Clinical trial results:
A phase III non-comparative open-label clinical study to evaluate the response to and safety of Kuvan (sapropterin dihydrochloride) after 6 weeks of treatment in patients of 4 to 18 years of age with phenylketonuria who have elevated blood Phenylalanine levels

Summary

EudraCT number	2015-001650-15
Trial protocol	Outside EU/EEA
Global end of trial date	04 October 2013

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	EMR 700773_510

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01732471
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.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 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is an open-label, non-comparative, Phase 3 study to evaluate the degree, frequency of response and safety of Kuvan® (sapropterin dihydrochloride) in subjects aged 4 to 18 years who have phenylketonuria and with elevated blood phenylalanine level of greater than or equal to 450 micromole per liter.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2012
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	Ukraine: 10
Country: Number of subjects enrolled	Russian Federation: 80
Worldwide total number of subjects	90
EEA total number of subjects	0

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)	50
Adolescents (12-17 years)	40
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:

One hundred eight subjects were screened. The trial included 90 subjects with Phenylketonuria. Thirty subjects responded to treatment and continued participation in the trial.

Period 1

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

Arms

Arm title	Kuvan®

Arm description:

Kuvan® (sapropterin dihydrochloride) was administered orally at a dose of 20 milligram per kilogram per day (mg/kg/day) once daily for 8 days. If there is 30 percent (%) decrease in blood phenylalanine levels from baseline at the end of Day 8, then treatment was continued at the same dose for further 6 weeks.

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

Dosage and administration details:

Sapropterin dihydrochloride was administered orally at a dose of 20 mg/kg/day once daily for 8 days.

Number of subjects in period 1	Kuvan®
Started	90
Completed	89
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	90	90	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	9.59		
standard deviation	± 4.09	-	
Gender, Male/Female Units: participants			
Female	41	41	
Male	49	49	

End points

End points reporting groups

Reporting group title	Kuvan®

Reporting group description:

Kuvan® (sapropterin dihydrochloride) was administered orally at a dose of 20 milligram per kilogram per day (mg/kg/day) once daily for 8 days. If there is 30 percent (%) decrease in blood phenylalanine levels from baseline at the end of Day 8, then treatment was continued at the same dose for further 6 weeks.

Primary: Percentage of subjects with response to Kuvan® (sapropterin dihydrochloride) treatment

End point title	Percentage of subjects with response to Kuvan® (sapropterin dihydrochloride) treatment[1]

End point description:

Response to Kuvan® (sapropterin dihydrochloride) treatment was defined as a reduction in blood phenylalanine levels of greater than or equal to 30% at Day 8 as compared to baseline. Overall (ITT) population included all participants who had efficacy assessment result from at least 1 visit except for the inclusion visit. Overall (ITT) population included all subjects who had efficacy assessment result from at least 1 visit except for the inclusion visit

End point type	Primary

End point timeframe:

Day 8

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: Only descriptive data was planned to be represented in the endpoint.

End point values	Kuvan®			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: percentage of Subjects				
number (confidence interval 95%)	33.3 (23.7 to 44.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline in blood phenylalanine levels at Day 8 in overall population

End point title	Percent change from Baseline in blood phenylalanine levels at Day 8 in overall population

End point description:

Percent change in blood phenylalanine levels after 8-day Kuvan® therapy (response test period) was calculated as (blood phenylalanine level at Day 8 minus blood phenylalanine level at baseline)*100/ blood phenylalanine level at baseline. Overall (ITT) population included all subjects who had efficacy assessment result from at least 1 visit except for the inclusion visit.

End point type	Secondary

End point timeframe:

Baseline, Day 8

End point values	Kuvan®			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: percent change				
arithmetic mean (standard deviation)	-14.14 (± 28.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline in blood phenylalanine levels at Day 8 in sub-population of responders

End point title	Percent change from Baseline in blood phenylalanine levels at Day 8 in sub-population of responders

End point description:

Percent change in blood phenylalanine levels after 8-day Kuvan® therapy (response test period) was calculated as (blood phenylalanine level at Day 8 minus blood phenylalanine level at baseline)*100/ blood phenylalanine level at baseline. Sub-population of responders included subjects with reduction in blood phenylalanine levels of greater than or equal to 30% at Day 8 as compared to baseline.

End point type	Secondary

End point timeframe:

Baseline, Day 8

End point values	Kuvan®			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percent change				
arithmetic mean (standard deviation)	-44.25 (± 15.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs) and serious adverse

events (SAEs) in overall safety population

End point title	Number of subjects with adverse events (AEs) and serious adverse events (SAEs) in overall safety population

End point description:

An adverse event (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. Overall safety population included all subjects who received at least 1 dose of investigational medicinal product.

End point type	Secondary

End point timeframe:

Baseline up to Week 11

End point values	Kuvan®			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: subjects				
number (not applicable)				
AEs	24			
SAEs	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 11

Adverse event reporting additional description:

An AE is any new untoward medical occurrences/worsening of pre-existing medical condition without regard to possibility of causal relationship. An SAE is an AE resulting in any of following outcomes:death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Kuvan®

Reporting group description:

Kuvan® (sapropterin dihydrochloride) was administered orally at a dose of 20 mg/kg/day once daily for 8 days. If there is 30 percent (%) decrease in blood phenylalanine levels from baseline at the end of Day 8, then treatment was continued at the same dose for further 6 weeks.

Serious adverse events	Kuvan®		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 90 (1.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Kuvan®		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 90 (25.56%)		
Injury, poisoning and procedural complications			
Heat stroke			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Vascular disorders			
Retinal vascular disorder			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Syncope			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Eye disorders			
Myopia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Faeces pale			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Gastroduodenitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	2		
Reproductive system and breast disorders			

Dysmenorrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Genital labial adhesions			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Respiratory tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Respiratory tract infection viral			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 90 (10.00%)		
occurrences (all)	11		
Skin and subcutaneous tissue disorders			
Skin odour abnormal			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Leukocyturia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		

Phenylketonuria alternative assessment type: Systematic subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 2		
Infections and infestations Oral herpes alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1		
Metabolism and nutrition disorders Iodine deficiency alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported