



## Clinical trial results:

### A Multicenter, Double-Blind, Placebo Controlled, Randomized, 2-Arm Phase IIa Pilot Trial Assessing the Effect of Sapropterin on Cognitive Abilities in Young Adults with Phenylketonuria

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2010-024311-13   |
| Trial protocol           | DE IT BE ES NL   |
| Global end of trial date | 07 November 2014 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 28 July 2016 |
| First version publication date | 28 July 2016 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | 700773-004 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01977820 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Merck Serono, a division of Merck KGaA  |
| Sponsor organisation address | Frankfurter Strasse 250, Darmstadt, Germany, 64293  |
| Public contact               | Communication Centre merck KGaA, Merck KGaA, Merck Serono, a division of Merck KGaA, +49 6151725200, service@merckgroup.com |
| Scientific contact           | Communication Centre merck KGaA, Merck KGaA, Merck Serono, a division of 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? | No |

Notes:

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**Results analysis stage**

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 07 November 2014 |
| Is this the analysis of the primary completion data? | No               |

|                                  |                  |
|----------------------------------|------------------|
| Global end of trial reached?     | Yes              |
| Global end of trial date         | 07 November 2014 |
| Was the trial ended prematurely? | Yes              |

Notes:

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**General information about the trial**

Main objective of the trial:

The purpose of this pilot trial is to assess the effect of sapropterin on the cognitive abilities of young adults with phenylketonuria (PKU).

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                          | 24 February 2014 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |                |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Italy: 1       |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Worldwide total number of subjects   | 2              |
| EEA total number of subjects         | 1              |

Notes:

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**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)                     | 0 |
| Adolescents (12-17 years)                 | 0 |
| Adults (18-64 years)                      | 2 |
| From 65 to 84 years                       | 0 |
| 85 years and over                         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

First/Last subject (informed consent): 24 Feb 2014/12 Aug 2014. Study premature termination date: 07 Nov 2014; Subjects were randomized at 2 study centers.

### Pre-assignment

Screening details:

A total of 10 subjects were screened for the trial. 2 subjects were randomized (1 subjects in the Sapropterin and 1 subjects in the placebo).

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Overall study (overall period)         |
| Is this the baseline period? | Yes                                    |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Subject, Investigator, Carer, Assessor |

### Arms

|                              |                           |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes                       |
| <b>Arm title</b>             | Experimental: Sapropterin |

Arm description:

Sapropterin tablets was administered orally once daily during both the 2-Week response test period and 24-Week study period. The subject underwent the study assessments and procedures according to the study protocol until the study was terminated by the Sponsor.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Sapropterin  |
| Investigational medicinal product code |              |
| Other name                             | Kuvan        |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Subjects received Sapropterin tablets orally once daily at a dose of 20 milligram per kilogram (mg/kg) during both the 2-Week response test period and 24-Week study period.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | Drug: Placebo |
|------------------|---------------|

Arm description:

Subjects was administered Sapropterin tablets orally once daily during the 2-Week response test period and Placebo tablets matching to Sapropterin was administered orally once daily during the 24-Week study period. The subject underwent the study assessments and procedures according to the study protocol until the study was terminated by the Sponsor.

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Placebo           |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Subjects received Sapropterin tablets orally once daily at a dose of 20 mg/kg during both the 2-Week response test period and Placebo tablets matching to Sapropterin was administered orally once daily during the 24-Week study period.

| <b>Number of subjects in period 1</b> | Experimental:<br>Sapropterin | Drug: Placebo |
|---------------------------------------|------------------------------|---------------|
| Started                               | 1                            | 1             |
| Completed                             | 0                            | 0             |
| Not completed                         | 1                            | 1             |
| Sponsor terminated the study          | 1                            | 1             |

## Baseline characteristics

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Experimental: Sapropterin |
|-----------------------|---------------------------|

Reporting group description:

Sapropterin tablets was administered orally once daily during both the 2-Week response test period and 24-Week study period. The subject underwent the study assessments and procedures according to the study protocol until the study was terminated by the Sponsor.

|                       |               |
|-----------------------|---------------|
| Reporting group title | Drug: Placebo |
|-----------------------|---------------|

Reporting group description:

Subjects was administered Sapropterin tablets orally once daily during the 2-Week response test period and Placebo tablets matching to Sapropterin was administered orally once daily during the 24-Week study period. The subject underwent the study assessments and procedures according to the study protocol until the study was terminated by the Sponsor.

| Reporting group values                | Experimental:<br>Sapropterin | Drug: Placebo | Total |
|---------------------------------------|------------------------------|---------------|-------|
| Number of subjects                    | 1                            | 1             | 2     |
| Age categorical<br>Units: Subjects    |                              |               |       |
| >=18 to 29 Years                      | 1                            | 1             | 2     |
| Gender categorical<br>Units: Subjects |                              |               |       |
| Female                                | 1                            | 0             | 1     |
| Male                                  | 0                            | 1             | 1     |

## End points

### End points reporting groups

|  |                           |
|--|---------------------------|
| Reporting group title  | Experimental: Sapropterin |
| Reporting group description:<br>Sapropterin tablets was administered orally once daily during both the 2-Week response test period and 24-Week study period. The subject underwent the study assessments and procedures according to the study protocol until the study was terminated by the Sponsor.   |                           |
| Reporting group title  | Drug: Placebo             |
| Reporting group description:<br>Subjects was administered Sapropterin tablets orally once daily during the 2-Week response test period and Placebo tablets matching to Sapropterin was administered orally once daily during the 24-Week study period. The subject underwent the study assessments and procedures according to the study protocol until the study was terminated by the Sponsor. |                           |

### Primary: Number of Subjects With Adverse Events (AEs), Serious AEs (SAEs), AEs Leading to Death and AEs Leading to Discontinuation

|  |  |
|--|--|
| End point title  | Number of Subjects With Adverse Events (AEs), Serious AEs (SAEs), AEs Leading to Death and AEs Leading to Discontinuation <sup>[1]</sup> |
| End point description:<br>An AE was defined as any new untoward medical occurrences/worsening of pre-existing medical condition without regard to possibility of causal relationship. A 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. The safety analysis population included all the randomized subjects who received at least one dose of study treatment. |  |
| End point type   | Primary  |
| End point timeframe:<br>Screening up to 24 weeks + 4-week follow-up  |  |
| Notes:<br>[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.<br>Justification: Only descriptive data was planned to be analyzed.  |  |

| End point values               | Experimental:<br>Sapropterin | Drug: Placebo   |  |  |
|--------------------------------|------------------------------|-----------------|--|--|
| Subject group type             | Reporting group              | Reporting group |  |  |
| Number of subjects analysed    | 1                            | 1               |  |  |
| Units: subjects                |                              |                 |  |  |
| AEs                            | 1                            | 0               |  |  |
| SAEs                           | 0                            | 0               |  |  |
| AEs leading to death           | 0                            | 0               |  |  |
| AEs leading to discontinuation | 0                            | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Screening up to 24 weeks + 4-week follow-up

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 14.1 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Sapropterin |
|-----------------------|-------------|

Reporting group description:

Subject was administered with 20 mg/kg sapropterin tablets orally once daily during the 2-week response test period. The subject upon completing the 2-Week response test period was randomized to receive sapropterin during the 24-week study period. The subject underwent the study assessments and procedures according to the study protocol until the study was terminated by the Sponsor.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subject was administered with 20 mg/kg sapropterin tablets orally once daily during the 2-week response test period. The subject upon completing the 2-Week response test period was randomized to receive placebo tablets matching to sapropterin orally once daily during the 24-week study period. The subject underwent the study assessments and procedures according to the study protocol until the study was terminated by the Sponsor.

| Serious adverse events                            | Sapropterin   | Placebo       |  |
|---|---------------|---------------|--|
| Total subjects affected by serious adverse events |               |               |  |
| subjects affected / exposed                       | 0 / 1 (0.00%) | 0 / 1 (0.00%) |  |
| number of deaths (all causes)                     | 0             | 0             |  |
| number of deaths resulting from adverse events    | 0             | 0             |  |

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

| Non-serious adverse events                            | Sapropterin     | Placebo       |  |
|---|-----------------|---------------|--|
| Total subjects affected by non-serious adverse events |                 |               |  |
| subjects affected / exposed                           | 1 / 1 (100.00%) | 0 / 1 (0.00%) |  |
| Nervous system disorders                              |                 |               |  |
| Headache  |                 |               |  |
| subjects affected / exposed                           | 1 / 1 (100.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)                                     | 2               | 0             |  |
| Gastrointestinal disorders                            |                 |               |  |

|                             |                 |               |  |
|-----------------------------|-----------------|---------------|--|
| Abdominal Pain              |                 |               |  |
| subjects affected / exposed | 1 / 1 (100.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 2               | 0             |  |
| Aphthous stomatitis         |                 |               |  |
| subjects affected / exposed | 1 / 1 (100.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1               | 0             |  |
| Abdominal pain upper        |                 |               |  |
| subjects affected / exposed | 1 / 1 (100.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 2               | 0             |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|   |
|---|
| The study was prematurely discontinued by the Sponsor due to severe enrolment difficulties as a consequence of the limited availability of treatment naïve patients with a diagnosis of phenyl ketonuria. |
|---|

Notes: