Clinical trial results:
A Phase IIIb, Multicentre, Open-Label, Randomized, Controlled Study of the Efficacy, Safety, and Population Pharmacokinetics of Sapropterin Dihydrochloride (Kuvan®) in Phenylketonuria (PKU) Patients <4 Years Old

Summary

EudraCT number	2009-015768-33
Trial protocol	GB SK DE AT CZ PT BE NL IT
Global end of trial date	17 February 2017

Results information

Result version number	v1 (current)
This version publication date	02 September 2020
First version publication date	02 September 2020

Trial information

Trial identification

Sponsor protocol code	EMR700773-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01376908
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioMarin Pharmaceutical Inc.
Sponsor organisation address	105 Digital Drive, Novato, United States, CA 94949
Public contact	Clinical Trails Information, BioMarin Pharmaceutical Inc., clinicaltrials@bmrn.com
Scientific contact	Clinical Trails Information, BioMarin Pharmaceutical Inc., clinicaltrials@bmrn.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001476-PIP01-13
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	17 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. Evaluate the efficacy after 26 weeks of Kuvan® treatment + Phe-restricted diet therapy in increasing dietary Phe tolerance, as compared to dietary therapy alone in <4 year-old infants and children with phenylketonuria (PKU). Phe tolerance will be defined as the amount of dietary Phe (mg/kg/day) ingested while maintaining blood Phe levels within the range of 120-360 µmol/L (defined as ≥120 to < 360 µmol/L).
2. Evaluate the safety after 26 weeks of Kuvan® treatment in <4 year-old infants and children with PKU.
3. Evaluate BH4 (tetrahydrobiopterin; sapropterin) blood levels via scheduled PopPK samplings.

Protection of trial subjects:

The trial was performed in accordance with the protocol and subsequent protocol amendments and with the ethical principles laid down in the Declaration of Helsinki, in accordance with the International Council for Harmonisation (ICH), Note for Guidance on Good Clinical Practice (GCP) (ICH Topic E6, 1996) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Netherlands: 1
Worldwide total number of subjects	56
EEA total number of subjects	49

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)	33
Children (2-11 years)	23
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: -

Pre-assignment

Screening details:

Of the 56 subjects enrolled to study, 51 subjects remained through the end of the study.

Period 1

Period 1 title	Kuvan Continuous Stage
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Kuvan® + Phe-restricted Diet - Continuous

Arm description:

Kuvan® (sapropterin dihydrochloride) tablets were administered orally at a dose of 10 milligram/kilogram/day (mg/kg/day). If after 4 weeks, there was less than 20 percent (%) increase in subject's Phe tolerance versus baseline, the dose was escalated to 20 mg/kg/day. Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria.

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

Dosage and administration details:

100 mg soluble Kuvan tablets (sapropterin dihydrochloride). The appropriate number of Kuvan tablets, based on the dose calculated according to the subject’s weight, were dissolved in the protocol-defined volume of water and given to the child during breakfast. The solution was to be ingested within 15 to 20 minutes after dissolution.

Arm title	Phe-restricted Diet - Continuous

Arm description:

Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria. After 26 weeks, the starting dose of Kuvan will be 10 mg/kg/day, and the dose may be adjusted by the Investigator, if clinically indicated, but it may not exceed 20 mg/kg/day.

Arm type	Restricted diet

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Kuvan® + Phe-restricted Diet - Continuous	Phe-restricted Diet - Continuous
Started	27	29
Completed	25	26
Not completed	2	3
Unknown	2	3

Period 2

Period 2 title	Kuvan Extension Stage
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Kuvan® + Phe-restricted Diet - Extension

Arm description:

Kuvan® (sapropterin dihydrochloride) tablets were administered orally at a dose of 10 milligram/kilogram/day (mg/kg/day). If after 4 weeks, there was less than 20 percent (%) increase in subject's Phe tolerance versus baseline, the dose was escalated to 20 mg/kg/day. Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria.After 26 weeks, the dose may be adjusted by the Investigator, if clinically indicated, but it may not exceed 20 mg/kg/day.

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

Dosage and administration details:

Appropriate number of Kuvan® 100 mg soluble tablets (sapropterin dihydrochloride), based on the dose calculated according to the subject’s weight, were dissolved in the protocol-defined volume of water and given to the child during breakfast. The solution was to be ingested within 15 to 20 minutes after dissolution.

Arm title	Phe-restricted Diet - Extension

Arm description:

Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria. After 26 weeks, the starting dose of Kuvan will be 10 mg/kg/day, and the dose may be adjusted by the Investigator, if clinically indicated, but it may not exceed 20 mg/kg/day.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Kuvan® + Phe-restricted Diet - Extension	Phe-restricted Diet - Extension
Started	25	26
Completed	18	15
Not completed	7	11
Unknown	7	10
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Kuvan® + Phe-restricted Diet - Continuous
Reporting group description:	
Kuvan® (sapropterin dihydrochloride) tablets were administered orally at a dose of 10 milligram/kilogram/day (mg/kg/day). If after 4 weeks, there was less than 20 percent (%) increase in subject's Phe tolerance versus baseline, the dose was escalated to 20 mg/kg/day. Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria.	
Reporting group title	Phe-restricted Diet - Continuous
Reporting group description:	
Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria. After 26 weeks, the starting dose of Kuvan will be 10 mg/kg/day, and the dose may be adjusted by the Investigator, if clinically indicated, but it may not exceed 20 mg/kg/day.	

Reporting group values	Kuvan® + Phe-restricted Diet - Continuous	Phe-restricted Diet - Continuous	Total
Number of subjects	27	29	56
Age categorical Units: Subjects			
<12 Months	7	8	15
12 - <24 Months	9	9	18
24 - <48 Months	11	12	23
Age continuous Units: months			
arithmetic mean	21.1	21.2	
standard deviation	± 12.3	± 12.0	-
Gender categorical Units: Subjects			
Female	11	15	26
Male	16	14	30
Race Units: Subjects			
White	26	28	54
Asian	0	1	1
Other	1	0	1
Height Units: cm			
arithmetic mean	82.0	82.3	
standard deviation	± 11.3	± 11.6	-
Weight Units: kg			
arithmetic mean	11.3	11.3	
standard deviation	± 3.1	± 2.8	-
Body Mass Index Units: kg/m*2			
arithmetic mean	16.5	16.5	
standard deviation	± 1.0	± 1.4	-

End points

End points reporting groups

Reporting group title	Kuvan® + Phe-restricted Diet - Continuous

Reporting group description:

Kuvan® (sapropterin dihydrochloride) tablets were administered orally at a dose of 10 milligram/kilogram/day (mg/kg/day). If after 4 weeks, there was less than 20 percent (%) increase in subject's Phe tolerance versus baseline, the dose was escalated to 20 mg/kg/day. Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria.

Reporting group title	Phe-restricted Diet - Continuous

Reporting group description:

Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria. After 26 weeks, the starting dose of Kuvan will be 10 mg/kg/day, and the dose may be adjusted by the Investigator, if clinically indicated, but it may not exceed 20 mg/kg/day.

Reporting group title	Kuvan® + Phe-restricted Diet - Extension

Reporting group description:

Kuvan® (sapropterin dihydrochloride) tablets were administered orally at a dose of 10 milligram/kilogram/day (mg/kg/day). If after 4 weeks, there was less than 20 percent (%) increase in subject's Phe tolerance versus baseline, the dose was escalated to 20 mg/kg/day. Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria.After 26 weeks, the dose may be adjusted by the Investigator, if clinically indicated, but it may not exceed 20 mg/kg/day.

Reporting group title	Phe-restricted Diet - Extension

Reporting group description:

Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria. After 26 weeks, the starting dose of Kuvan will be 10 mg/kg/day, and the dose may be adjusted by the Investigator, if clinically indicated, but it may not exceed 20 mg/kg/day.

Subject analysis set title	Pharmacokinetic Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All enrolled subjects for whom at least one adequately documented BH4 concentration value and dose record were included in the population PK analysis. 'N' (number of subjects analyzed) =subjects evaluable for this outcome measure.

Subject analysis set title	Pharmacogenetics
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Phenylalanine hydroxylase (gene or protein) gene mutation analysis in 73 DNA samples

Phenylalanine hydroxylase genotype analysis had been performed prior to a subject being considered for the trial, all subjects were still to undergo sampling for PAH genotype analysis at Screening.

The number of subjects in subject analysis set are ITT population - Intention-to-treat (ITT) population consisted of all the randomized subjects at the start of the study and were analyzed according to the group allocated.

Primary: Dietary Phe Tolerance - Kuvan Continuous Study

End point title	Dietary Phe Tolerance - Kuvan Continuous Study[1]

End point description:

Phe tolerance is the amount of dietary Phe prescribed (milligram per kilogram per day [mg/kg/day]) while maintaining blood Phe levels within the selected therapeutic target range (defined as greater than or equal to [>=] 120 to less than [<] 360 micromoles per liter [mcmol/L]).

Dietary Phe tolerance after 26 weeks (6 months) of treatment with Kuvan®+ a Phe-restricted diet, as compared to just a Phe-restricted diet alone.

Intention-to-treat (ITT) population consisted of all the randomized subjects at the start of the study and

were analyzed according to the group allocated.

End point type	Primary

End point timeframe:

Week 26

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The following null hypothesis regarding the primary endpoint for the Extension Period was tested:
H0: The mean dietary Phe tolerance with Kuvan along with dietary therapy does not differ over time
vs
H1: The mean dietary Phe tolerance with Kuvan along with dietary therapy differs over time

End point values	Kuvan® + Phe-restricted Diet - Continuous	Phe-restricted Diet - Continuous		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	29		
Units: mg/kg/day				
arithmetic mean (standard error)	80.6 (± 4.2)	50.1 (± 4.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Dietary Phe Tolerance - Kuvan Extension Study

End point title	Dietary Phe Tolerance - Kuvan Extension Study[2]

End point description:

Dietary Phe Tolerance (mg/kg/day) over time by Age Group (ITTE Population)

End point type	Primary

End point timeframe:

Baseline, Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33 and 36 (End of Extension Period)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The following null hypothesis regarding the primary endpoint for the Extension Period was tested:
H0: The mean dietary Phe tolerance with Kuvan along with dietary therapy does not differ over time
vs
H1: The mean dietary Phe tolerance with Kuvan along with dietary therapy differs over time

End point values	Kuvan® + Phe-restricted Diet - Extension	Phe-restricted Diet - Extension		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: mg/kg/day				
arithmetic mean (standard deviation)				
Baseline (<12M) (n=25, n=26)	44.25 (± 11.00)	59.00 (± 28.51)		

Baseline (12 - <24M) (n=25, n=26)	48.63 (± 23.65)	49.25 (± 18.63)		
Baseline (24 - <48M) (n=25, n=26)	25.80 (± 8.41)	45.90 (± 24.85)		
Month 3 (<12M) (n=25, n=26)	92.20 (± 36.05)	61.86 (± 23.81)		
Month 3 (12 - <24M) (n=25, n=26)	102.25 (± 25.46)	59.33 (± 22.74)		
Month 3 (24 - <48M) (n=25, n=26)	64.75 (± 22.21)	46.00 (± 11.31)		
Month 6 (<12M) (n=25, n=26)	79.50 (± 33.24)	67.75 (± 27.32)		
Month 6 (12 - <24M) (n=25, n=26)	71.00 (± 46.29)	61.63 (± 17.15)		
Month 6 (24 - <48M) (n=25, n=26)	59.88 (± 24.26)	48.13 (± 11.04)		
Month 9 (<12M) (n=25, n=26)	94.00 (± 37.33)	66.50 (± 25.33)		
Month 9 (12 - <24M) (n=25, n=26)	90.60 (± 36.40)	61.60 (± 24.76)		
Month 9 (24 - <48M) (n=25, n=26)	54.80 (± 18.43)	55.40 (± 11.84)		
Month 12 (<12M) (n=25, n=26)	83.60 (± 39.06)	67.67 (± 29.33)		
Month 12 (12 - <24M) (n=25, n=26)	80.17 (± 37.62)	65.80 (± 25.88)		
Month 12 (24 - <48M) (n=25, n=26)	70.50 (± 32.96)	55.29 (± 14.01)		
Month 15 (<12M) (n=25, n=26)	82.33 (± 36.16)	74.80 (± 39.52)		
Month 15 (12 - <24M) (n=25, n=26)	83.86 (± 34.02)	60.17 (± 32.54)		
Month 15 (24 - <48M) (n=25, n=26)	48.00 (± 19.50)	54.75 (± 13.39)		
Month 18 (<12M) (n=25, n=26)	81.57 (± 31.88)	65.14 (± 31.82)		
Month 18 (12 - <24M) (n=25, n=26)	87.33 (± 24.58)	86.80 (± 33.53)		
Month 18 (24 - <48M) (n=25, n=26)	57.00 (± 17.13)	58.60 (± 16.83)		
Month 21 (<12M) (n=25, n=26)	78.86 (± 37.02)	63.33 (± 36.00)		
Month 21 (12 - <24M) (n=25, n=26)	78.71 (± 35.09)	64.60 (± 34.53)		
Month 21 (24 - <48M) (n=25, n=26)	49.20 (± 14.43)	59.00 (± 17.80)		
Month 24 (<12M) (n=25, n=26)	83.33 (± 30.63)	51.50 (± 38.02)		
Month 24 (12 - <24M) (n=25, n=26)	67.80 (± 36.34)	61.00 (± 26.01)		
Month 24 (24 - <48M) (n=25, n=26)	57.75 (± 5.25)	46.00 (± 4.58)		
Month 27 (<12M) (n=25, n=26)	86.80 (± 31.41)	58.67 (± 27.65)		
Month 27 (12 - <24M) (n=25, n=26)	82.20 (± 28.15)	62.50 (± 22.04)		
Month 27 (24 - <48M) (n=25, n=26)	42.00 (± 23.52)	55.75 (± 12.42)		
Month 30 (<12M) (n=25, n=26)	84.43 (± 46.10)	61.43 (± 34.49)		
Month 30 (12 - <24M) (n=25, n=26)	76.50 (± 28.22)	56.80 (± 26.77)		

Month 30 (24 - <48M) (n=25, n=26)	40.33 (± 22.50)	46.67 (± 4.16)		
Month 33 (<12M) (n=25, n=26)	70.80 (± 31.85)	59.71 (± 35.18)		
Month 33 (12 - <24M) (n=25, n=26)	73.75 (± 33.03)	56.80 (± 28.92)		
Month 33 (24 - <48M) (n=25, n=26)	44.00 (± 16.37)	46.00 (± 5.66)		
End of Extension Period (EOS) (<12M) (n=25, n=26)	97.40 (± 48.00)	54.80 (± 33.82)		
End of Extension Period(EOS)(12 - <24M)(n=25,n=26)	78.20 (± 34.10)	63.25 (± 34.41)		
End of Extension Period(EOS)(24 - <48M)(n=25,n=26)	44.33 (± 23.71)	49.67 (± 7.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Blood Phe Levels - Kuvan Continuous Study

End point title	Mean Blood Phe Levels - Kuvan Continuous Study

End point description:

Mean blood phe levels were defined as the mean of blood phe levels assessed over each 2-week intervals.

Intention-to-treat (ITT) population consisted of all the randomized subjects at the start of the study and were analyzed according to the group allocated. 'n' signifies number of subjects evaluable for this measure at given time points for each reporting group respectively.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26

End point values	Kuvan® + Phe-restricted Diet - Continuous	Phe-restricted Diet - Continuous		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	29		
Units: micromole(s)/litre				
arithmetic mean (standard deviation)				
Baseline (n=27, 29)	287.3 (± 166.6)	352.9 (± 219.9)		
Week 2 (n=27, 26)	214.3 (± 89.3)	321.3 (± 133.5)		
Week 4 (n=27, 24)	202.1 (± 79.3)	308.0 (± 122.2)		
Week 6 (n=25, 26)	248.0 (± 85.4)	303.8 (± 87.4)		
Week 8 (n=26, 26)	268.7 (± 107.9)	318.0 (± 108.9)		
Week 10 (n=24, 27)	271.1 (± 109.4)	325.4 (± 106.2)		
Week 12 (n=22, 22)	317.6 (± 106.0)	328.9 (± 125.0)		

Week 14 (n=24, 26)	271.6 (± 79.0)	311.2 (± 118.6)		
Week 16 (n=25, 26)	320.3 (± 112.2)	356.3 (± 99.1)		
Week 18 (n=24, 26)	302.9 (± 122.7)	325.4 (± 80.4)		
Week 20 (n=25, 25)	305.1 (± 116.1)	326.3 (± 77.0)		
Week 22 (n=25, 24)	293.2 (± 86.8)	346.9 (± 97.8)		
Week 24 (n=24, 25)	278.8 (± 77.2)	326.1 (± 120.4)		
Week 26 (n=21, 22)	300.1 (± 115.2)	343.3 (± 118.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Dietary Phe Tolerance After 26 Weeks - Kuvan Continuous Study

End point title	Change From Baseline in Dietary Phe Tolerance After 26 Weeks - Kuvan Continuous Study

End point description:

Phe tolerance was defined as the amount of dietary Phe ingested (mg/kg/day) while maintaining blood Phe levels within the selected therapeutic target range (defined as >=120 to <360 mcmol/L).

End point type	Secondary

End point timeframe:

Baseline and at Week 26 (last observation carried-forward [LOCF])

Intention-to-treat (ITT) population consisted of all the randomized subjects at the start of the study and were analyzed according to the group allocated. 'n' signifies number of subject

End point values	Kuvan® + Phe-restricted Diet - Continuous	Phe-restricted Diet - Continuous		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	29		
Units: mg/kg/day				
arithmetic mean (standard error)				
Baseline (n=27, 29)	37.1 (± 17.3)	35.8 (± 20.9)		
Week 26: LOCF (n=27, 27)	74.0 (± 38.6)	49.8 (± 24.2)		
Change at Week 26: LOCF (n=27, 27)	36.9 (± 27.3)	13.1 (± 19.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Any TEAEs, AEs Related to Kuvan, Serious AEs, AEs Leading to Death, and AEs Leading to Discontinuation - Kuvan Continuous Study

End point title	Number of Subjects With Any TEAEs, AEs Related to Kuvan, Serious AEs, AEs Leading to Death, and AEs Leading to Discontinuation - Kuvan Continuous Study

End point description:

An AE was defined as any new untoward medical occurrences/worsening of pre-existing medical condition without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect. Treatment emergent are events between first dose of study treatment and up to 31 days after last dose that were absent before treatment or that worsened relative to pretreatment state.

Safety population included all subjects who either received at least one dose of Kuvan in the study period, or were randomized to Phe-restricted diet alone and who had some safety assessment data available.

End point type	Secondary

End point timeframe:

From the first dose of study drug administration up to 31 days after the last dose of study drug administration.

End point values	Kuvan® + Phe-restricted Diet - Continuous	Phe-restricted Diet - Continuous		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: Subjects				
number (not applicable)				
Treatment-emergent adverse events	27	27		
Adverse events related to Kuvan	8	0		
Serious adverse events	3	1		
Related serious adverse events	0	0		
Adverse events leading to death	0	0		
Adverse events Leading to discontinuation	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Neuromotor Developmental Milestones Assessed Using Denver Developmental Scale (DDS) - Kuvan Continuous Study

End point title	Number of Subjects With Neuromotor Developmental Milestones Assessed Using Denver Developmental Scale (DDS) - Kuvan Continuous Study

End point description:

Subjects with normal neuromotor development were assessed by standardized developmental milestones using a parent/guardian report form in the following areas: fine motor, gross motor, language, and personal-social using DDS Test. DDS Test is a widely used to examine the developmental progress of 0-6 years of children. The scale reflects what percentage of a certain age group is able to perform a certain task. Tasks are grouped into 4 categories (social contact, fine motor skill, language, and gross motor skill) and include items such as smiles spontaneously (performed by 90% of three-

month-olds), knocks 2 building blocks against each other (90% of 13-month-olds), speaks 3 words other than "mom" and "dad" (90% of 21-month-olds), or hops on 1 leg (90% of 5-year-olds). The more items a child fails to perform (passed by 90% of his/her peers), the more likely the child manifests a significant developmental problems.

End point type	Secondary
End point timeframe:	
Baseline, Weeks 12, 26	

End point values	Kuvan® + Phe-restricted Diet - Continuous	Phe-restricted Diet - Continuous		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	29		
Units: Subjects				
number (not applicable)				
Fine motor:Baseline-Normal(n=25,26)	18	21		
Fine motor:Baseline-Abnormal(n=25,26)	7	5		
Fine motor:Week 12-Normal(n=25,25)	21	23		
Fine motor:Week 12-Abnormal(n=25,25)	4	2		
Fine motor:Week 26-Normal (n=25,25)	20	23		
Fine motor:Week 26-Abnormal(n=25,25)	5	2		
Gross motor:Baseline-Normal(n=25,26)	23	23		
Gross motor:Baseline-Abnormal(n=25,26)	2	3		
Gross motor:Week 12-Normal(n=25,25)	21	20		
Gross motor:Week 12-Abnormal(n=25,25)	4	5		
Gross motor:Week 26-Normal(n=25,25)	20	19		
Gross motor:Week 26-Abnormal(n=25,25)	5	6		
Language:Baseline-Normal(n=25,26)	22	20		
Language:Baseline-Abnormal(n=25,26)	3	6		
Language:Week 12-Normal(n=25,25)	22	22		
Language:Week 12-Abnormal(n=25,25)	3	3		
Language:Week 26-Normal(n=25,25)	16	20		
Language:Week 26-Abnormal(n=25,25)	9	5		
Personal social:Baseline-Normal(n=25,26)	22	22		
Personal social:Baseline-Abnormal(n=25,26)	3	4		
Personal social:Week 12-Normal(n=25,25)	22	21		
Personal social:Week 12-Abnormal(n=25,25)	3	4		
Personal social:Week 26-Normal(n=25,25)	22	18		
Personal social:Week 26-Abnormal(n=25,25)	3	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Neurodevelopmental Status Assessed Using Bayley III Scales of Infant and Toddler Development - Kuvan Continuous Study

End point title	Neurodevelopmental Status Assessed Using Bayley III Scales of Infant and Toddler Development - Kuvan Continuous Study

End point description:

Neurodevelopmental assessments was done using the following age-dependent scales: Bayley III for subjects less than (<) 3.5 years of age and WPPSI III for subjects greater than or equal to (>=) 3.5 to <4 years of age, based on following scores: adaptive behavior composite (ABC) score, cognitive composite (CC) score, language composite (LC) score, motor composite (MC) score., and social-emotional composite (SEC) score. Composite scores ranged from 40 (very poor) to 160 (excellent) and are classified as following: >=115: accelerated performance; 85-114: development within normal limits; 70-84: mildly delayed development; less than or equal to (<=) 69: significant delayed development.

Intention-to-Treat (ITT) population consisted of all subjects who were randomized at the start of the Study Period and analyzed according to the group allocated. "n" signifies number of evaluable subjects in the specified categories, for each reporting group, respectively.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Kuvan® + Phe-restricted Diet - Continuous	Phe-restricted Diet - Continuous		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	29		
Units: Units on a scale				
arithmetic mean (standard deviation)				
ABC score: Baseline (n=15, 18)	106.5 (± 14.2)	96.2 (± 14.6)		
ABC score: Week 26 (n=19, 18)	102.4 (± 16.4)	93.4 (± 14.1)		
CC score: Baseline (n=19, 20)	100.0 (± 11.8)	101.2 (± 15.9)		
CC score: Week 26 (n=20, 19)	102.8 (± 12.9)	100.8 (± 13.0)		
LS score: Baseline (n=18, 19)	96.7 (± 12.4)	97.7 (± 19.5)		
LS score: Week 26 (n=20, 19)	98.3 (± 11.9)	93.6 (± 12.1)		
MC score: Baseline (n=19, 20)	97.8 (± 13.7)	94.9 (± 13.6)		
MC score: Week 26 (n=20, 19)	100.6 (± 15.2)	98.7 (± 9.5)		
SEC score: Baseline (n=17, 18)	102.9 (± 11.3)	106.0 (± 16.3)		
SEC score: Week 26 (n=19, 18)	106.3 (± 19.1)	102.5 (± 13.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Parameters Standard Deviation Scores (SDS) - Kuvan Continuous Study

End point title	Growth Parameters Standard Deviation Scores (SDS) - Kuvan Continuous Study

End point description:

Growth assessment was performed by monitoring body mass index, height (or length), weight, and maximal occipital-frontal head circumference (MOFHC). Supine length was measured up to 2 years of age thereafter standing height was measured unless subject was unable to stand upright, in which case supine length was measured. Respective parameter SDS was calculated as the value of parameter minus reference mean value of parameter divided by standard deviation of the reference population.

Intention-to-Treat (ITT) population consisted of all subjects who were randomized at the start of the Study Period and analyzed according to the group allocated. "n" signifies number of evaluable subjects in the specified categories for each reporting group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, and 26

End point values	Kuvan® + Phe-restricted Diet - Continuous	Phe-restricted Diet - Continuous		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	29		
Units: Standard Deviation Scores (SDS)				
arithmetic mean (standard deviation)				
Body mass index SDS: Baseline (n=27, 29)	0.37 (± 0.84)	0.34 (± 0.99)		
Body mass index SDS: Week 4 (n=26, 27)	0.33 (± 0.92)	0.36 (± 0.95)		
Body mass index SDS: Week 8 (n=25, 26)	0.47 (± 0.93)	0.38 (± 0.82)		
Body mass index SDS: Week 12 (n=25, 26)	0.37 (± 1.02)	0.48 (± 0.91)		
Body mass index SDS: Week 16 (n=25, 26)	0.34 (± 0.95)	0.39 (± 0.93)		
Body mass index SDS: Week 20 (n=25, 27)	0.46 (± 0.93)	0.44 (± 0.86)		
Body mass index SDS: Week 26 (n=25, 26)	0.58 (± 0.83)	0.41 (± 0.81)		
Height SDS: Baseline (n=27, 29)	-0.19 (± 1.17)	-0.21 (± 1.03)		
Height SDS: Week 4 (n=26, 27)	-0.19 (± 1.08)	-0.25 (± 1.00)		
Height SDS: Week 8 (n=25, 26)	-0.22 (± 1.08)	-0.13 (± 1.05)		
Height SDS: Week 12 (n=25, 26)	0.02 (± 1.62)	-0.14 (± 1.11)		
Height SDS: Week 16 (n=25, 26)	0.05 (± 1.36)	-0.05 (± 1.05)		
Height SDS: Week 20 (n=25, 27)	-0.08 (± 1.21)	-0.11 (± 0.95)		
Height SDS: Week 26 (n=25, 26)	-0.11 (± 1.16)	-0.06 (± 0.92)		
MOFHC SDS: Baseline (n=27, 29)	0.37 (± 1.38)	0.07 (± 1.10)		
MOFHC SDS: Week 4 (n=25, 26)	0.48 (± 1.41)	0.21 (± 1.03)		
MOFHC SDS: Week 8 (n=25, 26)	0.51 (± 1.40)	0.35 (± 1.05)		
MOFHC SDS: Week 12 (n=25, 26)	0.43 (± 1.23)	0.20 (± 1.19)		

MOFHC SDS: Week 16 (n=25, 26)	0.58 (± 1.26)	0.25 (± 1.18)		
MOFHC SDS: Week 20 (n=25, 26)	0.41 (± 1.30)	0.18 (± 1.24)		
MOFHC SDS: Week 26 (n=25, 26)	0.43 (± 1.34)	0.15 (± 1.26)		
Weight SDS: Baseline (n=27, 29)	0.12 (± 0.81)	0.12 (± 0.66)		
Weight SDS: Week 4 (n=26, 27)	0.11 (± 0.86)	0.12 (± 0.64)		
Weight SDS: Week 8 (n=25, 27)	0.18 (± 0.88)	0.18 (± 0.66)		
Weight SDS: Week 12 (n=25, 26)	0.23 (± 0.91)	0.25 (± 0.65)		
Weight SDS: Week 16 (n=25, 26)	0.23 (± 0.97)	0.25 (± 0.74)		
Weight SDS: Week 20 (n=25, 27)	0.25 (± 0.95)	0.24 (± 0.67)		
Weight SDS: Week 26 (n=25, 26)	0.32 (± 0.93)	0.19 (± 0.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Hypophenylalanemia - Kuvan Continuous Study

End point title	Number of Subjects With Hypophenylalanemia - Kuvan Continuous Study

End point description:

Hypophenylalanemia is defined as the condition of blood Phe levels <120 mcmol/L.

Safety population consisted of all subjects who had some safety assessment data available (at least one visit in vital signs, AE or laboratory results) in the Study Period and who received at least one dose of Kuvan in the Study Period, or who were randomized to Phe-restricted diet alone.

End point type	Secondary

End point timeframe:

Week 26

End point values	Kuvan® + Phe-restricted Diet - Continuous	Phe-restricted Diet - Continuous		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: Subjects				
number (not applicable)	10	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) - Kuvan Continuous Study

End point title	Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) - Kuvan Continuous Study

End point description:

Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP)

Intention-to-treat (ITT) population consisted of all the randomized subjects at the start of the study and were analyzed according to the group allocated. "n" signifies number of evaluable subjects in the specified categories for each reporting group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, and 26

End point values	Kuvan® + Phe-restricted Diet - Continuous	Phe-restricted Diet - Continuous		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	29		
Units: mmHg				
arithmetic mean (standard deviation)				
SBP: Baseline (n=25, 25)	93.5 (± 11.0)	93.1 (± 14.4)		
SBP: Week 4 (n=22, 25)	95.9 (± 14.6)	101.5 (± 17.6)		
SBP: Week 8 (n=23, 25)	95.9 (± 17.5)	95.7 (± 17.9)		
SBP: Week 12 (n=23, 26)	97.0 (± 13.2)	95.2 (± 9.8)		
SBP: Week 16 (n=23, 26)	95.0 (± 14.5)	98.2 (± 12.3)		
SBP: Week 20 (n=21, 27)	95.6 (± 14.1)	98.4 (± 12.6)		
SBP: Week 26 (n=22, 25)	97.5 (± 11.1)	96.8 (± 8.7)		
DBP: Baseline (n=25, 25)	55.8 (± 9.0)	57.1 (± 8.1)		
DBP: Week 4 (n=22, 25)	59.8 (± 9.8)	59.0 (± 13.3)		
DBP: Week 8 (n=23, 25)	59.1 (± 7.8)	55.2 (± 8.7)		
DBP: Week 12 (n=23, 26)	58.5 (± 6.2)	57.4 (± 9.7)		
DBP: Week 16 (n=23, 26)	57.7 (± 12.1)	58.5 (± 11.2)		
DBP: Week 20 (n=21, 27)	57.5 (± 12.1)	58.4 (± 6.3)		
DBP: Week 26 (n=22, 25)	59.0 (± 7.0)	59.2 (± 9.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Samples With Phenylalanine Hydroxylase (PAH) Gene Mutations - Kuvan Continuous Study

End point title	Number of Samples With Phenylalanine Hydroxylase (PAH) Gene Mutations - Kuvan Continuous Study

End point description:

The DNA samples received were quantified by using a nanophotometer, and were aliquoted to a concentration of 20 nanogram/microliter DNA and aliquots from each sample were distributed to one 96-well plate and Sanger sequenced. All samples showing only 1 mutation were analyzed by MLPA. All samples showing only 1 or no mutation were resequenced completely (exons 1 to 13) in both directions. Kuvan® (sapropterin dihydrochloride) tablets were administered orally at a dose of 10 milligram/kilogram/day (mg/kg/day). If after 4 weeks, there was less than 20 percent (%) increase in subject's Phe tolerance versus baseline, the dose was escalated to 20 mg/kg/day. Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria.

End point type	Secondary

End point timeframe:

Screening (within 42 days prior to Day 1 of the 26-week study period)

End point values	Pharmacogenetics			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: Sample				
number (not applicable)	73			

Statistical analyses

No statistical analyses for this end point

Secondary: Population Pharmacokinetic (PK) Parameter: Apparent Clearance (CL/f) - Kuvan Continuous Study

End point title	Population Pharmacokinetic (PK) Parameter: Apparent Clearance (CL/f) - Kuvan Continuous Study

End point description:

CL/f is the rate at which a drug is removed from the body via renal, hepatic and other clearance pathways.The reason for pooling subjects receiving Kuvan and subjects with Phe-restricted Diet was to facilitate the estimation of baseline endogenous value of BH4 which can only be observed in subjects not receiving the treatment.
All enrolled subjects for whom at least one adequately documented BH4 concentration value and dose record were included in the population PK analysis. This includes patients receiving either Kuvan® tablets were administered orally at a dose of 10 milligram/kilogram/day (mg/kg/day) in conjunction with a Phe-restricted diet, or diet alone. If after 4 weeks, there was less than 20 percent (%) increase in subject's Phe tolerance versus baseline, the Kuvan® dose was escalated to 20 mg/kg/day. Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria.

End point type	Secondary

End point timeframe:

Weeks 5 to 12

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	52			
Units: litre per hour				
arithmetic mean (standard error)	2780 (± 2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Population PK Parameter: Apparent Volume of Distribution (V/f) - Kuvan Continuous Study

End point title	Population PK Parameter: Apparent Volume of Distribution (V/f) - Kuvan Continuous Study

End point description:

V/f is defined as the distribution of a medication between the plasma and the rest of the body after the dose. It is the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of the drug. The reason for pooling subjects receiving Kuvan and subjects with Phe-restricted Diet was to facilitate the estimation of baseline endogenous value of BH4 which can only be observed in subjects not receiving the treatment. Ignoring this baseline endogenous value would have led to biased stimated of the Kuvan PK parameters. This pooling assumes that the addition of Kuvan does not confound the BH4 measurements in these analyses as a consequence the population PK parameters describing the PK of BH4 are the same for the 2 arms and so cannot be presented in terms of per arm/per treatment group based as per the planned analysis.

End point type	Secondary

End point timeframe:

Weeks 5 to 12

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	52			
Units: litre(s)				
arithmetic mean (standard error)	3870 (± 5.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Population PK Parameter: Area Under the Plasma Concentration Curve, Time 0 to Infinity (AUC [0-infinity]) - Kuvan Continuous Study

End point title	Population PK Parameter: Area Under the Plasma Concentration Curve, Time 0 to Infinity (AUC [0-infinity]) - Kuvan Continuous Study

End point description:

AUC [0-infinity] was estimated by determining total area under the curve of the concentration versus time curve extrapolated to infinity. Since AUC could not be obtained from non-compartmental analysis because of sparse data, AUC = Dose/(CL/F); CL/F was population apparent clearance estimated from the population PK model, & Dose the actual total dose received by the patient on one dosing interval. The reason for pooling subjects receiving Kuvan &subjects with Phe-restricted Diet was to facilitate estimation of baseline endogenous value of BH4 which can only be observed in subjects not receiving treatment. Ignoring this baseline endogenous value would have led to biased estimated of Kuvan PK parameters. This pooling assumes that the the addition of Kuvan does not confound the BH4 measurements in these analyses as a consequence the population PK parameters describing the PK of BH4 were same for the 2 arms and cannot be presented per arm/per treatment group as per planned analysis.

End point type	Secondary

End point timeframe:

Weeks 5 to 12

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	52			
Units: microgram*hour/litre				
arithmetic mean (standard deviation)				
Population PK Analysis Set: Age Group 1 (< 1 Year)	234.89 (± 89.82)			
Population PK Analysis Set: Age Group 2 (1-2 Yrs)	215.74 (± 63.88)			
Population PK Analysis Set: Age Group 2 (>= 2 Yrs)	206.22 (± 103.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Population PK Parameter: Terminal Elimination Half-life (t1/2) - Kuvan Continuous Study

End point title	Population PK Parameter: Terminal Elimination Half-life (t1/2) - Kuvan Continuous Study

End point description:

The t1/2 was defined as the time required for plasma concentration of drug to decrease 50 percent (%) in the final stage of elimination. Since t1/2 could not be obtained from non-compartmental analysis because of sparse data, t1/2 was estimated as Log(2)*(V/F)/(CL/F), where V/F & CL/F were the population apparent central Volume & clearance, estimated from population PK model. The reason for pooling subjects receiving Kuvan & subjects with Phe-restricted Diet was to facilitate the estimation of baseline endogenous value of BH4 which can only observed in subjects not receiving treatment. Ignoring this baseline endogenous value would have led biased stimated of the Kuvan PK parameters. This pooling assumes that the addition of Kuvan does not confound the BH4 measurements in these analyses as a consequence the population PK parameters describing the PK of BH4 are the same for the 2 arms and so cannot be presented in terms of per arm/per treatment group based as per the planned analysis.

End point type	Secondary

End point timeframe:

Weeks 5 to 12

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	52			
Units: hour				
number (not applicable)	0.96			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Dietary Phe Tolerance - Kuvan Extension study

End point title	Change from Baseline of Dietary Phe Tolerance - Kuvan Extension study

End point description:

Change from Baseline of Dietary Phe Tolerance (mg/kg/day) Over Time by Age Group (ITTE Population)

End point type	Secondary

End point timeframe:

Baseline value, Month 12 - Baseline, Month 24 - Baseline, End of Extension Period (EOS) – Baseline

End point values	Kuvan® + Phe-restricted Diet - Extension	Phe-restricted Diet - Extension		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: mg/kg/day				
arithmetic mean (standard deviation)				
Baseline value (<12M) (n=25, n=26)	42.86 (± 9.19)	59.00 (± 28.51)		
Baseline value (12 - <24M) (n=25, n=26)	46.00 (± 23.48)	49.25 (± 18.63)		
Baseline value (24 - <48M) (n=25, n=26)	23.89 (± 6.70)	45.90 (± 24.85)		
Month 12 – Baseline (<12M) (n=25, n=26)	38.20 (± 37.04)	6.00 (± 16.70)		
Month 12 – Baseline (12 - <24M) (n=25, n=26)	38.67 (± 19.94)	14.20 (± 21.22)		
Month 12 – Baseline (24 - <48M) (n=25, n=26)	46.00 (± 25.97)	6.57 (± 31.18)		
Month 24 – Baseline (<12M) (n=25, n=26)	40.50 (± 30.24)	-11.50 (± 33.39)		
Month 24 – Baseline (12 - <24M) (n=25, n=26)	26.60 (± 19.84)	6.50 (± 17.71)		
Month 24 – Baseline (24 - <48M) (n=25, n=26)	34.25 (± 9.74)	6.67 (± 7.02)		
EOS – Baseline (<12M) (n=25, n=26)	53.60 (± 52.20)	-4.00 (± 14.53)		
EOS – Baseline (12 - <24M) (n=25, n=26)	35.20 (± 22.68)	10.25 (± 17.75)		
EOS – Baseline (24 - <48M) (n=25, n=26)	23.67 (± 18.23)	2.33 (± 4.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline over Time in Blood Pressure - Kuvan Extension Study

End point title	Change from Baseline over Time in Blood Pressure - Kuvan Extension Study

End point description:

Change from Baseline over Time in Blood Pressure (mmHg) - Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) by Age Group (ITTE Population)

End point type	Secondary

End point timeframe:

Baseline value, Month 12 - Baseline, Month 24 - Baseline, EOS - Baseline

End point values	Kuvan® + Phe-restricted Diet - Extension	Phe-restricted Diet - Extension		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: mmHg				
arithmetic mean (standard deviation)				
SBP - Baseline value (<12M) (n=25, n=26)	94.86 (± 13.55)	96.25 (± 7.30)		
SBP - Baseline value (12 - <24M) (n=25, n=26)	87.71 (± 7.41)	97.50 (± 9.99)		
SBP - Baseline value (24 - <48M) (n=25, n=26)	104.44 (± 16.97)	95.30 (± 10.02)		
SBP - Month 12 – Baseline (<12M) (n=25, n=26)	2.50 (± 19.42)	11.43 (± 15.40)		
SBP - Month 12 – Baseline (12 - <24M) (n=25, n=26)	2.00 (± 12.15)	2.00 (± 12.90)		
SBP - Month 12 – Baseline (24 - <48M) (n=25, n=26)	-1.78 (± 13.51)	5.14 (± 13.99)		
SBP - Month 24 – Baseline (<12M) (n=25, n=26)	1.40 (± 14.74)	-1.50 (± 10.45)		
SBP - Month 24 – Baseline (12 - <24M) (n=25, n=26)	12.00 (± 10.02)	4.57 (± 15.90)		
SBP - Month 24 – Baseline (24 - <48M) (n=25, n=26)	2.33 (± 11.64)	2.83 (± 8.33)		
SBP - EOS – Baseline (<12M) (n=25, n=26)	-1.29 (± 16.31)	-4.00 (± 10.30)		
SBP - EOS – Baseline (12 - <24M) (n=25, n=26)	10.00 (± 9.35)	6.00 (± 23.16)		
SBP - EOS – Baseline (24 - <48M) (n=25, n=26)	18.25 (± 10.28)	8.33 (± 2.89)		
DBP - Baseline value (<12M) (n=25, n=26)	57.43 (± 13.88)	58.63 (± 10.88)		
DBP - Baseline value (12 - <24M) (n=25, n=26)	53.86 (± 6.09)	58.63 (± 8.72)		
DBP - Baseline value (24 - <48M) (n=25, n=26)	68.44 (± 13.00)	58.80 (± 10.14)		
DBP - Month 12 – Baseline (<12M) (n=25, n=26)	-1.17 (± 23.83)	10.29 (± 16.27)		
DBP - Month 12 – Baseline (12 - <24M) (n=25, n=26)	4.29 (± 6.16)	2.29 (± 8.36)		
DBP - Month 12 – Baseline (24 - <48M) (n=25, n=26)	-10.56 (± 13.59)	1.14 (± 12.77)		
DBP - Month 24 – Baseline (<12M) (n=25, n=26)	-1.40 (± 5.94)	-3.38 (± 10.35)		
DBP - Month 24 – Baseline (12 - <24M) (n=25, n=26)	6.50 (± 10.45)	2.00 (± 10.58)		

DBP - Month 24 – Baseline (24 - <48M) (n=25, n=26)	-7.83 (± 7.25)	-1.00 (± 10.30)		
DBP - EOS – Baseline (<12M) (n=25, n=26)	3.71 (± 15.68)	-4.14 (± 10.07)		
DBP - EOS – Baseline (12 - <24M) (n=25, n=26)	5.00 (± 5.29)	1.60 (± 7.47)		
DBP - EOS – Baseline (24 - <48M) (n=25, n=26)	7.25 (± 7.59)	10.00 (± 5.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline over Time in Growth Parameters - Kuvan Extension Study

End point title	Change from Baseline over Time in Growth Parameters - Kuvan Extension Study

End point description:

Change from Baseline over Time in Growth Parameters (Body Mass Index (BMI), Maximal Occipital-Frontal Head Circumference (MOFHC), Height and Weight) by Age Group (ITTE Population).

End point type	Secondary

End point timeframe:

Baseline value, Month 12 - Baseline, Month 24 - Baseline, EOS – Baseline

End point values	Kuvan® + Phe-restricted Diet - Extension	Phe-restricted Diet - Extension		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: Standard Deviation Scores				
arithmetic mean (standard deviation)				
BMI SDS: Baseline value (<12M) (n=25, n=26)	-0.39 (± 0.90)	0.26 (± 0.87)		
BMI SDS: Baseline value (12 - <24M) (n=25, n=26)	0.56 (± 0.49)	0.70 (± 0.91)		
BMI SDS: Baseline value (24 - <48M) (n=25, n=26)	0.78 (± 0.55)	0.30 (± 0.69)		
BMI SDS: Month 12-Baseline (<12M) (n=25, n=26)	0.96 (± 0.91)	0.21 (± 0.68)		
BMI SDS: Month 12-Baseline (12 - <24M)(n=25, n=26)	0.21 (± 0.94)	0.23 (± 0.80)		
BMI SDS: Month 12-Baseline (24 - <48M)(n=25, n=26)	0.17 (± 0.42)	-0.02 (± 0.50)		
BMI SDS: Month 24-Baseline (<12M) (n=25, n=26)	0.46 (± 0.56)	0.47 (± 0.75)		
BMI SDS: Month 24-Baseline (12 - <24M)(n=25, n=26)	-0.03 (± 0.74)	-0.11 (± 0.41)		
BMI SDS: Month 24-Baseline (24 - <48M)(n=25, n=26)	-0.16 (± 0.46)	-0.23 (± 0.51)		
BMI SDS: EOS - Baseline (<12M) (n=25, n=26)	0.45 (± 0.91)	0.53 (± 0.89)		

BMI SDS: EOS - Baseline (12 - <24M) (n=25, n=26)	0.47 (± 0.74)	-0.37 (± 0.07)		
MOFHC SDS: Baseline value (<12M) (n=25, n=26)	42.56 (± 2.52)	45.75 (± 1.89)		
MOFHC SDS: Baseline value (12-<24M) (n=25, n=26)	47.83 (± 2.25)	48.75 (± 2.92)		
MOFHC SDS: Baseline value (24-<48M) (n=25, n=26)	49.33 (± 2.42)	48.88 (± 1.65)		
MOFHC SDS: Month 12-Baseline (<12M) (n=25, n=26)	6.09 (± 2.06)	2.96 (± 1.59)		
MOFHC SDS: Month 12-Baseline (12-<24M) (n=25,n=26)	1.66 (± 1.23)	1.31 (± 1.39)		
MOFHC SDS: Month 12-Baseline (24-<48M) (n=25,n=26)	1.33 (± 0.98)	0.93 (± 2.62)		
MOFHC SDS: Month 24-Baseline (<12M) (n=25, n=26)	6.77 (± 2.44)	3.59 (± 1.01)		
MOFHC SDS: Month 24-Baseline (12-<24M) (n=25,n=26)	2.86 (± 0.80)	1.80 (± 1.10)		
MOFHC SDS: Month 24-Baseline (24-<48M) (n=25,n=26)	1.67 (± 1.03)	2.18 (± 1.61)		
MOFHC SDS: EOS - Baseline (<12M) (n=25, n=26)	7.95 (± 2.06)	4.47 (± 1.23)		
MOFHC SDS: EOS-Baseline (12-<24M) (n=25, n=26)	3.54 (± 1.09)	1.36 (± 0.84)		
MOFHC SDS: EOS-Baseline (24-<48M) (n=25, n=26)	2.68 (± 1.64)	2.63 (± 1.41)		
Height SDS: Baseline value (<12M) (n=25, n=26)	0.43 (± 0.94)	0.11 (± 1.03)		
Height SDS: Baseline value (12-<24M) (n=25, n=26)	-0.28 (± 1.42)	-0.19 (± 0.66)		
Height SDS: Baseline value (24-<48M) (n=25, n=26)	-0.49 (± 1.13)	-0.35 (± 1.03)		
Height SDS: Month 12-Baseline (<12M) (n=25, n=26)	-0.38 (± 0.58)	0.01 (± 0.65)		
Height SDS:Month 12-Baseline (12-<24M) (n=25,n=26)	-0.09 (± 0.80)	0.11 (± 0.48)		
Height SDS:Month 12-Baseline (24-<48M) (n=25,n=26)	0.12 (± 0.66)	0.10 (± 0.57)		
Height SDS: Month 24-Baseline (<12M) (n=25, n=26)	-0.46 (± 0.67)	-0.16 (± 0.75)		
Height SDS:Month 24-Baseline (12-<24M) (n=25,n=26)	0.28 (± 0.53)	0.19 (± 0.74)		
Height SDS:Month 24-Baseline (24-<48M) (n=25,n=26)	-0.37 (± 0.92)	0.11 (± 0.52)		
Height SDS: EOS-Baseline (<12M) (n=25, n=26)	-0.39 (± 0.81)	-0.18 (± 0.55)		
Height SDS: EOS-Baseline (12-<24M) (n=25, n=26)	-0.12 (± 0.62)	0.31 (± 0.62)		
Weight SDS: Baseline value (<12M) (n=25, n=26)	-0.04 (± 0.74)	0.25 (± 0.71)		
Weight SDS: Baseline value (12-<24M) (n=25, n=26)	0.21 (± 0.95)	0.38 (± 0.63)		
Weight SDS: Baseline value (24-<48M) (n=25, n=26)	0.22 (± 0.73)	-0.01 (± 0.67)		
Weight SDS: Month 12-Baseline (<12M) (n=25, n=26)	0.48 (± 0.48)	0.14 (± 0.36)		
Weight SDS:Month 12-Baseline (12-<24M) (n=25,n=26)	0.06 (± 0.60)	0.21 (± 0.38)		
Weight SDS:Month 12-Baseline (24-<48M) (n=25,n=26)	0.19 (± 0.31)	0.03 (± 0.25)		
Weight SDS: Month 24 - Baseline (<12M) (n=25,n=26)	0.10 (± 0.50)	0.22 (± 0.61)		

Weight SDS:Month 24-Baseline (12-<24M) (n=25,n=26)	-0.01 (± 0.67)	0.01 (± 0.33)		
Weight SDS:Month 24-Baseline (24-<48M) (n=25,n=26)	-0.34 (± 0.65)	-0.10 (± 0.11)		
Weight SDS: EOS - Baseline (<12M) (n=25, n=26)	0.12 (± 0.34)	0.22 (± 0.66)		
Weight SDS: EOS - Baseline (12-<24M) (n=25, n=26)	0.15 (± 0.83)	-0.10 (± 0.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Neuromotor Developmental Milestones (ITTE population) - Kuvan Extension Study

End point title	Neuromotor Developmental Milestones (ITTE population) - Kuvan Extension Study

End point description:

Neurodevelopmental Status Assessment by Age Group in Subjects ≥42 Months at End of Year 1, 2, and 3 (Wechsler Preschool and Primary Scale of Intelligence) - ITTE Population

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24 and EOS (Month 36 -End of Extension Period)

End point values	Kuvan® + Phe-restricted Diet - Extension	Phe-restricted Diet - Extension		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: Standard Deviation Scores (SDS)				
arithmetic mean (standard deviation)				
Full Scale IQ:Month12-Baseline(24-<48M)(n=25,n=26)	110.44 (± 17.58)	111.43 (± 26.22)		
Full Scale IQ:Month24-Baseline(12-<24M)(n=25,n=26)	98.00 (± 20.07)	94.40 (± 19.69)		
Full Scale IQ:Month24-Baseline(24-<48M)(n=25,n=26)	105.50 (± 12.12)	115.25 (± 7.27)		
Full Scale IQ: EOS - Baseline (<12M) (n=25, n=26)	120.67 (± 14.67)	108.60 (± 14.81)		
Full Scale IQ: EOS-Baseline (24-<48M) (n=25,n=26)	95.25 (± 8.26)	108.20 (± 14.75)		
Performance IQ:Month12Baseline(24-<48M)(n=25,n=26)	104.33 (± 19.76)	96.43 (± 20.26)		
Performance IQ:Month24Baseline(12-<24M)(n=25,n=26)	92.33 (± 22.01)	95.40 (± 22.79)		
Performance IQ:Month24Baseline(24-<48M)(n=25,n=26)	105.25 (± 4.99)	111.00 (± 12.19)		
Performance IQ:EOS-Baseline(<12M)(n=25, n=26)	116.33 (± 15.28)	96.80 (± 13.41)		
Performance IQ:EOS-Baseline(24-<48M)(n=25,n=26)	93.75 (± 11.24)	103.40 (± 18.17)		

Verbal IQ: Month12-Baseline (24-<48M)(n=25,n=26)	114.89 (± 17.29)	117.57 (± 22.27)		
Verbal IQ: Month24-Baseline (12-<24M)(n=25,n=26)	101.33 (± 18.23)	95.40 (± 14.03)		
Verbal IQ: Month24-Baseline (24-<48M)(n=25,n=26)	110.00 (± 15.56)	115.75 (± 6.85)		
Verbal IQ: EOS-Baseline (<12M) (n=25, n=26)	111.50 (± 13.11)	109.80 (± 12.17)		
Verbal IQ: EOS-Baseline (24-<48M) (n=25, n=26)	101.50 (± 9.04)	115.60 (± 11.95)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug administration up to 31 days after the last dose of study drug administration

Adverse event reporting additional description:

Safety population included all subjects who either received at least one dose of Kuvan in the study period, or were randomized to Phe-restricted diet alone and who had some safety assessment data available.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Kuvan® + Phe-restricted Diet - Continuous

Reporting group description:

Kuvan® (sapropterin dihydrochloride) tablets were administered orally at a dose of 10 milligram/kilogram/day (mg/kg/day). If after 4 weeks, there was less than 20 percent (%) increase in subject's Phe tolerance versus baseline, the dose was escalated to 20 mg/kg/day. Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria.

Reporting group title	Phe-restricted Diet - Continuous

Reporting group description:

Phenylalanine (Phe)-restricted diet was adjusted every 2 weeks, based on the mean Phe levels of the previous 2 weeks using pre-defined Phe adjustment criteria. After 26 weeks, the starting dose of Kuvan will be 10 mg/kg/day, and the dose may be adjusted by the Investigator, if clinically indicated, but it may not exceed 20 mg/kg/day.

Reporting group title	Kuvan® + Phe-restricted Diet - Extension

Reporting group description: -

Reporting group title	Phe-restricted Diet - Extension

Reporting group description: -

Serious adverse events	Kuvan® + Phe-restricted Diet - Continuous	Phe-restricted Diet - Continuous	Kuvan® + Phe-restricted Diet - Extension
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 27 (11.11%)	1 / 27 (3.70%)	6 / 25 (24.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Animal bite			

subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle Fracture			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Febrile Convulsion			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Immune Thrombocytopenic			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Balanoposthitis			

subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Adenoidal Hypertrophy			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis Media			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Viral Infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phe-restricted Diet - Extension		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 26 (26.92%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Animal bite			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clavicle Fracture			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Febrile Convulsion			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Immune Thrombocytopenic			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Adenoidal Hypertrophy			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Otitis Media			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral Infection			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Kuvan® + Phe-restricted Diet - Continuous	Phe-restricted Diet - Continuous	Kuvan® + Phe-restricted Diet - Extension
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)	27 / 27 (100.00%)	25 / 25 (100.00%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	17 / 27 (62.96%)	18 / 27 (66.67%)	23 / 25 (92.00%)
occurrences (all)	32	37	127
Fatigue			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	3 / 25 (12.00%)
occurrences (all)	0	0	5
Immune system disorders			

House Dust Allergy			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 27 (48.15%)	13 / 27 (48.15%)	19 / 25 (76.00%)
occurrences (all)	29	25	97
Rhinorrhoea			
subjects affected / exposed	2 / 27 (7.41%)	8 / 27 (29.63%)	5 / 25 (20.00%)
occurrences (all)	8	17	26
Nasal Congestion			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Oropharyngeal pain			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	3 / 25 (12.00%)
occurrences (all)	0	0	3
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Investigations			
Body Temperature Increased			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	4
Cardiac Murmur			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Cardiac Murmur Functional			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Amino Acid Level Decreased			

subjects affected / exposed	12 / 27 (44.44%)	11 / 27 (40.74%)	11 / 25 (44.00%)
occurrences (all)	43	29	45
Amino Acid Level Increased			
subjects affected / exposed	10 / 27 (37.04%)	9 / 27 (33.33%)	3 / 25 (12.00%)
occurrences (all)	39	22	6
Amino Acid Level Abnormal			
subjects affected / exposed	1 / 27 (3.70%)	4 / 27 (14.81%)	0 / 25 (0.00%)
occurrences (all)	1	15	0
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	2	0	2
Clavicle Fracture			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Face Injury			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Lip Injury			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Fall			
subjects affected / exposed	2 / 27 (7.41%)	3 / 27 (11.11%)	4 / 25 (16.00%)
occurrences (all)	3	3	5
Contusion			
subjects affected / exposed	3 / 27 (11.11%)	1 / 27 (3.70%)	4 / 25 (16.00%)
occurrences (all)	3	1	4
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	8
Nervous system disorders			
Hyperreflexia			
subjects affected / exposed	2 / 27 (7.41%)	3 / 27 (11.11%)	0 / 25 (0.00%)
occurrences (all)	2	5	0
Headache			

subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	1 / 25 (4.00%)
occurrences (all)	0	4	3
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	4 / 25 (16.00%)
occurrences (all)	0	0	4
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	1 / 27 (3.70%)	3 / 27 (11.11%)	4 / 25 (16.00%)
occurrences (all)	4	4	11
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 27 (7.41%)	3 / 27 (11.11%)	6 / 25 (24.00%)
occurrences (all)	3	3	7
Gastrointestinal disorders			
Dental Caries			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Enteritis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Stomatitis			
subjects affected / exposed	3 / 27 (11.11%)	1 / 27 (3.70%)	2 / 25 (8.00%)
occurrences (all)	3	1	2
Teething			
subjects affected / exposed	1 / 27 (3.70%)	2 / 27 (7.41%)	2 / 25 (8.00%)
occurrences (all)	3	5	4
Toothache			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	10 / 27 (37.04%)	9 / 27 (33.33%)	17 / 25 (68.00%)
occurrences (all)	18	12	59
Diarrhoea			
subjects affected / exposed	9 / 27 (33.33%)	6 / 27 (22.22%)	12 / 25 (48.00%)
occurrences (all)	14	13	29
Abdominal Pain			

subjects affected / exposed	3 / 27 (11.11%)	2 / 27 (7.41%)	4 / 25 (16.00%)
occurrences (all)	7	2	12
Constipation			
subjects affected / exposed	2 / 27 (7.41%)	1 / 27 (3.70%)	4 / 25 (16.00%)
occurrences (all)	2	2	5
Abdominal pain upper			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	6 / 27 (22.22%)	2 / 27 (7.41%)	2 / 25 (8.00%)
occurrences (all)	8	4	2
Eczema			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Rash			
subjects affected / exposed	8 / 27 (29.63%)	6 / 27 (22.22%)	7 / 25 (28.00%)
occurrences (all)	13	9	9
Dry Skin			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences (all)	3	0	0
Infections and infestations			
Coxsackie Viral Infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Exanthema Subitum			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Laryngitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	4
Lower Respiratory Tract Infection			

subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Otitis Media Acute			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Respiratory Tract Infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	3
Nasopharyngitis			
subjects affected / exposed	13 / 27 (48.15%)	11 / 27 (40.74%)	17 / 25 (68.00%)
occurrences (all)	30	27	99
Rhinitis			
subjects affected / exposed	8 / 27 (29.63%)	6 / 27 (22.22%)	13 / 25 (52.00%)
occurrences (all)	9	10	39
Pharyngitis			
subjects affected / exposed	7 / 27 (25.93%)	3 / 27 (11.11%)	13 / 25 (52.00%)
occurrences (all)	10	3	20
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 27 (3.70%)	6 / 27 (22.22%)	4 / 25 (16.00%)
occurrences (all)	1	7	7
Gastroenteritis			
subjects affected / exposed	4 / 27 (14.81%)	3 / 27 (11.11%)	6 / 25 (24.00%)
occurrences (all)	4	3	11
Otitis Media			
subjects affected / exposed	2 / 27 (7.41%)	3 / 27 (11.11%)	5 / 25 (20.00%)
occurrences (all)	2	5	7
Bronchitis			
subjects affected / exposed	2 / 27 (7.41%)	2 / 27 (7.41%)	6 / 25 (24.00%)
occurrences (all)	2	5	18
Acute Tonsillitis			
subjects affected / exposed	2 / 27 (7.41%)	1 / 27 (3.70%)	2 / 25 (8.00%)
occurrences (all)	2	1	2
Ear infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	4 / 25 (16.00%)
occurrences (all)	0	0	6
Hand-foot-and-mouth disease			

subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Pharyngotonsillitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	3 / 25 (12.00%)
occurrences (all)	0	0	3
Scarlet fever			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Varicella			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	7 / 25 (28.00%)
occurrences (all)	0	0	9
Viral infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	3 / 25 (12.00%)
occurrences (all)	0	0	5
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	3 / 25 (12.00%)
occurrences (all)	0	3	6

Non-serious adverse events	Phe-restricted Diet - Extension		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 26 (92.31%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	22 / 26 (84.62%)		
occurrences (all)	86		
Fatigue			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Immune system disorders			
House Dust Allergy			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		

Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 26 (57.69%)		
occurrences (all)	52		
Rhinorrhoea			
subjects affected / exposed	8 / 26 (30.77%)		
occurrences (all)	31		
Nasal Congestion			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	6		
Psychiatric disorders			
Irritability			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Investigations			
Body Temperature Increased			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Cardiac Murmur			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Cardiac Murmur Functional			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Amino Acid Level Decreased			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	6		
Amino Acid Level Increased			

subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	19		
Amino Acid Level Abnormal			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Clavicle Fracture			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Face Injury			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Lip Injury			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	2		
Nervous system disorders			
Hyperreflexia			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Blood and lymphatic system disorders			

Lymphadenopathy subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all)	8 / 26 (30.77%) 12		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	6 / 26 (23.08%) 8		
Gastrointestinal disorders Dental Caries subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Enteritis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Stomatitis subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Teething subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 12		
Toothache subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Vomiting subjects affected / exposed occurrences (all)	16 / 26 (61.54%) 33		
Diarrhoea subjects affected / exposed occurrences (all)	11 / 26 (42.31%) 19		
Abdominal Pain subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 5		
Constipation			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	5		
Dry Skin			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Coxsackie Viral Infection			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Exanthema Subitum			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Laryngitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Otitis Media Acute			

subjects affected / exposed	2 / 26 (7.69%)			
occurrences (all)	3			
Respiratory Tract Infection				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	7			
Nasopharyngitis				
subjects affected / exposed	12 / 26 (46.15%)			
occurrences (all)	64			
Rhinitis				
subjects affected / exposed	6 / 26 (23.08%)			
occurrences (all)	27			
Pharyngitis				
subjects affected / exposed	3 / 26 (11.54%)			
occurrences (all)	6			
Upper Respiratory Tract Infection				
subjects affected / exposed	4 / 26 (15.38%)			
occurrences (all)	9			
Gastroenteritis				
subjects affected / exposed	8 / 26 (30.77%)			
occurrences (all)	12			
Otitis Media				
subjects affected / exposed	4 / 26 (15.38%)			
occurrences (all)	7			
Bronchitis				
subjects affected / exposed	5 / 26 (19.23%)			
occurrences (all)	6			
Acute Tonsillitis				
subjects affected / exposed	2 / 26 (7.69%)			
occurrences (all)	2			
Ear infection				
subjects affected / exposed	7 / 26 (26.92%)			
occurrences (all)	8			
Hand-foot-and-mouth disease				
subjects affected / exposed	3 / 26 (11.54%)			
occurrences (all)	3			
Influenza				

subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Pharyngotonsillitis			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Scarlet fever			
subjects affected / exposed	5 / 26 (19.23%)		
occurrences (all)	6		
Varicella			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	4		
Viral infection			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2009	(UK only) To specifically define the duration of treatment in the Extension Period as requested by the Medicines and Healthcare Products Regulatory Agency.
26 April 2011	1. To add a new safety visit at Month 1 in the 3 year Extension Period only for subjects who did not receive Kuvan treatment during the preceding 26-week Study Period 2. To clarify what constitutes an 'overdose' with regards to each daily Kuvan administration 3. To clarify the preparation and timing of each Kuvan dose with regards to administration with meals and in the event a preferred morning administration time is missed 4. To document that a Steering Committee has been established
31 October 2011	1. To clarify inclusion criterion number 6 with regard to the number of blood Phe values and the period during which these values are assessed prior to screening. 2. To increase the screening period time in order to facilitate the BH4 testing procedure for subjects who have not undergone such a test prior to screening.
23 January 2013	1. To increase the maximum number of enrolled subjects aged <12 months from 10 to 20. 2. Administrative changes
08 April 2014	1. Amendment of PGx ICF 2. Deletion of central diary reading 3. Administrative changes
17 October 2014	(Czech Republic only) To prolong the Extension Period for trial participants in the Czech Republic.
09 November 2015	To modify the Sponsor information and responsible individuals to reflect the updated Sponsor, BioMarin International Ltd.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported