Clinical trial results:
ENDURE: A Phase IV, prospective, open-label, uncontrolled, multi-centre cohort trial to assess the responsiveness of subjects with phenylketonuria (PKU) to treatment with Kuvan® 20 mg/kg/day for 28 days

Summary

EudraCT number	2009-018168-81
Trial protocol	DK NO
Global end of trial date	02 May 2012

Results information

Result version number	v1
This version publication date	23 May 2016
First version publication date	24 July 2015

Trial information

Trial identification

Sponsor protocol code	EMR700773-503 (ENDURE)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01082328
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Str. 250, Darmstadt, Germany, 64293
Public contact	Merck KGaA Communication Center, Merck KGaA, 49 6151 72 5200, service@merckgroup.com
Scientific contact	Merck KGaA Communication Center, Merck KGaA, 49 6151 72 5200, 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	02 May 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 May 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the proportion of responders (at least 30 percent [%] reduction from baseline in blood Phenylalanine [Phe] level) to 20 milligram per kilogram per day (mg/kg/day) Sapropterin dihydrochloride treatment at several time points during 28 +/- 1 days.

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	18 May 2010
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	Norway: 40
Country: Number of subjects enrolled	Denmark: 19
Worldwide total number of subjects	59
EEA total number of subjects	59

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)	15
Adolescents (12-17 years)	13
Adults (18-64 years)	31
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject in: 11 May 2010 Last subject in: 20 Mar 2012

Pre-assignment

Screening details:

A total of 61 subjects were screened and gave signed informed consent to participate in the study. Two subjects did not pass entry criteria and were withdrawn before the baseline visit, therefore 59 subjects were randomized and given treatment.

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) oral solution 20 milligram per kilogram (mg/kg) once daily for 28 +/- 1 days.

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

Dosage and administration details:

Subjects received once daily oral soluble tablet of Kuvan® (100mg sapropterin dihydrochloride) for 28 +/- 1 days with meal.The dose were calculated based on subject's body weight.

Number of subjects in period 1	Kuvan
Started	59
Completed	58
Not completed	1
Adverse event	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	59	59	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	21		
standard deviation	± 12.1	-	
Gender categorical Units: Subjects			
Female	34	34	
Male	25	25	

End points

End points reporting groups

Reporting group title	Kuvan

Reporting group description:

Kuvan® (sapropterin dihydrochloride) oral solution 20 milligram per kilogram (mg/kg) once daily for 28 +/- 1 days.

Primary: Percentage of Subjects With at Least 30 Percent Reduction From Baseline in Blood Phenylalanine (Phe) Level

End point title	Percentage of Subjects With at Least 30 Percent Reduction From Baseline in Blood Phenylalanine (Phe) Level[1]

End point description:

Response to treatment was defined as 30 percent reduction from Baseline in blood Phe Level during the 28 +/- 1 days.Full analysis set (FAS) population included all the subjects with a valid Baseline blood Phe level measure and who received at least one dose of Kuvan®.

End point type	Primary

End point timeframe:

Baseline up to Day 28 +/- 1

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: No statistical hypothesis tests were planned for Percentage of Participants With at Least 30 Percent Reduction From Baseline in Blood Phenylalanine (Phe) Level

End point values	Kuvan			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Percentage of subjects				
number (confidence interval 95%)	75 (62 to 85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs), Treatment Emergent Adverse Events, Treatment Related Adverse Events and AEs Leading to Withdrawal

End point title	Number of Subjects With Adverse Events (AEs), Treatment Emergent Adverse Events, Treatment Related Adverse Events and AEs Leading to Withdrawal

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to Baseline during a clinical study with an investigational medicinal product (IMP), regardless of causal relationship and even if no IMP has been administered. Safety population included all the subjects with a valid baseline blood Phe level measure and who received at least one dose of Kuvan®.

End point type	Secondary

End point timeframe:

Baseline up to Day 42 +/- 3

End point values	Kuvan			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Subjects				
AEs	58			
Treatment Emergent AEs	57			
Treatment Related AEs	36			
AEs leading to withdrawal	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Early-, Late-, Partial-Responders and Non-responders to Treatment With Kuvan®

End point title	Percentage of Early-, Late-, Partial-Responders and Non-responders to Treatment With Kuvan®

End point description:

Early responders defined as percentage of subjects with at least 30 percent reduction in Phe levels within the first seven days of treatment. Late responders defined as percentage of subjects with less than 30 percent reduction in Phe levels within first seven days of treatment, but at least 30 percent reduction in Phe levels within 28 +/- 1 days of treatment. Partial responders defined as percentage of participants with Phe levels reduction between 10 and 30 percent at any blood measurement within the 28 +/- 1 days of treatment. Non-responders defined as percentage of subjects with a Phe level reduction of less than 10 percent within 28 +/- 1 days. FAS population included all the subjects with a valid Baseline blood Phe level measure and who received at least one dose of Kuvan®.

End point type	Secondary

End point timeframe:

Baseline up to Day 28 +/- 1

End point values	Kuvan			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Percentage of subjects				
number (confidence interval 95%)				
Early Responders	64.4 (50.9 to 76.4)			
Late Responders	10.2 (3.8 to 20.8)			
Partial Responders	25.4 (15 to 38.4)			
Non-responders	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Greater Than or Equal to (>=) 30 Percent, 20 to 30 Percent, 10 to 20 Percent and Less Than (<) 10 Percent Reduction in Blood Phe Levels According to Phenylketonuria (PKU) Phenotypes

End point title	Percentage of Subjects With Greater Than or Equal to (>=) 30 Percent, 20 to 30 Percent, 10 to 20 Percent and Less Than (<) 10 Percent Reduction in Blood Phe Levels According to Phenylketonuria (PKU) Phenotypes

End point description:

The Phenylketonuria (PKU) is categorized as per phenotype into classical PKU: (blood Phe levels greater than [>] 1200 micromole per liter [mcmol/l]), mild PKU (blood Phe levels 600 to 1200 mcmol/l), mild Hyperphenylalaninaemia (HPA) (blood Phe levels 300 to 600 mcmol/l). FAS population included all the subjects with a valid Baseline blood Phe level measure and who received at least one dose of Kuvan®. 'n' signifies number of subjects who were evaluable for specified categories at different time points.

End point type	Secondary

End point timeframe:

Baseline up to Day 28 +/- 1

End point values	Kuvan			
Subject group type	Reporting group			
Number of subjects analysed	55[2]			
Units: percentage of subjects				
Mild HPA: >= 30 percent (n=7)	57			
Mild HPA: 20 to 30 percent (n=7)	29			
Mild HPA: 10 to 20 percent (n=7)	0			
Mild HPA: < 10 percent (n=7)	14			
Mild PKU: >= 30 percent (n=26)	69			
Mild PKU: 20 to 30 percent (n=26)	8			
Mild PKU: 10 to 20 percent (n=26)	4			
Mild PKU: < 10 percent (n=26)	19			
Classical PKU: >= 30 percent (n=22)	45			
Classical PKU: 20 to 30 percent (n=22)	0			
Classical PKU: 10 to 20 percent (n=22)	23			
Classical PKU: < 10 percent (n=22)	32			

Notes:

[2] - 'N' (number of subjects analyzed) signifies subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Early-, Late- and Partial-Responders According to Phenotype

End point title	Percentage of Early-, Late- and Partial-Responders According to Phenotype

End point description:

The PKU is categorized as per phenotype into classical PKU: (blood Phe levels > 1200 mcmol/l), mild PKU (blood Phe levels 600 to 1200 mcmol/l), mild HPA (blood Phe levels 300 to 600 mcmol/l). Early responders defined as percentage of subjects with at least 30 % reduction in Phe levels within the first 7

days of treatment. Late responders defined as percentage of subjects with < 30 % reduction in Phe levels within first seven days of treatment, but at least 30 % reduction in Phe levels within 28 +/- 1 days of treatment. Partial responders defined as percentage of subjects with Phe levels reduction between 10 and 30 % at any blood measurement within the 28 +/- 1 days of treatment. FAS population included all the subjects with a valid baseline blood Phe level measure and who received at least one dose of Kuvan®. 'n' signifies number of subjects who were evaluable for specified categories at different time points.

End point type	Secondary

End point timeframe:

Baseline up to Day 28 +/- 1

End point values	Kuvan			
Subject group type	Reporting group			
Number of subjects analysed	56[3]			
Units: percentage of subjects				
Mild HPA: Early Responders (n=7)	86			
Mild HPA: Late Responders (n=7)	0			
Mild HPA: Partial Responders (n=7)	14			
Mild PKU: Early Responders (n=26)	85			
Mild PKU: Late Responders (n=26)	4			
Mild PKU: Partial Responders (n=26)	12			
Classical PKU: Early Responders (n=23)	39			
Classical PKU: Late Responders (n=23)	17			
Classical PKU: Partial Responders (n=23)	43			

Notes:

[3] - 'N' (number of subjects analyzed) signifies subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Blood Phenylalanine-to-tyrosine Ratio

End point title	Mean Change From Baseline in Blood Phenylalanine-to-tyrosine Ratio

End point description:

Phenylalanine-to-tyrosine ratio is the best indicator of dopamine availability in PKU. The change in blood phenylalanine-to-tyrosine ratio at Day 28 was calculated as blood phenylalanine-to-tyrosine ratio at Day 28 minus blood phenylalanine-to-tyrosine ratio at Baseline. FAS population included all the subjects with a valid Baseline blood Phe level measure and who received at least one dose of Kuvan®. ‘n’ signifies number of subjects who were evaluable for specified categories at different time points.

End point type	Secondary

End point timeframe:

Baseline, Day 28

End point values	Kuvan			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=59)	10.978 (± 5.978)			
Change at Day 28 (n=58)	-2.316 (± 3.948)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Day 42 +/- 3

Adverse event reporting additional description:

An adverse event is defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to Baseline during a clinical study with an IMP, regardless of causal relationship and even if no IMP has been administered.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Kuvan

Reporting group description:

Kuvan® (sapropterin dihydrochloride) oral solution 20 milligram per kilogram (mg/kg) once daily for 28 +/- 1 days.

Serious adverse events	Kuvan		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 59 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	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	58 / 59 (98.31%)		
Vascular disorders			
Migraine			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Asthenia			

subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Discomfort			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
Influenza like illness			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Listless			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	10 / 59 (16.95%)		
occurrences (all)	10		
Dyspnoea			

subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Somatoform disorder			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Investigations			
Amino acid level decreased			
subjects affected / exposed	21 / 59 (35.59%)		
occurrences (all)	21		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Injury			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Joint injury			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Muscle strain			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Road traffic accident			

subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Cardiac disorders			
Dizziness			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	24 / 59 (40.68%)		
occurrences (all)	24		
Psychomotor hyperactivity			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Eye disorders			
Eye pruritus			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	6		
Aphthous stomatitis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	14 / 59 (23.73%)		
occurrences (all)	14		

Flatulence			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Gingival pruritus			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	14 / 59 (23.73%)		
occurrences (all)	14		
Tongue blistering			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Rash			

subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Rash maculo-papular			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Joint lock			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Tendon pain			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Oral herpes			

subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Viral infection			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Iron deficiency			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2010	Laboratory assessment were modified to be performed prior to the Kuvan treatment initiation. Blood Phe and tyrosine levels assessment was to be performed at 0, 8, 16 and 24 hours.
08 November 2011	The number of subjects (Earlier N=150; Now N=70) planned in the study and the number of recruiting sites were reduced. Consequently, the statistical section has been amended, since the reduction in sample size impacts the statistical method used. The reduction in sample size also impacts the precision of the primary endpoint. Considering the descriptive nature of the study, the precision is considered as acceptable. The treatment period with Kuvan® is amended to 28±1 days rather than 28 days. The method of administration of Kuvan was clarified (must be taken with water) and the definition of Kuvan overdose was clarified in this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/19261295

http://www.ncbi.nlm.nih.gov/pubmed/17693179