Clinical trial results:
A Phase IV Open-Label, Single-Cohort Study of the Long-Term Neurocognitive Outcomes in 4 to 5 Year-Old Children with Phenylketonuria Treated with Sapropterin Dihydrochloride (Kuvan®) for 7 Years.

Summary

EudraCT number	2009-015844-41
Trial protocol	GB DE IT ES
Global end of trial date	04 January 2023

Results information

Result version number	v1 (current)
This version publication date	26 November 2023
First version publication date	26 November 2023
Summary attachment (see zip file)	BMN 162-502_Endpoint_Screenshot (BMN 162-502_Endpoint_Screenshot.pdf)

Trial information

Trial identification

Sponsor protocol code	EMR700773-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01965912
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioMarin Pharmaceutical Inc
Sponsor organisation address	105 Digital Drive, Novato, United States, 94949
Public contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., MedInfo@bmrn.com
Scientific contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., MedInfo@bmrn.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	04 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2023
Global end of trial reached?	Yes
Global end of trial date	04 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the long-term neurocognitive (NC) outcomes in children with hyperphenylalaninemia (HPA) due to phenylketonuria (PKU) treated with Kuvan® and a phenylalanine (Phe)-restricted diet for 7 years.

Protection of trial subjects:

The study was conducted in compliance with the protocol, with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), and with all applicable Regulatory Authority requirements and national laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	34
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)	0
Children (2-11 years)	34
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multi-center study conducted at 12 study centers in four countries Germany (2), Italy (3), Spain (3) and the United Kingdom (4).

Pre-assignment

Screening details:

A total of 50 subjects were screened to participate in the study, 16 subjects did not meet the eligibility criteria and were considered screen failures and 34 were enrolled in the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Kuvan

Arm description:

Kuvan® oral soluble tablet will be administered once daily along with Phenylalanine-restricted diet for a period of 7 years. Dosage of Kuvan® could range from 5 to 20 milligram per kilogram per day (mg/kg/day), as per Summary of Product Characteristics (SmPC).

Arm type	Experimental
Investigational medicinal product name	Kuvan
Investigational medicinal product code	
Other name	Sapropterin dihydrochloride
Pharmaceutical forms	Soluble tablet
Routes of administration	Oral use

Dosage and administration details:

Kuvan was administered dissolved in water orally once daily. During the study period, the Kuvan dose administered was adjusted between 5 and 20 mg/kg/day, following recommendations of the SmPC. The aim of the dose adjustment was to fulfill the therapeutic goal: maintain, by adjustment of dietary Phe intake and/or Kuvan dosage, the blood Phe levels within the recommended target range of ≥120 to <360 µmol/L. Total daily dose was adjusted according to body weight every 3 months if necessary.

Number of subjects in period 1	Kuvan
Started	34
Completed	32
Not completed	2
Consent withdrawn by subject	1
Due to Kuvan having no beneficial effect after 4 m	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	34	34	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	4.91		
standard deviation	± 0.737	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	17	17	
Race Units: Subjects			
White	33	33	
Black or African American	0	0	
Asian	1	1	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Other	0	0	
Country Units: Subjects			
Germany	3	3	
Italy	7	7	
Spain	11	11	
United Kingdom	13	13	
Height Units: cm			
arithmetic mean	108.99		
standard deviation	± 6.540	-	
Weight Units: kg			
arithmetic mean	19.76		
standard deviation	± 3.928	-	
BMI			
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	16.50		
standard deviation	± 1.967	-	

Subject analysis sets	
Subject analysis set title	Naive Subjects
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects that had taken at least one dose of study treatment (Kuvan) on or after Day 1 visit of study period were included in the ITT analysis set.

Subjects were classified as naïve, if on the eCRF page "Medical History of PKU" [Item 7] "Was the subject pre-treated with BH4/Kuvan?" was recorded "No."

Subject analysis set title	Previously Treated
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects were classified as previously treated, if on the eCRF page "Medical History of PKU" [Item 7] "Was the subject pre-treated with BH4/Kuvan?" was recorded "Yes."

Reporting group values	Naive Subjects	Previously Treated	
Number of subjects	11	23	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	5.15	4.79	
standard deviation	± 0.800	± 0.692	
Gender categorical Units: Subjects			
Female	6	11	
Male	5	12	
Race Units: Subjects			
White	10	23	
Black or African American	0	0	
Asian	1	0	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Other	0	0	
Country Units: Subjects			
Germany	0	3	
Italy	3	4	
Spain	0	11	
United Kingdom	8	5	
Height Units: cm			
arithmetic mean	111.96	107.57	
standard deviation	± 7.752	± 5.505	
Weight Units: kg			
arithmetic mean	22.51	18.45	
standard deviation	± 4.671	±	
BMI			
Body Mass Index (BMI)			

Units: kg/m^2			
arithmetic mean	17.81	15.88	
standard deviation	± 2.384	± 1.400	

End points

End points reporting groups

Reporting group title	Kuvan

Reporting group description:

Kuvan® oral soluble tablet will be administered once daily along with Phenylalanine-restricted diet for a period of 7 years. Dosage of Kuvan® could range from 5 to 20 milligram per kilogram per day (mg/kg/day), as per Summary of Product Characteristics (SmPC).

Subject analysis set title	Naive Subjects
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects that had taken at least one dose of study treatment (Kuvan) on or after Day 1 visit of study period were included in the ITT analysis set.

Subjects were classified as naïve, if on the eCRF page "Medical History of PKU" [Item 7] "Was the subject pre-treated with BH4/Kuvan?" was recorded "No."

Subject analysis set title	Previously Treated
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects were classified as previously treated, if on the eCRF page "Medical History of PKU" [Item 7] "Was the subject pre-treated with BH4/Kuvan?" was recorded "Yes."

Primary: Mean Full Scale Intelligence Quotient (FSIQ) Score of the Wechsler Intelligence Scale for Children (WISC)-IV

End point title	Mean Full Scale Intelligence Quotient (FSIQ) Score of the Wechsler Intelligence Scale for Children (WISC)-IV

End point description:

IQ scores of the general population have a normal distribution and are standardized for age to have an average of 100 points (±15) (13;14). IQ between 85 and 115 and are considered to have a normal IQ, i.e., within 1 standard deviation (SD) of the norm. IQ scores between 70 and 85 are considered as borderline intellectual functioning, and mental retardation is diagnosed when IQ scores are below -2 SD (<70) (13;14).

Overall: Year 2 Full Scale IQ (n=32), Year 4 Full Scale IQ (n=32), Year 7 Full Scale IQ (n=31)
Naïve Subjects: Year 2 Full Scale IQ (n=9), Year 4 Full Scale IQ (n=9), Year 7 Full Scale IQ (n=9)
Previously Treated: Year 2 Full Scale IQ (n=23), Year 4 Full Scale IQ (n=23), Year 7 Full Scale IQ (n=22)

End point type	Primary

End point timeframe:

Up to 7 Years.

End point values	Kuvan	Naive Subjects	Previously Treated	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	9	23	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Year 2 Full Scale IQ	99.2 (± 12.92)	95.7 (± 16.24)	100.6 (± 11.49)	
Year 4 Full Scale IQ	101.9 (± 13.93)	99.7 (± 19.87)	102.7 (± 11.28)	
Year 7 Full Scale IQ	99.8 (± 14.63)	95.8 (± 20.10)	101.4 (± 11.92)	

Statistical analyses

Statistical analysis title	Change from BL in IQ scores- Last 2 yrs FSIQ diffe

Statistical analysis description:

Last 2 years FSIQ Difference- ITT Analysis Set

Comparison groups	Naive Subjects v Previously Treated
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.028 [1]
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	-0.4

Notes:

[1] - p-values obtained from a paired difference between the last two available FSIQ assessments that were at least two years apart for each subject.

Secondary: Height compared to the 2006 World Health Organization (WHO) Growth Standards at each timepoint.

End point title	Height compared to the 2006 World Health Organization (WHO) Growth Standards at each timepoint.

End point description:

Absolute values represent the differences between WHO Growth Standards and study subjects. Results are expressed in standard deviation score (SDS, also referred to as Z-score).

Baseline is defined as last value prior to or on first Kuvan treatment within study.

End of Treatment (EOT) is defined as last post-Baseline value for subjects who terminated Kuvan treatment

Standard Deviation Scores (SDS) calculated using 2006 WHO Child Growth Standards and the 2007 WHO SAS macro
package.

Baseline (BL)

ITT Analysis Set population: Boys (n=17) and Girls (n=17).

End point type	Secondary

End point timeframe:

Every 6 months from Baseline through the end of the study or ET.

End of Treatment (ET).

End point values	Kuvan			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: SDS				
arithmetic mean (standard deviation)				
Height SDS: Baseline-Absolute: Boys (n=17)	0.08 (± 1.095)			
Height SDS: Month 6-Absolute: Boys (n=17)	0.07 (± 1.035)			
Height SDS: Month 6-Change from BL: Boys (n=17)	-0.01 (± 0.472)			
Height SDS: Month 12-Absolute: Boys (n=17)	0.17 (± 0.947)			
Height SDS: Month 12-Change from BL: Boys (n=17)	0.09 (± 0.581)			
Height SDS: Month 18-Absolute: Boys (n=16)	0.16 (± 0.864)			
Height SDS: Month 18-Change from BL: Boys (n=16)	0.23 (± 0.439)			
Height SDS: Month 24-Absolute: Boys (n=16)	0.10 (± 0.855)			
Height SDS: Month 24-Change from BL: Boys (n=16)	0.16 (± 0.640)			
Height SDS: Month 30-Absolute: Boys (n=16)	-0.00 (± 0.961)			
Height SDS: Month 30-Change from BL: Boys (n=16)	0.06 (± 0.653)			
Height SDS: Month 36-Absolute: Boys (n=16)	0.10 (± 0.876)			
Height SDS: Month 36-Change from BL: Boys (n=16)	0.17 (± 0.668)			
Height SDS: Month 42-Absolute: Boys (n=16)	0.16 (± 0.906)			
Height SDS: Month 42-Change from BL: Boys (n=16)	0.22 (± 0.640)			
Height SDS: Month 48-Absolute: Boys (n=16)	0.14 (± 0.959)			
Height SDS: Month 48-Change from BL: Boys (n=16)	0.20 (± 0.671)			
Height SDS: Month 54-Absolute: Boys (n=15)	0.14 (± 0.887)			
Height SDS: Month 54-Change from BL: Boys (n=15)	0.22 (± 0.721)			
Height SDS: Month 60-Absolute: Boys (n=15)	0.20 (± 0.885)			
Height SDS: Month 60-Change from BL: Boys (n=15)	0.28 (± 0.760)			
Height SDS: Month 66-Absolute: Boys (n=16)	0.16 (± 0.827)			
Height SDS: Month 66-Change from BL: Boys (n=16)	0.22 (± 0.730)			
Height SDS: Month 72-Absolute: Boys (n=12)	0.01 (± 0.903)			
Height SDS: Month 72-Change from BL: Boys (n=12)	0.19 (± 0.720)			
Height SDS: Month 78-Absolute: Boys (n=13)	0.07 (± 0.809)			
Height SDS: Month 78-Change from BL: Boys (n=13)	0.14 (± 0.688)			
Height SDS: Month 84-Absolute: Boys (n=15)	0.31 (± 0.940)			

Height SDS: Month 84-Change from BL: Boys (n=15)	0.44 (± 0.759)			
Height SDS: End of treatment-Absolute: Boys(n=17	0.42 (± 1.041)			
Height SDS: EOT-Change from Baseline: Boys (n=17	0.34 (± 0.795)			
Height SDS: Baseline-Absolute: Girls (n=17)	-0.02 (± 0.818)			
Height SDS: Month 6-Absolute: Girls (n=15)	0.20 (± 0.865)			
Height SDS: Month 6-Change from BL: Girls (n=15)	0.26 (± 0.421)			
Height SDS: Month 12-Absolute: Girls (n=16)	0.15 (± 0.867)			
Height SDS: Month 12-Change from BL: Girls (n=16	0.24 (± 0.326)			
Height SDS: Month 18-Absolute: Girls (n=16)	0.20 (± 0.860)			
Height SDS: Month 18-Change from BL: Girls (n=16	0.29 (± 0.423)			
Height SDS: Month 24-Absolute: Girls (n=16)	0.16 (± 0.890)			
Height SDS: Month 24-Change from BL: Girls (n=16	0.25 (± 0.425)			
Height SDS: Month 30-Absolute: Girls (n=16)	0.23 (± 0.946)			
Height SDS: Month 30-Change from BL: Girls (n=16	0.32 (± 0.504)			
Height SDS: Month 36-Absolute: Girls (n=16)	0.16 (± 0.904)			
Height SDS: Month 36-Change from BL: Girls (n=16	0.25 (± 0.469)			
Height SDS: Month 42-Absolute: Girls (n=16)	0.12 (± 0.889)			
Height SDS: Month 42-Change from BL: Girls (n=16	0.21 (± 0.464)			
Height SDS: Month 48-Absolute: Girls (n=16)	0.08 (± 0.943)			
Height SDS: Month 48-Change from BL: Girls (n=16	0.17 (± 0.462)			
Height SDS: Month 54-Absolute: Girls (n=15)	-0.05 (± 0.814)			
Height SDS: Month 54-Change from BL: Girls (n=15	0.14 (± 0.520)			
Height SDS: Month 60-Absolute: Girls (n=15)	-0.12 (± 0.798)			
Height SDS: Month 60-Change from BL: Girls (n=15	0.07 (± 0.580)			
Height SDS: Month 66-Absolute: Girls (n=16)	0.06 (± 0.937)			
Height SDS: Month 66-Change from BL: Girls (n=16	0.16 (± 0.586)			
Height SDS: Month 72-Absolute: Girls (n=14)	0.15 (± 0.807)			
Height SDS: Month 72-Change from BL: Girls (n=14	0.10 (± 0.601)			
Height SDS: Month 78-Absolute: Girls (n=14)	0.42 (± 0.815)			
Height SDS: Month 78-Change from BL: Girls (n=14	0.45 (± 0.626)			
Height SDS: Month 84-Absolute: Girls (n=16)	0.20 (± 0.952)			

Height SDS: Month 84-Change from BL: Girls (n=16)	0.29 (± 0.624)			
Height SDS:End of treatment-Absolute: Girls(n=17	0.26 (± 0.960)			
Height SDS: EOT-Change from Baseline: Girls(n=17)	0.28 (± 0.606)			

Statistical analyses

No statistical analyses for this end point

Secondary: Weight compared to the 2006 World Health Organization (WHO) Growth Standards at each timepoint.

End point title	Weight compared to the 2006 World Health Organization (WHO) Growth Standards at each timepoint.

End point description:

ITT Analysis Set: Boys (n=17) & Girls (n=17).

Refer attached file for Values of month 72, 78 and 84 for both boys and girls as number of subject analyzed is zero.

End point type	Secondary

End point timeframe:

Upto 7 years

End point values	Kuvan			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: SDS				
arithmetic mean (standard deviation)				
Weight SDS: Baseline-Absolute: Boys (n=17)	0.41 (± 1.192)			
Weight SDS: Month 6-Absolute: Boys (n=17)	0.47 (± 1.118)			
Weight SDS: Month 6-Change from BL: Boys (n=17)	0.07 (± 0.243)			
Weight SDS: Month 12-Absolute: Boys (n=17)	0.54 (± 1.095)			
Weight SDS: Month 12-Change from BL: Boys (n=17)	0.13 (± 0.334)			
Weight SDS: Month 18-Absolute: Boys (n=16)	0.50 (± 0.945)			
Weight SDS: Month 18-Change from BL: Boys (n=16)	0.29 (± 0.400)			
Weight SDS: Month 24-Absolute: Boys (n=16)	0.50 (± 0.967)			
Weight SDS: Month 24-Change from BL: Boys (n=16)	0.29 (± 0.558)			
Weight SDS: Month 30-Absolute: Boys (n=16)	0.46 (± 0.962)			
Weight SDS: Month 30-Change from BL: Boys (n=16)	0.25 (± 0.532)			

Weight SDS: Month 36-Absolute: Boys (n=16)	0.55 (± 0.918)			
Weight SDS: Month 36-Change from BL: Boys (n=16)	0.34 (± 0.550)			
Weight SDS: Month 42-Absolute: Boys (n=16)	0.70 (± 0.962)			
Weight SDS: Month 42-Change from BL: Boys (n=16)	0.49 (± 0.657)			
Weight SDS: Month 48-Absolute: Boys (n=16)	0.71 (± 0.976)			
Weight SDS: Month 48-Change from BL: Boys (n=16)	0.49 (± 0.695)			
Weight SDS: Month 54-Absolute: Boys (n=11)	0.62 (± 0.877)			
Weight SDS: Month 54-Change from BL: Boys (n=11)	0.82 (± 0.686)			
Weight SDS: Month 60-Absolute: Boys (n=8)	0.50 (± 1.119)			
Weight SDS: Month 60-Change from BL: Boys (n=8)	0.96 (± 0.795)			
Weight SDS: Month 66-Absolute: Boys (n=7)	0.46 (± 0.811)			
Weight SDS: Month 66-Change from BL: Boys (n=7)	0.71 (± 0.466)			
Weight SDS: End of treatment-Absolute: Boys(n=17)	1.01 (± 1.060)			
Weight SDS: EOT-Change from Baseline: Boys (n=17)	0.60 (± 0.684)			
Weight SDS: Baseline-Absolute: Girls (n=17)	0.60 (± 1.065)			
Weight SDS: Month 6-Absolute: Girls (n=15)	0.55 (± 1.014)			
Weight SDS: Month 6-Change from BL: Girls (n=15)	0.10 (± 0.217)			
Weight SDS: Month 12-Absolute: Girls (n=16)	0.69 (± 1.033)			
Weight SDS: Month 12-Change from BL: Girls (n=16)	0.20 (± 0.245)			
Weight SDS: Month 18-Absolute: Girls (n=16)	0.80 (± 0.963)			
Weight SDS: Month 18-Change from BL: Girls (n=16)	0.31 (± 0.337)			
Weight SDS: Month 24-Absolute: Girls (n=16)	0.76 (± 1.053)			
Weight SDS: Month 24-Change from BL: Girls (n=16)	0.28 (± 0.422)			
Weight SDS: Month 30-Absolute: Girls (n=16)	0.79 (± 1.064)			
Weight SDS: Month 30-Change from BL: Girls (n=16)	0.30 (± 0.516)			
Weight SDS: Month 36-Absolute: Girls (n=16)	0.74 (± 1.122)			
Weight SDS: Month 36-Change from BL: Girls (n=16)	0.25 (± 0.520)			
Weight SDS: Month 42-Absolute: Girls (n=16)	0.78 (± 1.165)			
Weight SDS: Month 42-Change from BL: Girls (n=16)	0.29 (± 0.539)			
Weight SDS: Month 48-Absolute: Girls (n=14)	0.67 (± 1.287)			
Weight SDS: Month 48-Change from BL: Girls (n=14)	0.25 (± 0.602)			

Weight SDS: Month 54-Absolute: Girls (n=10)	0.61 (± 0.490)			
Weight SDS: Month 54-Change from BL: Girls (n=10)	0.20 (± 0.590)			
Weight SDS: Month 60-Absolute: Girls (n=8)	0.61 (± 0.417)			
Weight SDS: Month 60-Change from BL: Girls (n=8)	0.16 (± 0.570)			
Weight SDS: Month 66-Absolute: Girls (n=7)	1.19 (± 1.046)			
Weight SDS: Month 66-Change from BL: Girls (n=7)	0.48 (± 0.666)			
Weight SDS: End of treatment-Absolute: Girls(n=17)	0.82 (± 1.112)			
Weight SDS: EOT-Change from Baseline: Girls(n=17)	0.22 (± 0.588)			

Statistical analyses

No statistical analyses for this end point

Secondary: Blood levels of tyrosine & tryptophan compared to age-related norms.

End point title	Blood levels of tyrosine & tryptophan compared to age-related norms.

End point description:

Tyrosine (the precursor of dopamine and an essential amino-acid in PKU patients measured as part of standard-of-care to verify if dietary intake of Tyr is adequate).

Tryptophan (an essential amino acid and precursor of the neurotransmitter serotonin).

End point type	Secondary

End point timeframe:

Screening, Every 6 months and at ET Visit.

End point values	Kuvan			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: µmol/L				
arithmetic mean (standard deviation)				
Tyrosine: Baseline-Absolute (n=31)	61.73 (± 41.353)			
Tyrosine: Month 6-Absolute (n=31)	65.39 (± 37.916)			
Tyrosine: Month 6-Change from Baseline (n=28)	4.31 (± 40.139)			
Tyrosine: Month 12-Absolute (n=32)	76.42 (± 48.715)			
Tyrosine: Month 12-Change from Baseline (n=29)	10.57 (± 36.377)			
Tyrosine: Month 18-Absolute (31)	69.12 (± 38.494)			
Tyrosine: Month 18-Change from Baseline (n=29)	8.54 (± 31.130)			

Tyrosine: Month 24-Absolute (n=31)	73.47 (± 48.148)			
Tyrosine: Month 24-Change from Baseline (n=28)	12.00 (± 35.216)			
Tyrosine: Month 30-Absolute (n=30)	72.73 (± 37.864)			
Tyrosine: Month 30- Change from Baseline (n=27)	10.30 (± 23.656)			
Tyrosine: Month 36-Absolute (n=32)	68.91 (± 39.842)			
Tyrosine: Month 36- Change from Baseline (n=29)	7.90 (± 37.220)			
Tyrosine: Month 42-Absolute (n=31)	71.54 (± 42.393)			
Tyrosine: Month 42-Change from Baseline (n=28)	9.67 (± 35.511)			
Tyrosine: Month 48-Absolute (n=32)	67.55 (± 37.065)			
Tyrosine: Month 48-Change from Baseline (n=29)	8.25 (± 30.397)			
Tyrosine: Month 54-Absolute (n=29)	58.52 (± 26.076)			
Tyrosine: Month 54-Change from Baseline (n=28)	4.99 (± 36.114)			
Tyrosine: Month 60-Absolute (n=27)	60.99 (± 24.068)			
Tyrosine: Month 60-Change from Baseline (n=26)	2.83 (± 32.292)			
Tyrosine: Month 66-Absolute (n=28)	61.00 (± 29.208)			
Tyrosine: Month 66-Change from Baseline (n=26)	4.36 (± 26.800)			
Tyrosine: Month 72-Absolute (n=19)	52.87 (± 23.427)			
Tyrosine: Month 72-Change from Baseline (n=17)	-3.78 (± 29.404)			
Tyrosine: Month 78-Absolute (n=22)	58.50 (± 21.035)			
Tyrosine: Month 78-Change from Baseline (n=20)	8.32 (± 27.904)			
Tyrosine: Month 84-Absolute (n=25)	62.85 (± 22.573)			
Tyrosine: Month 84-Change from Baseline (n=22)	7.59 (± 27.905)			
Tyrosine: End of Treatment- Absolute (n=34)	61.97 (± 24.186)			
Tyrosine:End of Treatment-Change from BL (n=31)	-1.56 (± 35.418)			
Tryptophane: Baseline-Absolute (n=32)	49.87 (± 21.437)			
Tryptophane: Month 6-Absolute (n=31)	58.39 (± 18.360)			
Tryptophane: Month 6-Change from Baseline (n=29)	6.90 (± 21.379)			
Tryptophane: Month 12-Absolute (n=32)	60.92 (± 18.717)			
Tryptophane: Month 12-Change from Baseline (n=30)	10.68 (± 16.924)			
Tryptophane: Month 18-Absolute (n=31)	56.75 (± 17.500)			
Tryptophane: Month 18-Change from Baseline (n=30)	8.05 (± 23.343)			

Tryptophane: Month 24-Absolute (n=31)	55.48 (± 15.640)			
Tryptophane: Month 24-Change from Baseline (n=29)	7.24 (± 19.228)			
Tryptophane: Month 30-Absolute (n=30)	57.38 (± 16.139)			
Tryptophane: Month 30- Change from Baseline (n=28)	7.74 (± 19.814)			
Tryptophane: Month 36-Absolute (n=32)	57.96 (± 14.691)			
Tryptophane: Month 36- Change from Baseline (n=30)	8.64 (± 21.998)			
Tryptophane: Month 42-Absolute (n=31)	58.48 (± 18.117)			
Tryptophane: Month 42-Change from Baseline (n=29)	8.79 (± 22.865)			
Tryptophane: Month 48-Absolute (n=32)	53.72 (± 12.888)			
Tryptophane: Month 48-Change from Baseline (n=30)	5.58 (± 20.633)			
Tryptophane: Month 54-Absolute (n=29)	51.76 (± 12.437)			
Tryptophane: Month 54-Change from Baseline (n=29)	5.11 (± 23.255)			
Tryptophane: Month 60-Absolute (n=27)	55.59 (± 11.446)			
Tryptophane: Month 60-Change from Baseline (n=27)	8.17 (± 21.023)			
Tryptophane: Month 66-Absolute (n=28)	51.96 (± 10.654)			
Tryptophane: Month 66-Change from Baseline (n=27)	3.11 (± 17.442)			
Tryptophane: Month 72-Absolute ((n=19)	50.28 (± 10.626)			
Tryptophane: Month 72-Change from Baseline ((n=18)	2.90 (± 18.653)			
Tryptophane: Month 78-Absolute (n=22)	54.59 (± 10.706)			
Tryptophane: Month 78-Change from Baseline ((n=21)	9.19 (± 16.714)			
Tryptophane: Month 84-Absolute ((n=25)	53.47 (± 12.106)			
Tryptophane: Month 84-Change from Baseline (n=23)	8.88 (± 19.700)			
Tryptophane: End of Treatment-Absolute (n=34)	55.45 (± 13.543)			
Tryptophane:End of Treatment-Change from BL (n=32)	5.12 (± 20.673)			

Statistical analyses

No statistical analyses for this end point

Secondary: Blood levels of pre-albumin compared to age-related norms

End point title	Blood levels of pre-albumin compared to age-related norms

End point description:

End point type	Secondary

End point timeframe:

Baseline, every 6 months and end of treatment.

End point values	Kuvan			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: g/L				
arithmetic mean (standard deviation)				
Prealbumin: Baseline- Absolute (n=32)	0.174 (± 0.0391)			
Prealbumin: Month 6-Absolute (n=31)	0.196 (± 0.0478)			
Prealbumin: Month 6-Change from Baseline (n=29)	0.024 (± 0.0521)			
Prealbumin: Month 12-Absolute (n=32)	0.198 (± 0.0341)			
Prealbumin: Month 12-Change from Baseline (n=30)	0.023 (± 0.0351)			
Prealbumin: Month 18-Absolute (n=32)	0.203 (± 0.0304)			
Prealbumin: Month 18-Change from Baseline (n=30)	0.030 (± 0.0376)			
Prealbumin: Month 24-Absolute (n=30)	0.193 (± 0.0321)			
Prealbumin: Month 24-Change from Baseline (n=28)	0.022 (± 0.0403)			
Prealbumin: Month 30-Absolute (n=30)	0.209 (± 0.0359)			
Prealbumin: Month 30-Change from Baseline (n=28)	0.036 (± 0.0334)			
Prealbumin: Month 36-Absolute (n=32)	0.203 (± 0.0302)			
Prealbumin: Month 36-Change from Baseline (n=30)	0.029 (± 0.0390)			
Prealbumin: Month 42-Absolute (n=32)	0.211 (± 0.0319)			
Prealbumin: Month 42-Change from Baseline (n=30)	0.038 (± 0.0451)			
Prealbumin: Month 48-Absolute (n=31)	0.205 (± 0.0284)			
Prealbumin: Month 48-Change from Baseline (n=29)	0.037 (± 0.0388)			
Prealbumin: Month 54-Absolute (n=30)	0.204 (± 0.0284)			
Prealbumin: Month 54-Change from Baseline (n=30)	0.033 (± 0.0389)			
Prealbumin: Month 60-Absolute (n=27)	0.208 (± 0.0327)			
Prealbumin: Month 60-Change from Baseline (n=27)	0.038 (± 0.0427)			
Prealbumin: Month 66-Absolute (n=30)	0.214 (± 0.0388)			
Prealbumin: Month 66-Change from Baseline (n=28)	0.036 (± 0.0359)			

Prealbumin: Month 72-Absolute (n=20)	0.220 (± 0.0369)			
Prealbumin: Month 72-Change from Baseline (n=18)	0.046 (± 0.0473)			
Prealbumin: Month 78-Absolute (n=22)	0.216 (± 0.0347)			
Prealbumin: Month 78-Change from Baseline (n=20)	0.046 (± 0.0429)			
Prealbumin: Month 84-Absolute (n=27)	0.226 (± 0.0332)			
Prealbumin: Month 84-Change from Baseline (n=25)	0.053 (± 0.0350)			
Prealbumin: End of Treatment-Absolute (n=34)	0.221 (± 0.0336)			
Prealbumin: EOT-Change from Baseline (n=32)	0.044 (± 0.0384)			

Statistical analyses

No statistical analyses for this end point

Secondary: Blood levels of methylmalonic acid compared to age-related norms.

End point title	Blood levels of methylmalonic acid compared to age-related norms.
End point description:	
End point type	Secondary
End point timeframe:	
Up to 7 years.	

End point values	Kuvan			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: nmol/L				
arithmetic mean (standard deviation)				
Methylmalonic acid: Baseline-Absolute (n=32)	143.00 (± 50.931)			
Methylmalonic acid: Month 6-Absolute (n=31)	129.19 (± 51.688)			
Methylmalonic acid: Month 6-Change from BL (n=29)	-16.14 (± 44.051)			
Methylmalonic acid: Month 12-Absolute (n=31)	139.61 (± 50.302)			
Methylmalonic acid: Month 12-Change from BL (n=29)	-4.76 (± 49.530)			
Methylmalonic acid: Month 18-Absolute (n=31)	140.90 (± 58.793)			
Methylmalonic acid: Month 18-Change from BL (n=30)	-6.63 (± 52.901)			
Methylmalonic acid: Month 24-Absolute (n=31)	127.90 (± 49.556)			

Methylmalonic acid: Month 24-Change from BL (n=29)	-15.17 (± 42.777)			
Methylmalonic acid: Month 30-Absolute (n=30)	127.53 (± 45.890)			
Methylmalonic acid: Month 30-Change from BL (n=28)	-16.32 (± 45.622)			
Methylmalonic acid: Month 36-Absolute (n=32)	136.97 (± 55.907)			
Methylmalonic acid: Month 36-Change from BL (n=30)	-4.00 (± 53.718)			
Methylmalonic acid: Month 42-Absolute (n=31)	135.55 (± 46.326)			
Methylmalonic acid: Month 42-Change from BL (n=29)	-7.45 (± 53.348)			
Methylmalonic acid: Month 48-Absolute (n=32)	133.63 (± 48.463)			
Methylmalonic acid: Month 48-Change from BL (n=30)	-8.50 (± 50.078)			
Methylmalonic acid: Month 54-Absolute (n=29)	129.31 (± 38.843)			
Methylmalonic acid: Month 54-Change from BL (n=29)	-14.10 (± 49.861)			
Methylmalonic acid: Month 60-Absolute (n=27)	137.07 (± 45.473)			
Methylmalonic acid: Month 60-Change from BL (n=27)	-2.96 (± 53.840)			
Methylmalonic acid: Month 66-Absolute (n=27)	139.59 (± 45.487)			
Methylmalonic acid: Month 66-Change from BL (n=26)	-7.04 (± 48.962)			
Methylmalonic acid: Month 72-Absolute (n=19)	145.05 (± 80.098)			
Methylmalonic acid: Month 72-Change from BL (n=18)	7.17 (± 98.547)			
Methylmalonic acid: Month 78-Absolute (n=22)	153.05 (± 58.359)			
Methylmalonic acid: Month 78-Change from BL (n=21)	6.48 (± 82.927)			
Methylmalonic acid: Month 84-Absolute (n=25)	167.60 (± 69.135)			
Methylmalonic acid: Month 84-Change from BL (n=23)	24.87 (± 80.983)			
Methylmalonic acid:End of Treatment-Absolute(n=34)	162.50 (± 70.984)			
Methylmalonic acid:EOT Change from Baseline (n=32)	20.06 (± 87.214)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intelligence Quotient (IQ) score and sub-scores such as, verbal IQ, performance IQ, Full Scale Intelligence Quotient (FSIQ) of Wechsler Preschool and Primary Scale of Intelligence (WPPSI)-III

End point title	Intelligence Quotient (IQ) score and sub-scores such as, verbal IQ, performance IQ, Full Scale Intelligence Quotient (FSIQ) of Wechsler Preschool and Primary Scale of Intelligence (WPPSI)-III

End point description:

WPPSITM-III (Wechsler Preschool and Primary Scale of Intelligence 3rd edition) for subjects >=4 and <6 years-old at baseline. Scores are: Full Scale IQ (overall score), Verbal IQ and Performance IQ . This validated test has two parts: Part 1 for children aged 2 years 6 months to 3 years 11 months and Part 2 for children 4 years to 7 years and 3 months. The second part of the WPPSITM-III will be used to assess baseline IQ.

Baseline is defined as last value prior to or on first Kuvan treatment within study.

End point type	Secondary

End point timeframe:

At Baseline.

End point values	Kuvan	Naive Subjects	Previously Treated	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	11	23	
Units: Score on a scale				
arithmetic mean (standard deviation)				
WPPSI-III: Full Scale IQ	100.9 (± 13.03)	102.9 (± 12.86)	100.0 (± 13.29)	
WPPSI-III: Verbal IQ	104.2 (± 13.91)	103.9 (± 10.68)	104.4 (± 15.44)	
WPPSI-III: Performance IQ	95.9 (± 12.49)	96.0 (± 14.26)	95.8 (± 11.90)	

Statistical analyses

No statistical analyses for this end point

Secondary: Intelligence Quotient (IQ) score and sub-scores such as verbal comprehension, perceptual reasoning, working memory, and processing speed indexes and Full Scale Intelligence Quotient (FSIQ) of the Wechsler Intelligence Scale for Children (WISC)-IV

End point title	Intelligence Quotient (IQ) score and sub-scores such as verbal comprehension, perceptual reasoning, working memory, and processing speed indexes and Full Scale Intelligence Quotient (FSIQ) of the Wechsler Intelligence Scale for Children (WISC)-IV

End point description:

WISC®-IV (Wechsler Intelligence Scale for Children 4th edition) for children for children aged 6 years to 16 years and 11 months at post-baseline visits.

Year2 Full Scale IQ: Overall(n=32),Naive(n=9)&Previously Treated(n=23)
Year2 Verbal Comprehension Index: Overall(n=32),Naive(n=9)&Previously Treated(n=23)
Year2 Perceptual Reasoning Index: Overall (n=31),Naive (n=9)&Previously Treated(n=22)
Year2 Working Memory Index: Overall (n=31),Naive (n=9)&Previously Treated(n=22)
Year2 Processing Speed Index: Overall(n=32),Naive(n=9)&Previously Treated(n=23)
Year4 Full Scale IQ, Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index, Processing Speed Index: Overall (n=32),Naive (n=9)&Previously Treated(n=23).
Year7 Full Scale IQ, Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index, Processing Speed Index: Overall (n=31),Naive (n=9)&Previously Treated(n=22).

End point type	Secondary

End point timeframe:

At 2, 4, 7 Years.

End point values	Kuvan	Naive Subjects	Previously Treated	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	9	23	
Units: Score on a scale				
arithmetic mean (standard deviation)				
WPPSI-IV: Year 2 Full Scale IQ	99.2 (± 12.92)	95.7 (± 16.24)	100.6 (± 11.49)	
WPPSI-IV: Year 2 Verbal Comprehension Index	104.0 (± 12.36)	98.4 (± 13.91)	106.2 (± 11.28)	
WPPSI-IV: Year 2 Perceptual Reasoning Index	101.4 (± 12.74)	99.8 (± 16.05)	102.0 (± 11.50)	
WPPSI-IV: Year 2 Working Memory Index	93.9 (± 12.40)	91.2 (± 16.69)	95.0 (± 10.44)	
WPPSI-IV: Year 2 Processing Speed Index	94.1 (± 13.70)	94.0 (± 18.19)	94.1 (± 12.01)	
WISC-IV : Year 4 Full Scale IQ	101.9 (± 13.93)	99.7 (± 19.87)	102.7 (± 11.28)	
WISC-IV : Year 4 Verbal Comprehension Index	104.9 (± 12.19)	104.6 (± 18.36)	105.0 (± 9.31)	
WISC-IV : Year 4 Perceptual Reasoning Index	100.4 (± 12.82)	96.7 (± 15.16)	101.8 (± 11.85)	
WISC-IV : Year 4 Working Memory Index	99.0 (± 13.54)	95.3 (± 16.70)	100.4 (± 12.21)	
WISC-IV : Year 4 Processing Speed Index	98.8 (± 15.04)	99.0 (± 20.70)	98.8 (± 12.76)	
WISC-IV : Year 7 Full Scale IQ	99.8 (± 14.63)	95.8 (± 20.10)	101.4 (± 11.92)	
WPPSI-IV: Year 7 Verbal Comprehension Index	100.8 (± 15.51)	99.4 (± 22.42)	101.4 (± 12.29)	
WISC-IV : Year 7 Perceptual Reasoning Index	99.6 (± 13.94)	98.1 (± 22.00)	100.2 (± 9.60)	
WISC-IV : Year 7 Working Memory Index	98.2 (± 13.55)	93.1 (± 21.22)	100.2 (± 8.67)	
WISC-IV : Year 7 Processing Speed Index	99.2 (± 15.29)	94.2 (± 15.11)	101.2 (± 15.23)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FSIQ score and Verbal IQ subscore at 2, 4, and 7 years

End point title	Change from Baseline in FSIQ score and Verbal IQ subscore at 2, 4, and 7 years

End point description:

ITT Analysis Set

Year 2 Full Scale IQ : Overall (n=32), Naïve (n=9), & Previously Treated (n=23)
Year 2 Verbal IQ: Overall (n=32), Naïve (n=9), & Previously Treated (n=23)
Year 4 Full Scale IQ: Overall (n=32), Naïve (n=9), & Previously Treated (n=23)
Year 4 Verbal IQ: Overall (n=32), Naïve (n=9), & Previously Treated (n=23)
Year 7 Full Scale IQ: Overall (n=31), Naïve (n=9), & Previously Treated (n=22)

Year 7 Verbal IQ: Overall (n=31), Naïve (n=9), & Previously Treated (n=22)

End point type	Secondary

End point timeframe:

At 2, 4 and 7 years.

End point values	Kuvan	Naive Subjects	Previously Treated	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	9	23	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Year 2: Full Scale IQ	-1.5 (± 12.87)	-6.9 (± 13.70)	0.6 (± 12.19)	
Year 2: Verbal IQ	-0.5 (± 16.13)	-6.2 (± 15.91)	1.8 (± 16.00)	
Year 4: Full Scale IQ	1.2 (± 14.40)	-2.9 (± 17.69)	2.7 (± 13.00)	
Year 4: Verbal IQ	0.4 (± 14.10)	-0.1 (± 17.10)	0.7 (± 13.18)	
Year 7: Full Scale IQ	-1.0 (± 14.31)	-6.8 (± 16.98)	1.4 (± 12.75)	
Year 7: Verbal IQ	-3.8 (± 16.81)	-5.2 (± 20.99)	-3.3 (± 15.32)	

Statistical analyses

No statistical analyses for this end point

Secondary: Dietary Phe tolerance over the 7-year period

End point title	Dietary Phe tolerance over the 7-year period

End point description:

Dietary Phe tolerance over the 7-year period, as represented by the average amount of dietary Phe (mg/kg/day) ingested while maintaining overall control of blood Phe levels within target range of >=120 to <360 µmol/L). The amount of dietary Phe ingested was estimated using the average daily Phe intake based on mean Phe prescription as well as the average daily intake calculated from the 3-day diary bi-annually.

Overall, Naive, & Previously Treated: Phe Intake: Day 1 to M6 (n=33, 10, 23), Phe Intake: M6 to M12 (n=33, 10, 23), Phe Intake: M12 to M18 (n=31, 9, 22), Phe Intake: M18 to M24 (n=32, 9, 23), Phe Intake: M24 to M30 (n=31, 9, 22), Phe Intake: M30 to M36 (n=32, 9, 23), Phe Intake: M36 to M42 (n=31, 8, 23), Phe Intake: M42 to M48 (n=32, 9, 23), Phe Intake: M48 to M54 (n=32, 9, 23), Phe Intake: M54 to M60 (n=31, 8, 23), Phe Intake: M60 to M66 (n=30, 8, 22), Phe Intake: M66 to M72 (n=30, 8, 22), Phe Intake: M72 to M78 (n=31, 9, 22), Phe Intake: M78 to M84 (n=29, 8, 21).

End point type	Secondary

End point timeframe:

Up to 7 years.

End point values	Kuvan	Naive Subjects	Previously Treated	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	11	23	
Units: mg/day				
arithmetic mean (standard deviation)				
Phe Intake: Day 1 to M6	1053.2 (± 661.32)	871.4 (± 340.99)	1132.3 (± 753.01)	
Phe Intake: M6 to M12	1020.9 (± 598.42)	978.3 (± 314.70)	1039.4 (± 692.23)	
Phe Intake: M12 to M18	1188.1 (± 618.69)	907.9 (± 390.77)	1302.7 (± 664.25)	
Phe Intake: M18 to M24	1212.5 (± 560.49)	1006.0 (± 360.90)	1293.3 (± 609.11)	
Phe Intake: M24 to M30	1196.7 (± 651.83)	967.9 (± 502.57)	1290.4 (± 692.19)	
Phe Intake: M30 to M36	1217.1 (± 583.63)	995.2 (± 525.72)	1304.0 (± 592.83)	
Phe Intake: M36 to M42	1255.8 (± 614.52)	1131.5 (± 273.05)	1299.1 (± 695.46)	
Phe Intake: M42 to M48	1391.5 (± 734.53)	1146.0 (± 353.05)	1487.6 (± 824.99)	
Phe Intake: M48 to M54	1316.4 (± 709.48)	1125.1 (± 336.92)	1391.2 (± 804.48)	
Phe Intake: M54 to M60	1321.9 (± 662.06)	1205.3 (± 423.33)	1362.4 (± 730.78)	
Phe Intake: M60 to M66	1297.5 (± 735.47)	1140.3 (± 273.05)	1354.7 (± 842.18)	
Phe Intake: M66 to M72	1328.7 (± 772.85)	1134.5 (± 406.91)	1399.3 (± 866.06)	
Phe Intake: M72 to M78	1377.9 (± 774.21)	1279.8 (± 730.49)	1418.0 (± 804.49)	
Phe Intake: M78 to M84	1416.5 (± 795.58)	1369.6 (± 545.40)	1434.4 (± 883.63)	

Statistical analyses

No statistical analyses for this end point

Secondary: Monthly blood Phe levels and Phe levels on the day of the IQ test

End point title	Monthly blood Phe levels and Phe levels on the day of the IQ test

End point description:

Overall, Naïve & Previously Trt
BL Ab 33,10,23; M3 Ab 33,11,22 & Ch 32,10,22; M6 Ab 33,10,23 & Ch 32,9,23; M9 Ab 33,10,23 & Ch 32,9,23; M12 Ab 33,10,23 & Ch 32,9,23; M15 Ab 32,9,23 & Ch 31,8,23; M18 Ab 32,9,23 & Ch 31,8,23; M21 Ab 32,9,23 & Ch 31,8,23; M24 Ab 32,9,23 & Ch 31,8,23; M27 Ab 30,9,21 & Ch 29,8,21; M30 Ab 31,9,22 & Ch 30,8,22; M33 Ab 32,9,23 & Ch 31,8,23; M36 Ab 32,9,23 & Ch 31,8,23; M39 Ab 32,9,23 & Ch 31,8,23; M42 Ab 32,9,23 & Ch 31,8,23; M45 Ab 32,9,23 & Ch 31,8,23; M48 Ab 32,9,23 & Ch 31,8,23; M51 Ab 31,9,22 & Ch 30,8,22; M54 Ab 32,9,23 & Ch 31,8,23; M57 Ab 32,9,23 & Ch 31,8,23; M60 Ab 31,9,22 & Ch 30,8,22; M63 Ab 31,9,22 & Ch 30,8,22; M66 Ab 32,9,23 & Ch 31,8,23; M69 Ab 31,8,23 & Ch 30,7,23; M72 Ab 32,9,23 & Ch 31,8,23; M75 Ab 30,8,22 & Ch 29,7,22; M78 Ab 30,9,21 & Ch 29,8,21; M81 Ab 29,8,21 & Ch 28,7,21; M84 Ab 31,9,22 & Ch 30,8,22

Refer attached file for Values of M1 Ab 11,11,0 & Ch 10,10,0; End of Treatment Ab 2,2,0 & Ch 2,2,0 as number of sub analyzed is zero.

End point type	Secondary

End point timeframe:
Up to End of treatment.

End point values	Kuvan	Naive Subjects	Previously Treated	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	11	23	
Units: µmol/L				
arithmetic mean (standard deviation)				
Baseline: Absolute	306.09 (± 153.427)	371.68 (± 188.509)	277.57 (± 129.988)	
Month 3: Absolute	265.30 (± 82.688)	252.72 (± 99.698)	271.59 (± 74.573)	
Month 3: Change from Baseline	-43.26 (± 131.026)	-109.84 (± 156.693)	-12.99 (± 108.397)	
Month 6: Absolute	286.42 (± 88.241)	251.35 (± 112.817)	301.66 (± 72.918)	
Month 6: Change from Baseline	-11.12 (± 175.910)	-101.11 (± 250.877)	24.09 (± 126.915)	
Month 9: Absolute	308.06 (± 114.398)	337.30 (± 170.552)	295.35 (± 81.107)	
Month 9: Change from Baseline	4.06 (± 178.331)	-31.00 (± 277.636)	17.77 (± 126.817)	
Month 12: Absolute	309.93 (± 91.657)	281.35 (± 103.565)	322.36 (± 85.433)	
Month 12: Change from Baseline	13.43 (± 155.953)	-66.71 (± 202.314)	44.79 (± 125.424)	
Month 15: Absolute	332.33 (± 96.575)	276.97 (± 75.748)	353.99 (± 96.498)	
Month 15: Change from Baseline	40.43 (± 53.626)	-63.04 (± 213.923)	76.41 (± 111.245)	
Month 18: Absolute	303.78 (± 83.069)	306.28 (± 102.022)	302.80 (± 77.039)	
Month 18: Change from Baseline	12.84 (± 158.723)	-22.76 (± 220.177)	25.23 (± 135.307)	
Month 21: Absolute	315.37 (± 94.663)	292.85 (± 94.431)	324.19 (± 95.372)	
Month 21: Change from Baseline	22.74 (± 154.798)	-45.90 (± 232.377)	46.61 (± 114.829)	
Month 24: Absolute	330.02 (± 84.348)	348.39 (± 126.451)	322.83 (± 63.393)	
Month 24: Change from Baseline	37.41 (± 144.485)	14.82 (± 215.842)	45.26 (± 115.732)	
Month 27: Absolute	295.54 (± 86.691)	302.59 (± 123.464)	292.52 (± 69.051)	
Month 27: Change from Baseline	4.88 (± 158.412)	-45.83 (± 247.722)	24.20 (± 110.605)	
Month 30: Absolute	327.44 (± 112.803)	329.82 (± 173.921)	326.46 (± 81.555)	
Month 30: Change from Baseline	35.30 (± 194.754)	1.94 (± 294.156)	47.43 (± 151.517)	
Month 33: Absolute	308.09 (± 107.417)	301.11 (± 115.997)	310.83 (± 106.480)	
Month 33: Change from Baseline	14.91 (± 153.253)	-37.81 (± 202.131)	33.25 (± 132.909)	
Month 36: Absolute	325.35 (± 82.485)	364.05 (± 92.755)	310.21 (± 74.875)	

Month 36: Change from Baseline	30.02 (± 148.388)	22.51 (± 197.266)	32.63 (± 132.728)	
Month 39: Absolute	328.81 (± 85.429)	317.88 (± 106.494)	333.08 (± 78.049)	
Month 39: Change from Baseline	32.92 (± 47.577)	-32.03 (± 200.693)	55.51 (± 121.719)	
Month 42: Absolute	360.77 (± 91.288)	357.01 (± 110.227)	362.25 (± 85.536)	
Month 42: Change from Baseline	68.94 (± 165.132)	23.71 (± 191.138)	84.67 (± 156.707)	
Month 45: Absolute	348.22 (± 112.540)	323.70 (± 107.009)	357.82 (± 115.500)	
Month 45: Change from Baseline	53.47 (± 156.523)	-23.50 (± 157.352)	80.24 (± 150.420)	
Month 48: Absolute	354.78 (± 97.902)	351.87 (± 96.801)	355.92 (± 100.466)	
Month 48: Change from Baseline	59.49 (± 165.697)	5.28 (± 166.705)	78.35 (± 164.792)	
Month 51: Absolute	361.97 (± 103.328)	360.21 (± 131.235)	362.69 (± 93.218)	
Month 51: Change from Baseline	64.92 (± 158.105)	13.41 (± 159.469)	83.65 (± 157.049)	
Month 54: Absolute	398.53 (± 131.917)	395.27 (± 140.048)	399.80 (± 131.845)	
Month 54: Change from Baseline	107.52 (± 198.359)	65.24 (± 220.428)	122.23 (± 193.178)	
Month 57: Absolute	418.99 (± 175.828)	375.45 (± 153.167)	436.03 (± 184.263)	
Month 57: Change from Baseline	126.75 (± 246.010)	35.61 (± 288.487)	158.45 (± 227.984)	
Month 60: Absolute	387.58 (± 87.746)	364.20 (± 92.929)	397.14 (± 85.903)	
Month 60: Change from Baseline	95.48 (± 162.098)	11.42 (± 188.929)	126.05 (± 143.934)	
Month 63: Absolute	408.53 (± 145.820)	414.51 (± 226.952)	406.09 (± 103.600)	
Month 63: Change from Baseline	121.72 (± 198.224)	81.80 (± 317.316)	136.24 (± 140.963)	
Month 66: Absolute	394.47 (± 112.065)	396.22 (± 102.756)	393.79 (± 117.707)	
Month 66: Change from Baseline	101.67 (± 167.822)	59.87 (± 177.148)	116.21 (± 166.024)	
Month 69: Absolute	410.79 (± 102.230)	394.86 (± 139.266)	416.33 (± 89.195)	
Month 69: Change from Baseline	119.60 (± 165.888)	56.65 (± 213.392)	138.76 (± 149.033)	
Month 72: Absolute	404.23 (± 97.686)	396.93 (± 57.880)	407.09 (± 110.443)	
Month 72: Change from Baseline	110.54 (± 158.739)	55.97 (± 191.676)	129.52 (± 145.641)	
Month 75: Absolute	440.01 (± 132.362)	493.48 (± 154.273)	420.57 (± 121.554)	
Month 75: Change from Baseline	145.33 (± 195.980)	157.26 (± 298.757)	141.54 (± 160.146)	
Month 78: Absolute	436.43 (± 149.454)	518.06 (± 124.610)	401.44 (± 147.960)	
Month 78: Change from Baseline	139.27 (± 206.550)	187.68 (± 247.979)	120.83 (± 192.122)	
Month 81: Absolute	438.00 (± 156.075)	470.35 (± 105.872)	425.67 (± 172.052)	
Month 81: Change from Baseline	147.15 (± 218.779)	153.43 (± 268.978)	145.06 (± 207.108)	

Month 84: Absolute	479.07 (± 181.230)	505.69 (± 188.972)	468.17 (± 181.351)	
Month 84: Change from Baseline	186.17 (± 252.675)	177.97 (± 335.507)	189.15 (± 224.967)	

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio of Phe/Tyr levels at Baseline and every 6 months.

End point title	Ratio of Phe/Tyr levels at Baseline and every 6 months.

End point description:

Overall: Baseline (n=30), Month 6 (n=31), Month 12 (n=32), Month 18 (n=31), Month 24 (n=31), Month 30 (n=30), Month 36 (n=32), Month 42 (n=31), Month 48 (n=32), Month 54 (n=29), Month 60 (n=26), Month 66 (n=28), Month 72 (n=19), Month 78 (n=22), Month 84 (n=25), & End of Treatment (n=34)
Naive: Baseline (n=8), Month 6 (n=9), Month 12 (n=10), Month 18 (n=8), Month 24 (n=9), Month 30 (n=9), Month 36 (n=9), Month 42 (n=9), Month 48 (n=9), Month 54 (n=6), Month 60 (n=6), Month 66 (n=7), Month 72 (n=6), Month 78 (n=5), Month 84 (n=7), & End of Treatment (n=11)
Previously Treated : Baseline (n=22), Month 6 (n=22), Month 12 (n=22), Month 18 (n=23), Month 24 (n=22), Month 30 (n=21), Month 36 (n=23), Month 42 (n=22), Month 48 (n=23), Month 54 (n=23), Month 60 (n=20), Month 66 (n=21), Month 72 (n=13), Month 78 (n=17), Month 84 (n=18), & End of Treatment (n=23)

End point type	Secondary

End point timeframe:

Baseline and every 6 months.

End point values	Kuvan	Naive Subjects	Previously Treated	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	11	23	
Units: Ratio				
arithmetic mean (standard deviation)				
Baseline	7.71 (± 5.839)	8.01 (± 8.540)	7.61 (± 4.767)	
Month 6	6.51 (± 3.440)	5.62 (± 4.477)	6.87 (± 2.965)	
Month 12	6.67 (± 4.178)	5.70 (± 4.971)	7.11 (± 3.812)	
Month 18	6.65 (± 3.780)	5.73 (± 3.539)	6.96 (± 3.884)	
Month 24	5.84 (± 2.964)	5.10 (± 3.447)	6.15 (± 2.774)	
Month 30	6.39 (± 4.390)	5.65 (± 5.072)	6.70 (± 4.160)	
Month 36	6.46 (± 3.573)	6.49 (± 4.697)	6.45 (± 3.157)	
Month 42	7.03 (± 5.177)	4.17 (± 2.583)	8.20 (± 5.549)	
Month 48	7.08 (± 3.980)	6.33 (± 4.156)	7.37 (± 3.965)	
Month 54	7.13 (± 3.823)	7.31 (± 5.390)	7.08 (± 3.462)	
Month 60	6.75 (± 4.326)	7.05 (± 6.882)	6.66 (± 3.481)	
Month 66	5.89 (± 3.731)	5.77 (± 3.479)	5.93 (± 3.893)	
Month 72	6.94 (± 3.843)	7.68 (± 5.637)	6.60 (± 2.917)	
Month 78	6.18 (± 2.864)	8.11 (± 3.032)	5.62 (± 2.639)	
Month 84	5.66 (± 3.585)	4.28 (± 2.888)	6.19 (± 3.758)	
End of Treatment	5.95 (± 3.729)	4.61 (± 2.869)	6.60 (± 3.972)	

Statistical analyses

No statistical analyses for this end point

Secondary: Index of Dietary Control (IDC)

End point title	Index of Dietary Control (IDC)

End point description:

IDC (Index of Dietary Control) = half-year Phe level medians averaged from baseline to 2, 4, and 7 years).

End point type	Secondary

End point timeframe:

From baseline to 2, 4 and 7 years.

End point values	Kuvan	Naive Subjects	Previously Treated	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	11	23	
Units: mg/dL				
median (full range (min-max))				
Baseline to Month 24	316.6 (157 to 436)	302.1 (189 to 436)	316.8 (157 to 425)	
Baseline to Month 48	319.0 (196 to 436)	326.6 (202 to 436)	317.6 (196 to 427)	
Baseline to Month 84	348.5 (239 to 481)	380.4 (255 to 478)	343.0 (239 to 481)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence to Kuvan Treatment

End point title	Adherence to Kuvan Treatment

End point description:

Adherence to Kuvan treatment is defined as the percentage of actual Kuvan dose administered compared to the Kuvan dose prescribed.

Overall: Day 1 to M12 (n=34), M12 to M24 (n=33), M24 to M36 (n=32), M36 to M48 (n=32), M48 to M60 (n=32), M60 to M72 (n=32), & M72 to M84 (n=32).

Naïve Subjects: Day 1 to M12 (n=11), M12 to M24 (n=10), M24 to M36 (n=9), M36 to M48 (n=9), M48 to M60 (n=9), M60 to M72 (n=9), & M72 to M84 (n=9)
Previously Treated: Day 1 to M12 (n=23), M12 to M24 (n=23), M24 to M36 (n=23), M36 to M48 (n=23), M48 to M60 (n=23), M60 to M72 (n=23), & M72 to M84 (n=23).

Overall: Overall (n=34), Naive (n=11), Previously Treated (n=23)

End point type	Secondary

End point timeframe:

Yearly (up to 7 years)

End point values	Kuvan	Naive Subjects	Previously Treated	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	11	23	
Units: Percentage				
arithmetic mean (standard deviation)				
Day 1 to M12	98.5 (± 30.27)	89.5 (± 49.56)	102.8 (± 14.06)	
M12 to M24	98.2 (± 16.33)	104.5 (± 8.10)	95.4 (± 18.30)	
M24 to M36	102.4 (± 17.53)	99.7 (± 5.48)	103.4 (± 20.45)	
M36 to M48	101.2 (± 8.98)	100.1 (± 5.46)	101.7 (± 10.10)	
M48 to M60	104.2 (± 8.78)	104.3 (± 3.95)	104.2 (± 10.15)	
M60 to M72	97.8 (± 11.89)	104.0 (± 4.55)	95.4 (± 13.04)	
M72 to M84	94.6 (± 21.52)	96.5 (± 17.30)	93.9 (± 23.28)	
Overall	98.7 (± 8.97)	97.4 (± 12.88)	99.4 (± 6.63)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence to Dietary Phe Prescription

End point title	Adherence to Dietary Phe Prescription

End point description:

Adherence to dietary Phe prescription is defined as the percentage of actual dietary Phe intake compared to prescribed dietary Phe intake.

To assess adherence, the dietician calculated several dietary nutrients such as total protein (g/day), total kilocalories (kcal/day), actual Phe intake per day (mg/day), etc., and compared those parameters with the Phe prescription.

Day 1 to M12: Overall (n=34), Naive (n=11), Previously Treated (n=23)
M12 to M24: Overall (n=32), Naive (n=10), Previously Treated (n=22)
M24 to M36: Overall (n=31), Naive (n=9), Previously Treated (n=22)
M36 to M48: Overall (n=31), Naive (n=9), Previously Treated (n=22)
M48 to M60: Overall (n=31), Naive (n=9), Previously Treated (n=22)
M60 to M72: Overall (n=31), Naive (n=9), Previously Treated (n=22)
M72 to M84: Overall (n=30), Naive (n=9), Previously Treated (n=21)
Overall: Overall (n=34), Naive (n=11), Previously Treated (n=23)

End point type	Secondary

End point timeframe:

Yearly (up to 7 years)

End point values	Kuvan	Naive Subjects	Previously Treated	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	11	23	
Units: Percentage				
arithmetic mean (standard deviation)				
Day 1 to M12	102.8 (± 31.50)	121.3 (± 28.72)	94.0 (± 29.33)	
M12 to M24	106.1 (± 29.62)	101.7 (± 20.18)	108.2 (± 33.26)	
M24 to M36	104.3 (± 24.81)	95.5 (± 24.44)	107.9 (± 24.59)	
M36 to M48	112.9 (± 53.05)	106.3 (± 22.29)	115.7 (± 61.68)	
M48 to M60	107.1 (± 41.52)	105.5 (± 14.67)	107.7 (± 48.77)	
M60 to M72	101.9 (± 27.93)	101.7 (± 18.17)	101.9 (± 31.45)	
M72 to M84	107.7 (± 21.51)	109.2 (± 24.00)	107.0 (± 20.95)	
Overall	107.6 (± 20.57)	106.3 (± 14.79)	108.2 (± 23.11)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence to Diet+Kuvan Treatment: defined as the percentage of monthly mean blood Phe levels within target blood Phe levels: >=120 to <360 µmol/L

End point title	Adherence to Diet+Kuvan Treatment: defined as the percentage of monthly mean blood Phe levels within target blood Phe levels: >=120 to <360 µmol/L

End point description:

Overall, Naïve & Previously Treated
D1 to M6: n=34,11,23; M6 to M12: n=33,10,23; Day1 to M12: n=34,11,23; M12 to M18: n=33,10,23; M18 to M24: n=32,9,23; M12 to 24: n=33,10,23; M24 to M30: n=31,9,22; M30 to M36: n=32,9,23; M24 to M36: n=32,9,23; M36 to M42: n=32,9,23; M42 to M48: n=32,9,23; M36 to M48: n=32,9,23; M48 to M54: n=32,9,23; M54 to M60: n=32,9,23; M48 to M60: n=32,9,23; M60 to M66: n=32,9,23; M66 to M72: n=32,9,23; M60 to M72: n=32,9,23; M72 to M78: n=31,9,22; M78 to M84: n=31,9,22; M72 to M84: n=32,9,23; Overall: n=34,11,23

End point type	Secondary

End point timeframe:

Yearly and per 6 months.

End point values	Kuvan	Naive Subjects	Previously Treated	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	11	23	
Units: Percentage				
arithmetic mean (standard deviation)				
Day 1 to M6	84.3 (± 23.90)	78.8 (± 26.97)	87.0 (± 22.45)	
M6 to M12	66.7 (± 38.86)	60.0 (± 39.44)	69.6 (± 39.14)	
Day 1 to M12	75.7 (± 22.89)	70.3 (± 19.86)	78.3 (± 24.20)	
M12 to M18	69.7 (± 39.41)	75.0 (± 42.49)	67.4 (± 38.76)	
M18 to M24	70.3 (± 30.74)	66.7 (± 25.00)	71.7 (± 33.12)	
M12 to M24	70.5 (± 23.76)	72.5 (± 24.86)	69.6 (± 23.78)	
M24 to M30	75.8 (± 33.84)	61.1 (± 41.67)	81.8 (± 29.05)	
M30 to M36	71.9 (± 33.45)	66.7 (± 43.30)	73.9 (± 29.66)	
M24 to M36	74.2 (± 26.55)	63.9 (± 35.60)	78.3 (± 21.72)	
M36 to M42	56.3 (± 39.66)	50.0 (± 43.30)	58.7 (± 38.88)	
M42 to M48	56.3 (± 43.53)	61.1 (± 48.59)	54.3 (± 42.41)	
M36 to M48	56.3 (± 35.92)	55.6 (± 39.09)	56.5 (± 35.53)	
M48 to M54	46.9 (± 43.88)	50.0 (± 43.30)	45.7 (± 45.01)	
M54 to M60	40.6 (± 39.02)	50.0 (± 43.30)	37.0 (± 37.59)	
M48 to M60	44.5 (± 35.46)	50.0 (± 35.36)	42.4 (± 36.05)	
M60 to M66	37.5 (± 40.16)	33.3 (± 43.30)	39.1 (± 39.76)	
M66 to M72	31.3 (± 35.36)	27.8 (± 36.32)	32.6 (± 35.70)	
M60 to M72	34.6 (± 33.41)	31.5 (± 36.98)	35.9 (± 32.71)	
M72 to M78	27.4 (± 38.38)	5.6 (± 16.67)	36.4 (± 41.35)	
M78 to M84	27.4 (± 40.49)	16.7 (± 35.36)	31.8 (± 42.39)	
M72 to M84	26.6 (± 32.34)	11.1 (± 18.16)	32.6 (± 34.90)	
Overall	55.5 (± 21.39)	53.3 (± 24.09)	56.6 (± 20.47)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Adverse Events and Serious Adverse Events

End point title	Number of subjects with Adverse Events and Serious Adverse Events

End point description:

End point type	Secondary

End point timeframe:

Up to Safety Follow-Up (approximately 96 months).

End point values	Kuvan			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Number of participants				
Any Adverse Event	33			
Any Treatment-Emergent Adverse Event	33			
Any Treatment-Emergent Adverse Event related to St	0			
Any Severe Treatment-Emergent Adverse Event	1			
Any Serious Adverse Events	0			
Any Serious Adverse Events related to Study Treatm	0			
Any Adverse Events leading to regimen modification	1			
Any Adverse Events leading to dose reduction	0			
Any Adverse Events leading to temporary treatment	6			
Any Adverse Events leading to permanent treatment	0			
Any Adverse Events leading to trial discontinuatio	0			
Any Adverse Events leading to death	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to Safety Follow-Up (approximately 96 months).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Kuvan

Reporting group description:

Safety analysis set: All enrolled subjects taking at least one dose of study treatment (Kuvan) and having some safety assessment data available were included in the safety analysis set. all subjects who were part of the ITT analysis set were included in the safety analysis set, as it could be assumed that all treated subjects would have safety data available (i.e., a 1-month safety follow-up visit was mandatory for all subjects).

Serious adverse events	Kuvan		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 34 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Kuvan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 34 (97.06%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	6		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	16 / 34 (47.06%)		
occurrences (all)	58		
Immune system disorders			

Seasonal allergy subjects affected / exposed occurrences (all) Hypersensitivity subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 4 2 / 34 (5.88%) 2		
Reproductive system and breast disorders Balanoposthitis subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 4		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Asthma subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	12 / 34 (35.29%) 23 9 / 34 (26.47%) 11 3 / 34 (8.82%) 12 3 / 34 (8.82%) 7		
Investigations Body temperature increased subjects affected / exposed occurrences (all) Amino acid level decreased subjects affected / exposed occurrences (all)	4 / 34 (11.76%) 4 2 / 34 (5.88%) 4		
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) Arthropod sting	3 / 34 (8.82%) 3		

subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all) Skin laceration subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 4 2 / 34 (5.88%) 2 2 / 34 (5.88%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all)	 10 / 34 (29.41%) 16 2 / 34 (5.88%) 2		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	 6 / 34 (17.65%) 6		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Dental caries subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	 14 / 34 (41.18%) 50 11 / 34 (32.35%) 14 4 / 34 (11.76%) 7 3 / 34 (8.82%) 3 2 / 34 (5.88%) 3		
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
Eczema			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	5		
Erythema			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Rash erythematous			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Urticaria			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	13		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	17 / 34 (50.00%)		
occurrences (all)	75		
Gastroenteritis			
subjects affected / exposed	12 / 34 (35.29%)		
occurrences (all)	22		
Upper respiratory tract infection			
subjects affected / exposed	12 / 34 (35.29%)		
occurrences (all)	45		
Corona virus infection			
subjects affected / exposed	8 / 34 (23.53%)		
occurrences (all)	9		
Conjunctivitis			

subjects affected / exposed	5 / 34 (14.71%)			
occurrences (all)	6			
Pharyngitis				
subjects affected / exposed	5 / 34 (14.71%)			
occurrences (all)	10			
Viral infection				
subjects affected / exposed	5 / 34 (14.71%)			
occurrences (all)	10			
Viral upper respiratory tract infection				
subjects affected / exposed	5 / 34 (14.71%)			
occurrences (all)	15			
Ear infection				
subjects affected / exposed	4 / 34 (11.76%)			
occurrences (all)	5			
Lower respiratory tract infection				
subjects affected / exposed	4 / 34 (11.76%)			
occurrences (all)	4			
Rhinitis				
subjects affected / exposed	4 / 34 (11.76%)			
occurrences (all)	4			
Varicella				
subjects affected / exposed	4 / 34 (11.76%)			
occurrences (all)	4			
Bronchitis				
subjects affected / exposed	3 / 34 (8.82%)			
occurrences (all)	7			
Impetigo				
subjects affected / exposed	3 / 34 (8.82%)			
occurrences (all)	3			
Influenza				
subjects affected / exposed	3 / 34 (8.82%)			
occurrences (all)	6			
Molluscum contagiosum				
subjects affected / exposed	3 / 34 (8.82%)			
occurrences (all)	3			
Respiratory tract infection				

subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	4		
Gastroenteritis viral			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Lice infestation			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	3		
Oral herpes			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	3		
Otitis media			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Tonsillitis			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	7		
Urinary tract infection			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2015	• Added BioMarin study identifier in cover page • Updated coordinating investigator information in cover page • Updated Sponsor and Medical Responsible in cover page • Updated confidentiality statement in cover page • Updated medical monitor in Signature of medical monitor section • Removed protocol lead information • Updated coordinating investigator information in Coordinating investigator signature page • Removal of further responsible persons information in Further responsible Persons section • BioMarin study identifier included in Synopsis and Trial Number section • Updated Sponsor details in Synopsis and Sponsor section • Updated Sponsor responsibility information in Synopsis, trial design and plan sections • Updated Sponsor details in Sections 2, 3.2.3.2 and 5.2.3 • Updated Diary card instruction in Section 6.5.1 • Updated Capillary blood sampling instruction in Sections 7.1.2.7, 7.1.3 and 7.1.4 • Updated diary instructions in Section 7.4.2 • Updated Sponsor details in Sections 7.8 and 9.4 • Updated Capillary blood sampling instruction in Appendix II • Included BioMarin study identifier in page header

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported