



## 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	2014-003249-82
Trial protocol	Outside EU/EEA
Global end of trial date	04 April 2013

#### 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, MD, 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	04 April 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 April 2013
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 10-day 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: 23
Worldwide total number of subjects	23
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)	7
Children (2-11 years)	16
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: April 4, 2013

### Pre-assignment

Screening details:

The first part of this open-label study consisted of a switch-over period during which subjects were switched from the current medication (NaPBA) to HPN-100. All subjects in the switch-over were enrolled into the 12-month long-term treatment phase.

### 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	HPN-100
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Arm description:

12-month long-term treatment with HPN-100.

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.

Number of subjects in period 1	HPN-100
Started	23
Completed	21
Not completed	2
Adverse event, non-fatal	1
Liver Transplant	1

## 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	23	23	
Age Categorical Units: participants			
Age continuous Units: years arithmetic mean standard deviation	2.7 ± 1.845	-	
Gender, Male/Female Units: participants			
Female	12	12	
Male	11	11	

## End points

### End points reporting groups

Reporting group title	HPN-100
Reporting group description: 12-month long-term treatment with HPN-100.	
Subject analysis set title	Pre-enrollment
Subject analysis set type	Full analysis
Subject analysis set description: 12-months preceding the study	
Subject analysis set title	Long-term Phase
Subject analysis set type	Full analysis
Subject analysis set description: The second part of this open-label study consisted of a 12-month long-term treatment phase with HPN-100. All subjects in the switch-over were enrolled into the long-term treatment phase.	

### 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 safety extension portion of the protocol.	
End point type	Primary
End point timeframe: 12 months	
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			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: subjects				
number (not applicable)	23			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean and Maximum Ammonia Levels During the Pre-enrollment Period and During Long-term HPN-100 Treatment

End point title	Mean and Maximum Ammonia Levels During the Pre-enrollment Period and During Long-term HPN-100 Treatment
End point description: Ammonia values were normalized based on a standard ULN of 35 µmol/L. All available values were included (including those obtained during hyperammonemic crises).	
End point type	Secondary
End point timeframe: 12 months pre-enrollment, 12 months	

End point values	Pre-enrollment	Long-term Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: umol/L*hours				
arithmetic mean (standard deviation)				
Maximum Ammonia	192.35 (± 218.687)	154.37 (± 250.558)		
Average Ammonia	56.43 (± 39.256)	38.72 (± 27.202)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Frequency of Ammonia Levels Greater Than the Upper Limit of Normal (ULN) During the 12 Months Preceding the Study and During the Long-term Treatment Phase

End point title	Frequency of Ammonia Levels Greater Than the Upper Limit of Normal (ULN) During the 12 Months Preceding the Study and During the Long-term Treatment Phase
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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
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End point timeframe:

12 months pre-enrollment, 12 months

End point values	Pre-enrollment	Long-term Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23 <sup>[2]</sup>	23 <sup>[3]</sup>		
Units: ammonia values > ULN	146	35		

Notes:

[2] - number of ammonia values analyzed=362

[3] - number of ammonia values analyzed=180

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Hyperammonemic Crises (HAC)

End point title	Number of Hyperammonemic Crises (HAC)
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End point description:

Number of HACs during pre-enrollment on NaPBA compared with HACs during HPN-100 treatment.

End point type	Secondary
End point timeframe:	
12 months pre-enrollment, 12 months	

<b>End point values</b>	Pre-enrollment	Long-term Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: number of crises				
number (not applicable)	29	12		

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During the Long-Term Treatment Phase: from approximately 2 weeks (end of switch-over period) through 12 months of long-term treatment, plus 30 days after study completion.

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:

12-month long-term treatment with HPN-100.

Serious adverse events	HPN-100		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 23 (47.83%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Chemical burn of skin			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			

subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperammonemia			
subjects affected / exposed	7 / 23 (30.43%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 0		
Hypophagia			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	HPN-100		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Blood bicarbonate decreased			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Nervous system disorders			
Hyporeflexia			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		

Lethargy subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 3		
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)  Neutropenia subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2  2 / 23 (8.70%) 2		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	9 / 23 (39.13%) 13		
Gastrointestinal disorders Gastroesophageal reflux disease subjects affected / exposed occurrences (all)  Diarrhea subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2  6 / 23 (26.09%) 10  11 / 23 (47.83%) 19		
Respiratory, thoracic and mediastinal disorders Nasal congestion subjects affected / exposed occurrences (all)  Cough subjects affected / exposed occurrences (all)  Rhinorrhea subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 3  6 / 23 (26.09%) 10  4 / 23 (17.39%) 4		
Skin and subcutaneous tissue disorders			

Rash papular subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 4		
Skin odor abnormal subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Infections and infestations			
Gastroenteritis subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 3		
Ear infection subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Otitis media subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 4		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	14 / 23 (60.87%) 29		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 4		

## 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:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24144944>

<http://www.ncbi.nlm.nih.gov/pubmed/23324524>