis title	Statistical Analysis 2 (Weeks 3 and 4)
Comparison groups	Part 2: Sepiapterin v Part 2: Placebo

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-61.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-70.02
upper limit	-52.03
Variability estimate	Standard error of the mean
Dispersion value	4.531

Secondary: Plasma Concentration of Tetrahydrobiopterin (BH4) and Sepiapterin in Part 1 Open-label Run-in Phase

End point title	Plasma Concentration of Tetrahydrobiopterin (BH4) and Sepiapterin in Part 1 Open-label Run-in Phase

End point description:

Pharmacokinetic (PK) Analysis Set included all participants who had at least 1 measurable plasma concentration of sepiapterin or BH4. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint. 'n' = participants evaluable at specified timepoint. '99999' signifies standard deviation (SD) data could not be calculated due to single participants.

End point type	Secondary

End point timeframe:

Predose, 0.5, 1, 2, 4, 6, 8, and 24 hours postdose at Day 1; 2 and 6 hours postdose at Day 14

End point values	Part 1: Sepiapterin			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: nanograms (ng)/milliliter (mL)				
arithmetic mean (standard deviation)				
BH4: Day 1 (predose) (n = 16)	10.6 (± 5.34)			
BH4: Day 1 (0.5 hr) (n = 16)	22.3 (± 13.2)			
BH4: Day 1 (1 hr) (n = 15)	107 (± 76.0)			
BH4: Day 1 (2 hrs) (n = 16)	236 (± 124)			
BH4: Day 1 (4 hrs) (n = 16)	289 (± 170)			
BH4: Day 1 (6 hrs) (n = 14)	245 (± 131)			
BH4: Day 1 (8 hrs) (n = 15)	205 (± 130)			
BH4: Day 1 (24 hrs) (n = 16)	25.5 (± 21.1)			
BH4: Day 14 (2 hrs) (n = 1)	94.1 (± 99999)			
BH4: Day 14 (6 hrs) (n = 1)	105 (± 99999)			
Sepiapterin: Day 1 (predose) (n = 16)	0.000 (± 0.000)			
Sepiapterin: Day 1 (0.5 hr) (n = 16)	0.939 (± 0.940)			
Sepiapterin: Day 1 (1 hr) (n = 16)	2.22 (± 1.11)			

Sepiapterin: Day 1 (2 hrs) (n = 16)	2.06 (± 1.10)			
Sepiapterin: Day 1 (4 hrs) (n = 17)	1.73 (± 1.58)			
Sepiapterin: Day 1 (6 hrs) (n = 16)	1.60 (± 2.13)			
Sepiapterin: Day 1 (8 hrs) (n = 16)	0.493 (± 0.598)			
Sepiapterin: Day 1 (24 hrs) (n = 16)	0.436 (± 0.987)			
Sepiapterin: Day 14 (2 hrs) (n = 1)	3.33 (± 99999)			
Sepiapterin: Day 14 (6 hrs) (n = 1)	2.82 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of BH4 and Sepiapterin in Part 2 Double-blind Phase

End point title	Plasma Concentration of BH4 and Sepiapterin in Part 2 Double-blind Phase

End point description:

PK Analysis Set included all participants who had at least 1 measurable plasma concentration of sepiapterin or BH4. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Predose and 4 hours postdose at Days 1, 14, 28, and 42

End point values	Part 2: Sepiapterin	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: ng/mL				
arithmetic mean (standard deviation)				
BH4: Day 1 (predose) (n= 4,2)	6.63 (± 3.60)	8.52 (± 4.36)		
BH4: Day 1 (4 hrs) (n= 3,4)	351 (± 184)	12.4 (± 1.74)		
BH4: Day 14 (predose) (n= 4,3)	7.04 (± 3.13)	4.27 (± 4.93)		
BH4: Day 14 (4 hrs) (n= 2,4)	401 (± 184)	11.3 (± 8.70)		
BH4: Day 28 (predose) (n= 3,4)	11.8 (± 6.29)	9.70 (± 4.18)		
BH4: Day 28 (4 hrs) (n= 3,4)	406 (± 57.5)	12.2 (± 4.46)		
BH4: Day 42 (predose) (n= 4,4)	10.0 (± 6.43)	9.41 (± 4.58)		
BH4: Day 42 (4 hrs) (n= 2,4)	442 (± 197)	11.4 (± 3.91)		
Sepiapterin: Day 1 (predose) (n= 4,4)	0.000 (± 0.000)	0.000 (± 0.000)		
Sepiapterin: Day 1 (4 hrs) (n= 3,4)	0.620 (± 1.07)	0.000 (± 0.000)		
Sepiapterin: Day 14 (predose) (n= 4,3)	0.000 (± 0.000)	0.000 (± 0.000)		
Sepiapterin: Day 14 (4 hrs) (n= 3,4)	1.23 (± 1.26)	0.000 (± 0.000)		
Sepiapterin: Day 28 (predose) (n= 4,3)	0.000 (± 0.000)	0.000 (± 0.000)		

Sepiapterin: Day 28 (4 hrs) (n= 3,4)	1.17 (± 1.09)	0.000 (± 0.000)		
Sepiapterin: Day 42 (predose) (n= 4,4)	0.000 (± 0.000)	0.000 (± 0.000)		
Sepiapterin: Day 42 (4 hrs) (n= 3,4)	1.03 (± 1.14)	0.000 (± 0.000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve From Time 0 to 24 Hours Postdose (AUC0-24h) of Sepiapterin and BH4 Following the First Dose of Sepiapterin at 60 mg/kg in Part 1 Open-label Run-in Phase

End point title	Area Under the Concentration-time Curve From Time 0 to 24 Hours Postdose (AUC0-24h) of Sepiapterin and BH4 Following the First Dose of Sepiapterin at 60 mg/kg in Part 1 Open-label Run-in Phase

End point description:

PK Analysis Set included all participants who had at least 1 measurable plasma concentration of sepiapterin or BH4. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

0 to 24 hours postdose at Day 1

End point values	Part 1: Sepiapterin			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours*ng/mL				
arithmetic mean (standard deviation)				
BH4	2990 (± 1450)			
Sepiapterin	19.6 (± 20.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) was as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. TEAEs were considered:
- Part 1 TEAEs, which included all AEs occurring after first dose in Part 1 but before first dose in Part 2;
- Part 2 TEAEs, which included all AEs after first randomized dose in Part 2.

A summary of all Serious Adverse Events and Other Adverse Events (nonserious) regardless of causality is located in the 'Reported Adverse Events' Section.
Safety analysis set included all participants who received at least 1 dose of study drug, including during Part 1.

End point type	Secondary

End point timeframe:

Baseline up to Day 42

End point values	Part 1: Sepiapterin	Part 2: Sepiapterin	Part 2: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	157	56	54	
Units: participants	68	33	18	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Change From Baseline in Blood Phe Level to Weeks 5 and 6 (Averaged Over a 2-week Period) in the Part 2 Double-blind Phase for Classical PKU Participants

End point title	Mean Change From Baseline in Blood Phe Level to Weeks 5 and 6 (Averaged Over a 2-week Period) in the Part 2 Double-blind Phase for Classical PKU Participants

End point description:

Classical PKU participants: Participants with severe forms of PKU, typically very high blood Phe levels (>1200 µmol/L). Baseline was defined as the average of Day -1 and Day 1 predose blood Phe levels in Part 2, and mean level at Weeks 5 and 6 was calculated as the average of blood Phe levels collected during the Week 5-6 analysis visit window. LS mean and SE were calculated using MMRM method. FAS included all participants who were randomized and received at least 1 dose of double-blind study drug in Part 2. Non-responders in Part 1 did not continue to Part 2 and were not included in the analysis. Here, 'Overall number of participants analyzed' = Classical PKU participants of FAS with Phe reduction from Baseline ≥30% during Part 1 and continued in Part 2.

End point type	Other pre-specified

End point timeframe:

Baseline, Weeks 5 and 6 (average of the 2-week period)

End point values	Part 2: Sepiapterin	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	9		
Units: µmol/L				
least squares mean (standard error)	-488.19 (± 50.532)	4.03 (± 46.496)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 2: Sepiapterin v Part 2: Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-492.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-614.59
upper limit	-369.87
Variability estimate	Standard error of the mean
Dispersion value	55.588

Other pre-specified: Mean Change From Baseline (Part 1) in Blood Phe Level to Weeks 1 and 2 (Averaged Over a 2-week Period) in the Part 1 Open-label Run-in Phase

End point title	Mean Change From Baseline (Part 1) in Blood Phe Level to Weeks 1 and 2 (Averaged Over a 2-week Period) in the Part 1 Open-label Run-in Phase

End point description:

Baseline was defined as the average of Day -1 and Day 1 predose blood Phe levels in Part 1, and mean level at Weeks 1 and 2 was calculated as the average of blood Phe levels collected during the Week 1-2 analysis visit window. LS mean and SE were calculated using MMRM method. FAS included all participants who were enrolled and received at least 1 dose of open-label study drug in Part 1. Here "Overall number of participants analyzed" = participants of FAS with Phe reduction from Baseline ≥30% during Part 1.

End point type	Other pre-specified

End point timeframe:

Baseline (Part 1), Weeks 1 and 2 (average of the 2-week period)

End point values	Part 1: Sepiapterin			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: µmol/L				
arithmetic mean (standard deviation)	-462.17 (± 203.620)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline in Blood Phe Level to Weeks 5 and 6 (Averaged Over a 2-week Period) in the Part 2 Double-blind Phase for Classical PKU Participants

End point title	Percent Change From Baseline in Blood Phe Level to Weeks 5 and 6 (Averaged Over a 2-week Period) in the Part 2 Double-blind Phase for Classical PKU Participants

End point description:

Classical PKU participants: Participants with severe forms of PKU, typically very high blood Phe levels (>1200 µmol/L). Baseline was defined as the average of Day -1 and Day 1 predose blood Phe levels in Part 2, and mean level at Weeks 5 and 6 was calculated as the average of blood Phe levels collected during the Week 5-6 analysis visit window. LS mean and SE were calculated using MMRM method. FAS included all participants who were randomized and received at least 1 dose of double-blind study drug in Part 2. Non-responders in Part 1 did not continue to Part 2 and were not included in the analysis. Here, 'Overall number of participants analyzed' = Classical PKU participants of FAS with Phe reduction from Baseline ≥30% during Part 1 and continued in Part 2.

End point type	Other pre-specified

End point timeframe:

Baseline, Weeks 5 and 6 (average of the 2-week period)

End point values	Part 2: Sepiapterin	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	9		
Units: percent change				
least squares mean (standard error)	-55.83 (± 9.182)	18.90 (± 8.286)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 2: Sepiapterin v Part 2: Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-74.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-97.72
upper limit	-51.74
Variability estimate	Standard error of the mean
Dispersion value	10.436

Other pre-specified: Percent Change From Baseline (Part 1) in Blood Phe Level to Weeks 1 and 2 (Averaged Over a 2-week Period) in the Part 1 Open-label Run-in Phase

End point title	Percent Change From Baseline (Part 1) in Blood Phe Level to Weeks 1 and 2 (Averaged Over a 2-week Period) in the Part 1 Open-label Run-in Phase

End point description:

Baseline was defined as the average of Day -1 and Day 1 predose blood Phe levels in Part 1, and mean level at Weeks 1 and 2 was calculated as the average of blood Phe levels collected during the Week 1-2 analysis visit window. LS mean and SE were calculated using MMRM method. FAS included all participants who were enrolled and received at least 1 dose of open-label study drug in Part 1. Here "Overall number of participants analyzed" = participants of FAS with Phe reduction from Baseline ≥30% during Part 1.

End point type	Other pre-specified

End point timeframe:

Baseline (Part 1), Weeks 1 and 2 (average of the 2-week period)

End point values	Part 1: Sepiapterin			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: percent change				
arithmetic mean (standard deviation)	-65.25 (± 15.764)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Day 42	
Adverse event reporting additional description:	
Safety analysis set included all participants who received at least 1 dose of study drug, including during Part 1.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Part 1: Sepiapterin
Reporting group description:	
Participants received sepiapterin 30 mg/kg (participants 12 months to <2 years of age) or 60 mg/kg (participants ≥2 years of age) orally once daily for 14 days.	
Reporting group title	Part 2: Placebo
Reporting group description:	
Participants received equivalent quantities of placebo to match the 20 to 40 to 60 mg/kg dose escalation of the sepiapterin treatment arm.	
Reporting group title	Part 2: Sepiapterin
Reporting group description:	
Participants received sepiapterin 20 mg/kg daily for Weeks 1 and 2, then sepiapterin 40 mg/kg daily for Weeks 3 and 4, then sepiapterin 60 mg/kg daily for Weeks 5 and 6.	

Serious adverse events	Part 1: Sepiapterin	Part 2: Placebo	Part 2: Sepiapterin
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 157 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part 1: Sepiapterin	Part 2: Placebo	Part 2: Sepiapterin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 157 (9.55%)	11 / 54 (20.37%)	14 / 56 (25.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 157 (0.00%)	1 / 54 (1.85%)	4 / 56 (7.14%)
occurrences (all)	0	1	4
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	8 / 157 (5.10%)	1 / 54 (1.85%)	4 / 56 (7.14%)
occurrences (all)	8	1	4
Vomiting			
subjects affected / exposed	0 / 157 (0.00%)	3 / 54 (5.56%)	1 / 56 (1.79%)
occurrences (all)	0	3	1
Nausea			
subjects affected / exposed	0 / 157 (0.00%)	3 / 54 (5.56%)	0 / 56 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 157 (4.46%)	1 / 54 (1.85%)	3 / 56 (5.36%)
occurrences (all)	7	1	3
Gastroenteritis			
subjects affected / exposed	0 / 157 (0.00%)	3 / 54 (5.56%)	3 / 56 (5.36%)
occurrences (all)	0	3	4
Nasopharyngitis			
subjects affected / exposed	0 / 157 (0.00%)	4 / 54 (7.41%)	0 / 56 (0.00%)
occurrences (all)	0	4	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2021	It included following changes: • The dosing schedule was updated throughout to detail age dependent dosing. • Screening visit was updated to up to 45 days. • Window for the early termination visit (ETV) was extended to 21 days of last dose. • Specified throughout that participants from birth can be included in this study. • Statement was removed throughout that all participants will receive PTC923 60 mg/kg in Part 1 of the study. • Statement was added throughout to include specific details on participants <2 years of age with ≥30% response to PTC923 and enrollment into Study PTC923-MD-004-PKU. • Statement was added throughout to state participants who experience <15% reduction (≥2 years of age) or <30% reduction (<2 years of age) will be classified as nonresponsive and will be contacted to schedule an ETV (on or between Day 28 to Day 35). • Specified throughout that the Days -1 and 1 samples for Parts 1 and 2 should be taken predose. • Specified that specific information pertaining to previous use of sepiapterin and pegvaliase-pqpz should be collected. • Specified that blood Phe levels should be measured on Days 1, 20, and 30 during the pegvaliase-pqpz washout. • Additional details added regarding collection of blood Phe and Tyr samples and timepoints for participants participating in the PK substudy. • Inclusion Criteria were updated to align with current (2020) Clinical Trials Facilitation Group (CTFG) guidance. • Inclusion Criterion was updated to clarify that the surgery was not permitted within 90 days of screening . • Exclusion Criteria were added to exclude participants with renal impairment/disease. • Total blood volume for Part 1 and Part 2 was updated. • Statement added regarding unblinding and continuing study participation. • Age-based dosing specifications were updated and added. • Specified that the sepiapterin washout should be a minimum of 14 days. Day 15 was removed. • Specified that the additional sample taken at the ETV should be a DBS.
06 December 2021	• Protocol was updated to state that Phe responsiveness is defined as mean Phe reduction is ≥15% for participants <2 years. • A risk/benefit assessment section was added. • Inclusion Criterion was updated to specify "uncontrolled" blood Phe levels while on current therapy. • Inclusion Criterion was updated to specify that effective contraception/abstinence must be utilized for up to 90 days after the last dose of study drug. • Total blood volume was updated. • Details of the excipients were added. • A section was added to detail assessment of laboratory abnormalities. • PK sampling timepoints were updated. • SAE reporting timeframe was updated.
13 January 2022	• A definition for End of Study was added. • Exclusion criterion was expanded to include specific pathogenic mutations.

24 June 2022	• Tables were updated to detail additional blood sampling timepoints for Part 2. • Clarification was added to ensure full alignments with CTFG throughout the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported