# 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<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 21 | | |
| standard deviation | ± 12.1 | - | |
| Gender categorical<br>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.<br>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.<br>The treatment period with Kuvan® is amended to 28±1 days rather than 28 days.<br>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