



## 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
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##### 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**

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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**

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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**

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**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**

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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
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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: 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
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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
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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: Sapropterin	Drug: Placebo	Total
Number of subjects	1	1	2
Age categorical Units: Subjects			
>=18 to 29 Years	1	1	2
Gender categorical Units: Subjects			
Female	1	0	1
Male	0	1	1

## End points

### End points 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.	

### 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: 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: Screening up to 24 weeks + 4-week follow-up	
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 analyzed.	

End point values	Experimental: 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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### Reporting groups

Reporting group title	Sapropterin
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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
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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.

<b>Serious adverse events</b>	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 %

<b>Non-serious adverse events</b>	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: