Clinical Trial Results:
A Phase 3, Randomized, Crossover, Open-label, Active-controlled Study of Sepiapterin Versus Sapropterin in Participants With Phenylketonuria Greater Than or Equal to 2 Years of Age

Summary	
CTIS ID	2023-506238-61-00
EudraCT number	
Global end of trial date	12 Mar 2025

Index

Trial Information
Subject Disposition
Baseline Characteristics
End Points
Adverse Events
More Information
CTIS

Trial information	
Trial identification	
Sponsor protocol code	PTC923-PKU-301
Additional study identifiers	
ISRCTN number	-
US NCT number	-
WHO universal trial number (UTN)	-
Sponsors	
Sponsor organisation name	PTC Therapeutics, Inc.
Sponsor organisation address	500 Warren Corp Centre Dr, Warren, United States, NJ 07059
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
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
Results analysis stage	
Analysis stage	Final

Trial information	
Date of interim/final analysis	12 Mar 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 Feb 2025
Global end of trial reached?	Yes
Global end of trial date	12 Mar 2025
Was the trial ended prematurely?	No
General information about the trial	
Main objective of the trial	The main objective of this study was to compare the efficacy of sepiapterin to sapropterin in reducing blood phenylalanine (Phe) levels in participants with phenylketonuria (PKU).
Protection of trial subjects	This study 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	10 Apr 2024
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No
Population of trial subjects	
Number of subjects enrolled per country	
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Netherlands: 5
Worldwide total number of subjects	82
EEA total number of subjects	44

Trial information	
Number of 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)	0
Children (2-11 years)	28
Adolescents (12-17 years)	38
Adults (18-64 years)	15
From 65 to 84 years	1
85 years and over	0

Subject Disposition	
Recruitment	
Recruitment details	-
Pre-assignment	
Screening details	A total of 111 participants were screened, and 82 participants were enrolled and tested for responsiveness to sepiapterin in Part 1 of the study. Of those, 62 participants were randomized and treated in Part 2, including 30 participants to Sequence 1 and 32 participants to Sequence 2.
Period 1	
Period 1 title	Part 1 (4 Weeks)
Is this the baseline period?	Yes
Allocation method	Not Applicable
Blinded?	false
Blinding used	Not-blind
Arms	
Are arms mutually exclusive	Yes
Arm title	Part 1: Sepiapterin
Arm description	Participants received 14 days of open-label treatment with sepiapterin administered orally once a day followed by a 14- to 21-day sepiapterin washout.
Arm type	Experimental

Subject Disposition	
Investigational medicinal product name	Sepiapterin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
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	82
Received at least 1 dose of study drug	82
Completed	62
Not completed	20
Did Not Meet Eligibility Criterion for Part 1	5
Non-responder in Part 1	15
Period 2	
Period 2 title	Part 2: (12 Weeks)
Is this the baseline period?	No
Allocation method	Randomised-Controlled
Blinded?	false
Blinding used	Not-blind
Arms	
Are arms mutually exclusive	Yes
Arm title	Sequence 1 (Sepiapterin Then Sapropterin)
Arm description	Participants received sepiapterin for 4 weeks in Treatment Period 1 and sapropterin for 4 weeks in Treatment Period 2. Each treatment period was followed by a 14-day washout period.
Arm type	Experimental
Investigational medicinal product name	Sepiapterin
Investigational medicinal product code	
Other name	

Subject Disposition		
Pharmaceutical forms	Powder for oral suspension	
Routes of administration	Oral use	
Dosage and administration details	Sepiapterin was administered per schedule specified in the arm description.	
Investigational medicinal product name	Sapropterin	
Investigational medicinal product code		
Other name		
Pharmaceutical forms	Tablet	
Routes of administration	Oral use	
Dosage and administration details	Sapropterin was administered per schedule specified in the arm description.	
Arm title	Sequence 2 (Sapropterin Then Sepiapterin)	
Arm description	Participants received sapropterin for 4 weeks in Treatment Period 1 and sepiapterin for 4 weeks in Treatment Period 2. Each treatment period was followed by a 14-day washout period.	
Arm type	Experimental	
Investigational medicinal product name	Sepiapterin	
Investigational medicinal product code		
Other name		
Pharmaceutical forms	Powder for oral suspension	
Routes of administration	Oral use	
Dosage and administration details	Sepiapterin was administered per schedule specified in the arm description.	
Investigational medicinal product name	Sapropterin	
Investigational medicinal product code		
Other name		
Pharmaceutical forms	Tablet	
Routes of administration	Oral use	
Dosage and administration details	Sapropterin was administered per schedule specified in the arm description.	
Number of subjects in period 2	Sequence 1 (Sepiapterin Then Sapropterin)	Sequence 2 (Sapropterin

Subject Disposition

		Then Sepiapterin)
Started	30	32
Received at least 1 dose of study drug	30	32
Completed	30	30
Not completed	0	2
Consent withdrawn by subject	-	1
Participant decision	-	1

Baseline Characteristics

How are baseline characteristics being reported?	Per Arm in the baseline period	
Baseline characteristics reporting groups		
Reporting group title	Part 1: Sepiapterin	
Reporting group description	Participants received 14 days of open-label treatment with sepiapterin administered orally once a day followed by a 14- to 21-day sepiapterin washout.	
Reporting group values	Part 1: Sepiapterin	Total
Number of subjects	82	82
Age Categorical		
Units: Subjects		
Age Continuous		
Units: years		
Arithmetic Mean (Standard Deviation)	15.3 ± 10.63	-
Gender Categorical		
Units: Subjects		
Female	43	43
Male	39	39
Race		
Units: participants		
Asian	2	2
White	71	71
Other	8	8
Multiple	1	1
Ethnicity		
Units: participants		
Hispanic or Latino	0	0

Baseline Characteristics		
Not Hispanic or Latino	80	80
Unknown	2	2

End points	
End points reporting groups	
Reporting group title	Part 1: Sepiapterin
Reporting group description	Participants received 14 days of open-label treatment with sepiapterin administered orally once a day followed by a 14- to 21-day sepiapterin washout.
Reporting group title	Sequence 1 (Sepiapterin Then Sapropterin)
Reporting group description	Participants received sepiapterin for 4 weeks in Treatment Period 1 and sapropterin for 4 weeks in Treatment Period 2. Each treatment period was followed by a 14-day washout period.
Reporting group title	Sequence 2 (Sapropterin Then Sepiapterin)
Reporting group description	Participants received sapropterin for 4 weeks in Treatment Period 1 and sepiapterin for 4 weeks in Treatment Period 2. Each treatment period was followed by a 14-day washout period.
Subject analysis set title	Part 2: Sapropterin
Subject analysis set type	Full analysis
Subject analysis set description	Participants received sapropterin for 4 weeks in Treatment Period 1 or 2.
Subject analysis set title	Part 2: Sepiapterin
Subject analysis set type	Full analysis
Subject analysis set description	Participants received sepiapterin for 4 weeks in Treatment Period 1 or 2.

Primary: Part 2: Mean Change From Baseline in Blood Phe Level to Weeks 3 and 4 (Averaged Over a 2-week Period) in Participants With Phe Reduction From Baseline ≥30% During Part 1	
End point title	Part 2: Mean Change From Baseline in Blood Phe Level to Weeks 3 and 4 (Averaged Over a 2-week Period) in Participants With Phe Reduction From Baseline ≥30% During Part 1
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 3-4 analysis visit window. Least square (LS) mean and standard error (SE) were calculated using mixed model repeated measures (MMRM) method. LS mean model included fixed effects for treatment group, sequence, period, visit (Weeks 3-4), treatment-by-visit interaction, and the baseline blood Phe for each period as a covariate. In addition, participant nested within sequence was included as a random effect. Primary analysis set (PAS) included all participants who achieved a ≥30% reduction in blood Phe concentrations in Part 1, were randomized, and took at least 1 dose of study drug in Part 2.

Primary: Part 2: Mean Change From Baseline in Blood Phe Level to Weeks 3 and 4 (Averaged Over a 2-week Period) in Participants With Phe Reduction From Baseline ≥30% During Part 1		
End point type	Primary	
End point timeframe	Baseline, Weeks 3 and 4 (average of the 2-week period)	
Countable or measurable?	Measurable	
	Part 1 (4 Weeks)	Part 2: (12 Weeks)
End point values	Part 2: Sapropterin	Part 2: Sepiapterin
Number of subjects analysed	56	58
Units: micromoles (µmol)/liter (L)		
Measure Type: Least Squares Mean (Standard Error)	-256.6 ± 28.22	-437.0 ± 27.95
Statistical analysis title	Statistical Analysis 1	
Statistical analysis description	The actual number of participants analyzed: N = 56 for Part 2: Sapropterin group and N = 58 for Part 2: Sepiapterin group.	
Comparison groups	Part 2: Sapropterin v Part 2: Sepiapterin	
Number of subjects included in analysis	114	
Analysis specification	Pre-specified	
Analysis type	Superiority	
P-value	< 0.0001	
Method	Mixed Models Analysis	
Parameter type	LS Mean Difference	
Point estimate	-180.4	
Confidence interval		
level	95%	
sides	2-Sided	
lower limit	-229.5	
upper limit	-131.4	

Primary: Part 2: Mean Change From Baseline in Blood Phe Level to Weeks 3 and 4 (Averaged Over a 2-week Period)	
End point title	Part 2: Mean Change From Baseline in Blood Phe Level to Weeks 3 and 4 (Averaged Over a 2-week Period)
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 3-4 analysis visit window. LS mean and SE were calculated using MMRM method. LS mean model included fixed effects for treatment group, sequence, period, visit (Weeks 3-4), treatment-by-visit interaction, and the baseline blood Phe for each period as a covariate. In addition, participant nested within sequence was included as a random effect. Full analysis set (FAS) included all participants who were randomized and took at least 1 dose of study drug in Part 2.
End point type	Primary

Primary: Part 2: Mean Change From Baseline in Blood Phe Level to Weeks 3 and 4 (Averaged Over a 2-week Period)		
End point timeframe	Baseline, Weeks 3 and 4 (average of the 2-week period)	
Countable or measurable?	Measurable	
	Part 1 (4 Weeks)	Part 2: (12 Weeks)
End point values	Part 2: Sapropterin	Part 2: Sepiapterin
Number of subjects analysed	60	62
Units: µmol/L		
Measure Type: Least Squares Mean (Standard Error)	-174.4 ± 48.34	-355.5 ± 48.42
Statistical analysis title	Statistical Analysis 1	
Statistical analysis description	The actual number of participants analyzed: N = 60 for Part 2: Sapropterin group and N = 62 for Part 2: Sepiapterin group.	
Comparison groups	Part 2: Sapropterin v Part 2: Sepiapterin	
Number of subjects included in analysis	122	
Analysis specification	Pre-specified	
Analysis type	Superiority	
P-value	< 0.0001	
Method	Mixed Models Analysis	
Parameter type	LS Mean Difference	
Point estimate	-181.1	
Confidence interval		
level	95%	
sides	2-Sided	
lower limit	-228.5	
upper limit	-133.7	

Secondary: Part 2: Percentage of Participants With Baseline Blood Phe Levels ≥600 µmol/L who Achieved Phe Levels <600 µmol/L in Participants With Phe Reduction From Baseline ≥30% During Part 1	
End point title	Part 2: Percentage of Participants With Baseline Blood Phe Levels ≥600 µmol/L who Achieved Phe Levels <600 µmol/L in Participants With Phe Reduction From Baseline ≥30% During Part 1
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 3 and 4 was calculated as the average of blood Phe levels collected during the Week 3-4 analysis visit window. PAS included all participants who achieved a ≥30% reduction in blood Phe concentrations in Part 1, were randomized, and took at least 1 dose of study drug in Part 2. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.
End point type	Secondary
End point timeframe	Weeks 3 and 4 (average of the 2-week period)
Countable or measurable?	Measurable

Secondary: Part 2: Percentage of Participants With Baseline Blood Phe Levels ≥600 µmol/L who Achieved Phe Levels <600 µmol/L in Participants With Phe Reduction From Baseline ≥30% During Part 1		
	Part 1 (4 Weeks)	Part 2: (12 Weeks)
End point values	Part 2: Sapropterin	Part 2: Sepiapterin
Number of subjects analysed	39	37
Units: percentage of participants		
Measure Type: Number (Not Applicable)	51.3	89.2
No statistical analyses for this end point		

Secondary: Part 2: Percentage of Participants With Baseline Blood Phe Levels ≥600 µmol/L who Achieved Phe Levels <600 µmol/L		
End point title	Part 2: Percentage of Participants With Baseline Blood Phe Levels ≥600 µmol/L who Achieved Phe Levels <600 µmol/L	
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 3 and 4 was calculated as the average of blood Phe levels collected during the Week 3-4 analysis visit window. FAS included all participants who were randomized and took at least 1 dose of study drug in Part 2. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.	
End point type	Secondary	
End point timeframe	Weeks 3 and 4 (average of the 2-week period)	
Countable or measurable?	Measurable	
	Part 1 (4 Weeks)	Part 2: (12 Weeks)
End point values	Part 2: Sapropterin	Part 2: Sepiapterin
Number of subjects analysed	42	39
Units: percentage of participants		
Measure Type: Number (Not Applicable)	52.4	89.7
No statistical analyses for this end point		

Secondary: Part 2: Percentage of Participants With Baseline Blood Phe Levels ≥360 µmol/L who Achieved Phe Levels <360 µmol/L in Participants With Phe Reduction From Baseline ≥30% During Part 1	
End point title	Part 2: Percentage of Participants With Baseline Blood Phe Levels ≥360 µmol/L who Achieved Phe Levels <360 µmol/L in Participants With Phe Reduction From Baseline ≥30% During Part 1
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 3 and 4 was calculated as the average of blood Phe levels collected during the Week 3-4 analysis visit window. PAS included all participants who achieved a ≥30% reduction in blood Phe concentrations in Part 1, were randomized, and took at least 1 dose of study drug in Part 2. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.
End point type	Secondary
End point timeframe	Weeks 3 and 4 (average of the 2-week period)

Secondary: Part 2: Percentage of Participants With Baseline Blood Phe Levels ≥360 µmol/L who Achieved Phe Levels <360 µmol/L in Participants With Phe Reduction From Baseline ≥30% During Part 1		
Countable or measurable?	Measurable	
	Part 1 (4 Weeks)	Part 2: (12 Weeks)
End point values	Part 2: Sapropterin	Part 2: Sepiapterin
Number of subjects analysed	51	52
Units: percentage of participants		
Measure Type: Number (Not Applicable)	39.2	69.2
No statistical analyses for this end point		

Secondary: Part 2: Percentage of Participants With Baseline Blood Phe Levels ≥360 µmol/L who Achieved Phe Levels <360 µmol/L		
End point title	Part 2: Percentage of Participants With Baseline Blood Phe Levels ≥360 µmol/L who Achieved Phe Levels <360 µmol/L	
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 3 and 4 was calculated as the average of blood Phe levels collected during the Week 3-4 analysis visit window. FAS included all participants who were randomized and took at least 1 dose of study drug in Part 2. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.	
End point type	Secondary	
End point timeframe	Weeks 3 and 4 (average of the 2-week period)	
Countable or measurable?	Measurable	
	Part 1 (4 Weeks)	Part 2: (12 Weeks)
End point values	Part 2: Sapropterin	Part 2: Sepiapterin
Number of subjects analysed	55	55
Units: percentage of participants		
Measure Type: Number (Not Applicable)	38.2	67.3
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 any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. TEAEs in Part 1 included all AEs occurring after first dose in Part 1 but before first dose in Part 2 for continuing participants, or up to 30 days from the last dose for discontinued participants. TEAEs in Part 2 included all AEs occurring after first randomized dose in Part 2 and up to 30 days from the last dose. A summary of other non-serious AEs and all serious adverse events (SAEs), regardless of causality is located in the 'Reported AE section'. Safety analysis set included all participants who received at least 1 dose of study drug, including during Part 1.

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs)			
End point type	Secondary		
End point timeframe	Up to Week 24		
Countable or measurable?	Countable		
	Part 1 (4 Weeks)	Part 2: (12 Weeks)	
End point values	Part 1: Sepiapterin	Part 2: Sapropterin	Part 2: Sepiapterin
Number of subjects analysed	82	60	62
Units: participants	44	37	41
No statistical analyses for this end point			

Other pre-specified: Part 1: Percentage of Participants With a ≥20% Reduction From Baseline in Blood Phe Level in Response to Sepiapterin		
End point title	Part 1: Percentage of Participants With a ≥20% Reduction From Baseline in Blood Phe Level in Response to Sepiapterin	
End point description	Baseline was defined as the average of Day -1 and Day 1 predose blood Phe concentration values, 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. Safety analysis set included all participants who received at least 1 dose of study drug, including during Part 1.	
End point type	Other pre-specified	
End point timeframe	Weeks 1 and 2 (average of the 2-week period)	
Countable or measurable?	Measurable	
	Part 1 (4 Weeks)	Part 2: (12 Weeks)
End point values	Part 1: Sepiapterin	
Number of subjects analysed	82	
Units: percentage of participants		
Measure Type: Number (Not Applicable)	81.7	
No statistical analyses for this end point		

Other pre-specified: Part 1: Percent Change From Baseline in Blood Phe Levels to Weeks 1 and 2 (Averaged Over a 2-week Period) in Participants who Were on Sapropterin at Screening	
End point title	Part 1: Percent Change From Baseline in Blood Phe Levels to Weeks 1 and 2 (Averaged Over a 2-week Period) in Participants who Were on Sapropterin at Screening
End point description	Baseline was defined as the average of Day -1 and Day 1 predose blood Phe concentration values, 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. Safety analysis set included all participants who received at least 1 dose of study drug, including during Part 1. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.
End point type	Other pre-specified
End point timeframe	Baseline, Weeks 1 and 2 (average of the 2-week period)
Countable or measurable?	Measurable

Other pre-specified: Part 1: Percent Change From Baseline in Blood Phe Levels to Weeks 1 and 2 (Averaged Over a 2-week Period) in Participants who Were on Sapropterin at Screening		
	Part 1 (4 Weeks)	Part 2: (12 Weeks)
End point values	Part 1: Sepiapterin	
Number of subjects analysed	38	
Units: percent change		
Measure Type: Arithmetic Mean (Standard Deviation)	-54.1 ± 38.76	
No statistical analyses for this end point		

Adverse events

Adverse events information	
Timeframe for reporting adverse events	Up to Week 24
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 for adverse event reporting	
Dictionary name	MedDRA
Dictionary version	26.1
Reporting groups	
Reporting group title	Part 1: Sepiapterin
Reporting group description	Participants received 14 days of open-label treatment with sepiapterin administered orally once a day followed by a 14- to 21-day sepiapterin washout.
Reporting group title	Part 2: Sapropterin
Reporting group description	Participants received sapropterin for 4 weeks in Treatment Period 1 or 2.
Reporting group title	Part 2: Sepiapterin
Reporting group description	Participants received sepiapterin for 4 weeks in Treatment Period 1 or 2.

Serious adverse events	Part 1: Sepiapterin	Part 2: Sapropterin	Part 2: Sepiapterin
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	0 / 62 (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: 0%			

Non-serious adverse events	Part 1: Sepiapterin	Part 2: Sapropterin	Part 2: Sepiapterin
Total subjects affected by non serious adverse events			
subjects affected / exposed	44 / 82 (53.66%)	37 / 60 (61.67%)	41 / 62 (66.13%)
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Lymphadenopathy			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	1	0	0
Ear pain			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 82 (8.54%)	1 / 60 (1.67%)	6 / 62 (9.68%)
occurrences all number	8	1	6
Abdominal pain			
subjects affected / exposed	3 / 82 (3.66%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	3	0	1
Faeces discoloured			
subjects affected / exposed	2 / 82 (2.44%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	2	0	0
Faeces pale			
subjects affected / exposed	2 / 82 (2.44%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	2	0	1
Flatulence			
subjects affected / exposed	2 / 82 (2.44%)	1 / 60 (1.67%)	1 / 62 (1.61%)

occurrences all number	2	1	1
Frequent bowel movements			
subjects affected / exposed	2 / 82 (2.44%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	2	0	0
Vomiting			
subjects affected / exposed	2 / 82 (2.44%)	2 / 60 (3.33%)	2 / 62 (3.23%)
occurrences all number	2	2	2
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	1	0	0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	1	0	0
Nausea			
subjects affected / exposed	1 / 82 (1.22%)	2 / 60 (3.33%)	6 / 62 (9.68%)
occurrences all number	1	2	6
Oral mucosal erythema			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	1	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 82 (0.00%)	2 / 60 (3.33%)	3 / 62 (4.84%)
occurrences all number	0	2	3
Abdominal discomfort			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Abdominal distension			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Constipation			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Colitis ulcerative			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
Gingival bleeding			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0

Irritable bowel syndrome			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 82 (4.88%)	1 / 60 (1.67%)	2 / 62 (3.23%)
occurrences all number	4	1	2
Hunger			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	1	0	0
Pyrexia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	3 / 62 (4.84%)
occurrences all number	1	0	3
Secretion discharge			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 82 (7.32%)	9 / 60 (15.00%)	8 / 62 (12.90%)
occurrences all number	6	9	11
Nasopharyngitis			
subjects affected / exposed	5 / 82 (6.10%)	4 / 60 (6.67%)	5 / 62 (8.06%)
occurrences all number	5	5	5
Conjunctivitis			
subjects affected / exposed	2 / 82 (2.44%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	2	1	0
Pneumonia			
subjects affected / exposed	2 / 82 (2.44%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	2	1	0
Paronychia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	1	0	1
Respiratory tract infection viral			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 82 (0.00%)	2 / 60 (3.33%)	3 / 62 (4.84%)

occurrences all number	0	2	3
Bronchitis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	2 / 62 (3.23%)
occurrences all number	0	0	2
Gastroenteritis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Molluscum contagiosum			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Oral herpes			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	2
Rhinitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	1 / 62 (1.61%)
occurrences all number	0	1	1
Viral infection			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	1 / 62 (1.61%)
occurrences all number	0	1	1
Viral rhinitis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Gastritis viral			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0

Gastroenteritis viral			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
Pertussis			
subjects affected / exposed	0 / 82 (0.00%)	2 / 60 (3.33%)	0 / 62 (0.00%)
occurrences all number	0	2	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	1	0	0
Skin injury			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	1	0	0
Arthropod bite			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Injury			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Tooth fracture			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Contusion			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
Joint dislocation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
Ligament sprain			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 82 (1.22%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	1	1	0
Urine analysis abnormal			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	1	0	1
Platelet count decreased			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
Urinary sediment present			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	1	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 82 (2.44%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	2	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 82 (12.20%)	8 / 60 (13.33%)	5 / 62 (8.06%)
occurrences all number	12	9	7
Disturbance in attention			
subjects affected / exposed	1 / 82 (1.22%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	1	1	0
Dizziness			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	1	0	0
Epistaxis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	3
Psychiatric disorders			
Depressed mood			

subjects affected / exposed	2 / 82 (2.44%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	2	0	0
Aggression			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	1 / 62 (1.61%)
occurrences all number	0	1	1
Anxiety			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	1 / 62 (1.61%)
occurrences all number	0	1	1
Emotional disorder			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Mood swings			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Anger			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Leukocyturia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences all number	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 82 (3.66%)	1 / 60 (1.67%)	1 / 62 (1.61%)
occurrences all number	3	1	1
Rhinorrhoea			
subjects affected / exposed	2 / 82 (2.44%)	2 / 60 (3.33%)	2 / 62 (3.23%)
occurrences all number	2	2	2
Oropharyngeal pain			
subjects affected / exposed	1 / 82 (1.22%)	2 / 60 (3.33%)	1 / 62 (1.61%)
occurrences all number	1	2	1
Tonsillar inflammation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0

Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	1	0
Rash erythematous			
subjects affected / exposed	0 / 82 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences all number	0	2	0
Vascular disorders			
Diastolic hypotension			
subjects affected / exposed	1 / 82 (1.22%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences all number	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 Mar 2024	It included following changes: - Additional subsections were added to provide additional benefit-risk information. - Primary endpoint was reworded for clarity. - Inclusion criterion was updated to provide further detail around incapacitated adults. - Inclusion criterion was updated to remove the word "uncontrolled." - Inclusion criterion was updated for consistency with Clinical Trial Facilitation Group (CTFG). - Exclusion criterion was updated to include ingredients and excipients. - Restriction around consumption of substrates and inhibitor of breast cancer resistance protein (BCRP) transporters was removed. - "Review of completed dosing diaries" was added as a measurement of compliance. - A new section was added to provide details for expedited reporting of suspected unexpected serious adverse reactions (SUSARs). - Additional detail was added around the analysis methods. - Additional statement was added around compliance with European Union (EU) Regulation No. 536/2014. - Record retention periods were updated.
11 Apr 2024	It included following changes: - Clarified that the maximum washout period for Part 1 was 21 days. - Clarified that each washout period in Part 2 consisted of 14 days (+3-day window). - Clarified the minimum and maximum duration of the Dietary Control Observation Period. - Inclusion criterion was updated to remove reference to "incapacitated adults." - Exclusion criterion was updated to specifically exclude "incapacitated adults." - Definition of Primary Analysis Set (PAS) was added. - Additional details were added to clarify analysis of efficacy endpoints. The definition for baseline blood Phe for each part and period was also clarified.
06 Sep 2024	It included following changes: - Added that the biochemically diagnosed classical PKU population would be capped at 30% in the Safety Analysis Set. - A +1-day window was added for virtual visits. - Explanation for the selection of the PAS was added. - Added acceptable methods for disposing of (destroying) study drug. - Indicated that Part 1, consisting of the open-label sepiapterin responsiveness test and sepiapterin washout period, might last up to 35 days. - Updated language regarding childhood vaccination and coronavirus disease 2019 (COVID-19) vaccination. - Updated to state that the Dietary Control Observation Period was 24 to 30 days.

Interruptions (globally)

Were there any global interruptions to the trial? No

More information
Limitations and caveats
Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.
None reported

CTIS	
CTIS ID	2023-506238-61-00
Additional Results Analysis Information	
Additional Information about the clinical trial	