



## Clinical trial results:

### A Switch-Over, Open-Label Study of the Safety, Pharmacokinetics, and Efficacy of HPN-100, Followed by Long-Term Treatment with HPN-100, in Pediatric Subjects under 6 Years of Age with Urea Cycle Disorders (UCDs)

#### Summary

EudraCT number	2014-003248-12
Trial protocol	Outside EU/EEA
Global end of trial date	02 December 2011

#### Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	06 July 2016

#### Trial information

##### Trial identification

Sponsor protocol code	HPN-100-012
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01347073
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Horizon Therapeutics Inc.
Sponsor organisation address	150 S. Saunders Road, Lake Forest, United States, 60045
Public contact	Elizabeth Robinson, Horizon Therapeutics Inc., clinicaltrials@horizonpharma.com
Scientific contact	Tom Vescio, Horizon Therapeutics Inc., clinicaltrials@horizonpharma.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000297-PIP02-12
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 December 2011
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 December 2011
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

This non-randomized, open-label study was approximately one year in duration and consisted of a short term sodium phenylbutyrate (NaPBA) to glycerol phenylbutyrate (HPN-100) switch-over part (EudraCT #2014-003248-12) involving two overnight stays followed by a 12-month long term treatment period (EudraCT #2014-003249-82) involving monthly visits.

The objectives of this study were to assess safety, pharmacokinetics, and ammonia control during treatment with HPN-100 in pediatric subjects (aged 29 days to < 6 years) with UCDs.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. The study was conducted in accordance with legal and regulatory requirements including Guidance for Good Clinical Practice (International Conference on Harmonization [ICH] 1996), and the Declaration of Helsinki (World Medical Association 2008). Only subjects who met the inclusion criteria and none of the exclusion criteria were enrolled to this study.

Written informed consent was to be obtained from the subject's legally acceptable representative and assent by the minor subject, as applicable, before screening or baseline assessments. Instructions were given to the subject's legally acceptable representative in case of emergency or other questions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	15
EEA total number of subjects	0

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	4
Children (2-11 years)	11
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Study Locations: Houston, TX; Minneapolis, MN; Washington, DC; New York, NY; Cleveland, OH; Portland, ME; Portland, OR

Study Initiation Date: September 9, 2011

Study Completion Date: December 2, 2011

### Pre-assignment

Screening details:

Subjects eligible for this study included children aged 29 days to < 6 years with either a diagnosed or clinically suspected UCD who were receiving a stable dose of the powder formulation of NaPBA.

### Period 1

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

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	HPN-100

Arm description:

On Day 2 of the study, subjects were switched from NaPBA to HPN-100 in an inpatient setting. Subjects were discharged once the investigator deemed them to be clinically controlled on HPN-100.

After receiving all of their PBA in the form of HPN-100 for at least 4 days and at the end of the 10-day switch-over phase, subjects may have continued in the long-term follow-up treatment phase with HPN-100 for up to 12 months.

Arm type	Experimental
Investigational medicinal product name	glycerol phenylbutyrate
Investigational medicinal product code	HPN-100
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

HPN-100 was to be administered just prior to breastfeeding or administration of formula or food.

The maximum recommended dose of HPN-100 in subjects weighing less than 20 kg is 0.52 mL/kg/day (equivalent to 600 mg/kg/day of NaPBA), and is 11.48 mL/m<sup>2</sup>/day in heavier subjects (equivalent to 13 g/m<sup>2</sup>/day of NaPBA). The maximum total daily HPN-100 dose allowed is 17.4 mL/day, which is approximately equivalent to 20 g/day of NaPBA.

<b>Arm title</b>	NaPBA
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Arm description:

On Day 1, subjects were observed for at least 24 hours while receiving NaPBA and underwent serial blood draws before being switched to HPN-100 in an inpatient setting.

Arm type	Experimental
Investigational medicinal product name	sodium phenylbutyrate
Investigational medicinal product code	NaPBA
Other name	AMMONAPS
Pharmaceutical forms	Powder and solvent for oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

NaPBA was to be administered orally at the dose levels recommended in the prescribing information,

450 to 600 mg/kg per day for subjects weighing less than 20 kg, or 9.9 to 13 g/m<sup>2</sup> per day for larger subjects. In clinical practice, the dose of NaPBA is individualized based on the severity of the enzyme deficiency, diet, and other factors.

<b>Number of subjects in period 1</b>	HPN-100	NaPBA
Started	15	15
Completed	15	15

## Baseline characteristics

### Reporting groups

Reporting group title	Overall Study
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Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	15	15	
Age Categorical Units: participants			
Age continuous Units: years arithmetic mean standard deviation	2.87 ± 1.885	-	
Gender, Male/Female Units: participants			
Female	7	7	
Male	8	8	

## End points

### End points reporting groups

Reporting group title	HPN-100
Reporting group description: On Day 2 of the study, subjects were switched from NaPBA to HPN-100 in an inpatient setting. Subjects were discharged once the investigator deemed them to be clinically controlled on HPN-100.  After receiving all of their PBA in the form of HPN-100 for at least 4 days and at the end of the 10-day switch-over phase, subjects may have continued in the long-term follow-up treatment phase with HPN-100 for up to 12 months.	
Reporting group title	NaPBA
Reporting group description: On Day 1, subjects were observed for at least 24 hours while receiving NaPBA and underwent serial blood draws before being switched to HPN-100 in an inpatient setting.	

### Primary: Number of Subjects With Treatment-Emergent Adverse Events

End point title	Number of Subjects With Treatment-Emergent Adverse
End point description: Number of subjects with treatment-emergent adverse events during the switch-over portion of the protocol.	
End point type	Primary
End point timeframe: 2 weeks	
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: Data are summarized for this endpoint per protocol.	

End point values	HPN-100	NaPBA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: subjects				
number (not applicable)	6	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: HPN-100-012 Blood Ammonia Area Under the Curve (AUC) by Treatment During the Switch-over

End point title	HPN-100-012 Blood Ammonia Area Under the Curve (AUC) by Treatment During the Switch-over
End point description: 24-hour ammonia AUC of blood ammonia levels on Days 1 (NaPBA) and 10 (HPN-100) were compared.	
End point type	Secondary
End point timeframe: Day 1 and Day 10: Hour 0 (pre-first dose, fasted), Hour 8 (~2-4 hours after lunch or the second main	

meal and dose of NaPBA or HPN-100), Hour 12 (~4 hours after the last main meal) and 24 hours post-first dose (pre-first dose on following day, fasted).

End point values	HPN-100	NaPBA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	15		
Units: umol/L*hours				
arithmetic mean (standard deviation)	647.63 (± 379.944)	914.43 (± 630.206)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Frequency of Ammonia Levels Greater Than the Upper Limit of Normal (ULN) on HPN-100 Compared With NaPBA

End point title	Frequency of Ammonia Levels Greater Than the Upper Limit of Normal (ULN) on HPN-100 Compared With NaPBA
End point description:	
Ammonia values were converted to SI units (umol/L) and normalized to a standard ULN of 35 umol/L prior to analysis.	
End point type	Secondary
End point timeframe:	
2 weeks	

End point values	HPN-100	NaPBA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15 <sup>[2]</sup>	15 <sup>[3]</sup>		
Units: Ammonia Values > ULN				
number (not applicable)	8	22		

Notes:

[2] - number of ammonia values analyzed=53

[3] - number of ammonia values analyzed=58

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Day 10

Adverse event reporting additional description:

Treatment-emergent adverse events are presented.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.1
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### Reporting groups

Reporting group title	HPN-100
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Reporting group description:

On Day 2 of the study, subjects were switched from NaPBA to HPN-100 in an inpatient setting. Subjects were discharged once the investigator deemed them to be clinically controlled on HPN-100.

After receiving all of their PBA in the form of HPN-100 for at least 4 days and at the end of the 10-day switch-over phase, subjects may have continued in the long-term follow-up treatment phase with HPN-100 for up to 12 months.

Reporting group title	NaPBA
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Reporting group description:

On Day 1, subjects were observed for at least 24 hours while receiving NaPBA and underwent serial blood draws before being switched to HPN-100 in an inpatient setting.

Serious adverse events	HPN-100	NaPBA	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	HPN-100	NaPBA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)	0 / 15 (0.00%)	
Investigations			
Cardiac murmur			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			

Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	
Gastrointestinal disorders			
Vomiting subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	0 / 15 (0.00%) 0	
Flatulence subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Rash papular subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 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 protocol was designed to capture information important for evaluating safety, pharmacokinetics, and efficacy while recognizing sampling limitations in young children and current standard of care.
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Notes: