



## 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 ( $\geq 2$  years of age) who experienced a  $\geq 15\%$  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  $\geq 2$  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                   |

|   |  |
|---|--|
| <b>Period 2</b>   |  |
| 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 |
| <b>Arms</b>   |  |
| Are arms mutually exclusive?  | Yes                                    |
| <b>Arm title</b>  | 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.   |  |
| <b>Arm title</b>  | 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 <sup>[1]</sup> | 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).<br>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<br>Units: Subjects |  |                     |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation  | 18.4<br>± 15.07 | 16.5<br>± 11.12 | 18.4<br>± 10.65 |
| Sex: Female, Male<br>Units: participants   |                 |                 |                 |
| Female   | 19              | 26              | 27              |
| Male   | 28              | 30              | 27              |
| Ethnicity (NIH/OMB)<br>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)<br>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).<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>Baseline, Weeks 5 and 6 (average of the 2-week period)   |  |

|                                     |                        |                      |  |  |
|-------------------------------------|------------------------|----------------------|--|--|
| <b>End point values</b>             | Part 2:<br>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 (±<br>24.066)  | -19.88 (±<br>24.223) |  |  |

## Statistical analyses

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | 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)   |

|                                     |                          |                     |  |  |
|-------------------------------------|--------------------------|---------------------|--|--|
| <b>End point values</b>             | Part 2:<br>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 ( $\pm$<br>3.537) | 0.82 ( $\pm$ 3.561) |  |  |

## Statistical analyses

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | 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 $\geq 600$ $\mu\text{mol/L}$ who Achieved Phe Levels $< 600$ $\mu\text{mol/L}$ in the Part 2 Double-blind Phase

|  |   |
|--|---|
| End point title                              | Percentage of Participants With Baseline Phe Levels $\geq 600$ $\mu\text{mol/L}$ who Achieved Phe Levels $< 600$ $\mu\text{mol/L}$ 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 $\geq 30\%$ during Part 1 and had Part 2 baseline Phe levels $\geq 600$ $\mu\text{mol/L}$ . |
| End point type                               | Secondary   |
| End point timeframe:                         |   |
| Weeks 5 and 6 (average of the 2-week period) |   |

|                                   |                        |                       |  |  |
|-----------------------------------|------------------------|-----------------------|--|--|
| <b>End point values</b>           | Part 2:<br>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

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | 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 $\geq 360$ $\mu\text{mol/L}$ who Achieved Phe Levels $< 360$ $\mu\text{mol/L}$ in the Part 2 Double-blind Phase

|   |   |
|---|---|
| End point title   | Percentage of Participants With Baseline Phe Levels $\geq 360$ $\mu\text{mol/L}$ who Achieved Phe Levels $< 360$ $\mu\text{mol/L}$ in the Part 2 Double-blind Phase |
| End point description:<br>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 $\geq 30\%$ during Part 1 and Part 2 baseline Phe levels $\geq 360$ $\mu\text{mol/L}$ . |   |
| End point type  | Secondary   |
| End point timeframe:<br>Weeks 5 and 6 (average of the 2-week period)  |   |

|                                   |                       |                     |  |  |
|-----------------------------------|-----------------------|---------------------|--|--|
| <b>End point values</b>           | 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

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | 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  $\geq 30\%$  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:<br>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                                 |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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  $\geq 30\%$  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)

| <b>End point values</b>             | Part 2:<br>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 ( $\pm$ 4.265)  | -6.04 ( $\pm$ 4.285) |  |  |
| Weeks 3 and 4 (n=49,48)             | -62.46 ( $\pm$ 3.220)  | -1.43 ( $\pm$ 3.257) |  |  |
| Weeks 5 and 6 (n=49,49)             | -63.40 ( $\pm$ 3.537)  | 0.82 ( $\pm$ 3.561)  |  |  |



## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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                                  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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                                  |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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:<br>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:<br>Sapiapterin | Part 2:<br>Sapiapterin | 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:<br>Sapiapterin | 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

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | 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: 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)

|                                     |                        |                    |  |  |
|-------------------------------------|------------------------|--------------------|--|--|
| <b>End point values</b>             | Part 2:<br>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 (±<br>9.182)    | 18.90 (±<br>8.286) |  |  |

## Statistical analyses

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | 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: 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  $\geq 30\%$  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)

|                                      |                             |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| <b>End point values</b>              | Part 1:<br>Sepiapterin      |  |  |  |
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 103                         |  |  |  |
| Units: $\mu\text{mol/L}$             |                             |  |  |  |
| arithmetic mean (standard deviation) | -462.17 ( $\pm$<br>203.620) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

---

**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  $\geq 30\%$  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)

---

|                                      |                           |  |  |  |
|--------------------------------------|---------------------------|--|--|--|
| <b>End point values</b>              | Part 1:<br>Sepiapterin    |  |  |  |
| Subject group type                   | Reporting group           |  |  |  |
| Number of subjects analysed          | 103                       |  |  |  |
| Units: percent change                |                           |  |  |  |
| arithmetic mean (standard deviation) | -65.25 ( $\pm$<br>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     | <p>It included following changes:</p> <ul style="list-style-type: none"><li>• The dosing schedule was updated throughout to detail age dependent dosing.</li><li>• Screening visit was updated to up to 45 days.</li><li>• Window for the early termination visit (ETV) was extended to 21 days of last dose.</li><li>• Specified throughout that participants from birth can be included in this study.</li><li>• Statement was removed throughout that all participants will receive PTC923 60 mg/kg in Part 1 of the study.</li><li>• Statement was added throughout to include specific details on participants &lt;2 years of age with <math>\geq 30\%</math> response to PTC923 and enrollment into Study PTC923-MD-004-PKU.</li><li>• Statement was added throughout to state participants who experience &lt;15% reduction (<math>\geq 2</math> years of age) or &lt;30% reduction (&lt;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).</li><li>• Specified throughout that the Days -1 and 1 samples for Parts 1 and 2 should be taken predose.</li><li>• Specified that specific information pertaining to previous use of sepiapterin and pegvaliase-pqpz should be collected.</li><li>• Specified that blood Phe levels should be measured on Days 1, 20, and 30 during the pegvaliase-pqpz washout.</li><li>• Additional details added regarding collection of blood Phe and Tyr samples and timepoints for participants participating in the PK substudy.</li><li>• Inclusion Criteria were updated to align with current (2020) Clinical Trials Facilitation Group (CTFG) guidance.</li><li>• Inclusion Criterion was updated to clarify that the surgery was not permitted within 90 days of screening .</li><li>• Exclusion Criteria were added to exclude participants with renal impairment/disease.</li><li>• Total blood volume for Part 1 and Part 2 was updated.</li><li>• Statement added regarding unblinding and continuing study participation.</li><li>• Age-based dosing specifications were updated and added.</li><li>• Specified that the sepiapterin washout should be a minimum of 14 days.</li><li>• Day 15 was removed.</li><li>• Specified that the additional sample taken at the ETV should be a DBS.</li></ul> |
| 06 December 2021 | <ul style="list-style-type: none"><li>• Protocol was updated to state that Phe responsiveness is defined as mean Phe reduction is <math>\geq 15\%</math> for participants &lt;2 years.</li><li>• A risk/benefit assessment section was added.</li><li>• Inclusion Criterion was updated to specify "uncontrolled" blood Phe levels while on current therapy.</li><li>• 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.</li><li>• Total blood volume was updated.</li><li>• Details of the excipients were added.</li><li>• A section was added to detail assessment of laboratory abnormalities.</li><li>• PK sampling timepoints were updated.</li><li>• SAE reporting timeframe was updated.</li></ul>   |
| 13 January 2022  | <ul style="list-style-type: none"><li>• A definition for End of Study was added.</li><li>• Exclusion criterion was expanded to include specific pathogenic mutations.</li></ul>   |

|              |  |
|--------------|--|
| 24 June 2022 | <ul style="list-style-type: none"> <li>• Tables were updated to detail additional blood sampling timepoints for Part 2.</li> <li>• Clarification was added to ensure full alignments with CTFG throughout the protocol.</li> </ul> |
|--------------|--|

Notes:

---

## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported