



## Clinical trial results:

### A Phase 2, Fixed-Sequence, Open-Label, Switch-Over Study of the Safety and Tolerability of HPN-100 Compared to Sodium Phenylbutyrate in Children

### 6-17 Years of Age with Urea Cycle Disorders, with a Long-Term Safety Extension

#### Summary

EudraCT number	2014-003247-36
Trial protocol	Outside EU/EEA
Global end of trial date	27 July 2011

#### Results information

Result version number	v1 (current)
This version publication date	10 June 2016
First version publication date	10 June 2016

#### Trial information

##### Trial identification

Sponsor protocol code	HPN-100-005
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00947544
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	27 July 2011
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 July 2011
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Protocol HPN-100-005 was the first study of HPN-100 in pediatric subjects with urea cycle disorders (UCDs) and was a fixed-sequence, open-label, switch over study of HPN-100 with a long-term (12 month) safety extension designed to assess the safety of HPN-100 and to prospectively assess its ability to control blood ammonia as compared with Sodium Phenylbutyrate (NaPBA). Upon DSMB review of the first ten subjects who completed the switch over part of the study, and with DSMB approval, up to an additional 20 subjects were enrolled into the safety extension part of the study. HPN-100 is a triglyceride that has a similar mechanism of action as NaPBA. It is a liquid with minimal taste and odor. Three teaspoons of HPN-100 (~17.4mL) delivers an equivalent amount of PBA to 40 tablets of NaPBA.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a 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 participants who met the inclusion criteria and none of the exclusion criteria were enrolled to this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2010
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	Canada: 1
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	17
EEA total number of subjects	0

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	0

months)	
Children (2-11 years)	11
Adolescents (12-17 years)	6
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study was to assess if HPN-100 could control blood ammonia compared with NaPBA. Subjects received NaPBA three times daily with meals during the first week and the same PBA mole equivalent dose of HPN-100 during the second week. Participants entered the safety extension part of the study and continued receiving open-label HPN-100 for 12 months.

### Period 1

Period 1 title	Safety-Extension Period (12 months) (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Switch Over and Safety Extension
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Arm description:

After the switch over, participants entered the safety extension part of the study and continued receiving open-label HPN-100 for up to 12 months.

Arm type	Experimental
Investigational medicinal product name	Glycerol phenylbutyrate
Investigational medicinal product code	HPN-100
Other name	GT4P, Glyceryl tri-(4-phenylbutyrate)
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

g/mL gram(s) millilitre 3 teaspoons of HPN-100 (approximately 17.4mL). For subjects who completed the switch-over phase, the starting dose in the safety extension was the same HPN-100 dose that was received while in the switch-over phase. For new subjects, the starting dose was the HPN-100 equivalent dose calculated from the subject's NaPBA dose:  $\text{NaPBA dose (g)} \times 0.95/1.1 = \text{total daily HPN-100 dose (mL)}$ .

<b>Arm title</b>	Safety Extension Only
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Arm description:

Subjects entered the safety extension part of the study only, and received open-label HPN-100 for up to 12 months.

Arm type	Experimental
Investigational medicinal product name	Glycerol Phenylbutyrate
Investigational medicinal product code	HPN-100
Other name	GT4P, Glyceryl tri-(4-phenylbutyrate)
Pharmaceutical forms	Oral liquid
Routes of administration	Other use

Dosage and administration details:

g/mL gram(s) millilitre 3 teaspoons of HPN-100 (approximately 17.4mL) Subjects dosed three times daily with meals. Subjects received open-label HPN-100 for up to 12 months.

<b>Number of subjects in period 1</b>	Switch Over and Safety Extension	Safety Extension Only
Started	11	6
Completed	10	6
Not completed	1	0
Consent withdrawn by subject	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Safety-Extension Period (12 months)
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Reporting group description: -

Reporting group values	Safety-Extension Period (12 months)	Total	
Number of subjects	17	17	
Age Categorical Units: participants			
<=18 years	17	17	
Between 18 and 65 years	0	0	
>=65 years	0	0	
Age Continuous Units: years			
arithmetic mean	10		
standard deviation	± 3.482	-	
Gender, Male/Female Units: participants			
Female	14	14	
Male	3	3	
Region of Enrollment Units: Subjects			
United States	16	16	
Canada	1	1	

## End points

### End points reporting groups

Reporting group title	Switch Over and Safety Extension
Reporting group description: After the switch over, participants entered the safety extension part of the study and continued receiving open-label HPN-100 for up to 12 months.	
Reporting group title	Safety Extension Only
Reporting group description: Subjects entered the safety extension part of the study only, and received open-label HPN-100 for up to 12 months.	
Subject analysis set title	Safety Extension (HPN-100)
Subject analysis set type	Full analysis
Subject analysis set description: There were 11 subjects who completed the switch over part of the study and 6 new subjects were enrolled in the safety extension part of the study due to DSMB approval.	
Subject analysis set title	HPN-100
Subject analysis set type	Full analysis
Subject analysis set description: Patients treated with HPN-100 who completed SF-15 at baseline and Month 12	

### Primary: Rate of Adverse Events during the safety extension part of the study

End point title	Rate of Adverse Events during the safety extension part of the study <sup>[1]</sup>
End point description: To evaluate the safety and PK characteristics of HPN-100 compared with sodium phenylbutyrate (NaPBA) in pediatric patients with urea cycle disorders.	
End point type	Primary
End point timeframe: One year (12 months) on HPN-100.	
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	Safety Extension (HPN-100)			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: subjects				
number (not applicable)	16			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number and causes of hyperammonemic events (safety extension)

End point title	Number and causes of hyperammonemic events (safety extension)
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End point description:

Number of Subjects with at Least One Hyperammonemic Crisis.

Hyperammonemic crisis is defined as follows:

- Clinical symptoms associated with ammonia of  $\geq 100 \mu\text{mol/L}$

End point type	Secondary
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End point timeframe:

1 year

End point values	Safety Extension (HPN-100)			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: subjects				
number (not applicable)				
Number of subjects with at least 1 HAC	3			
Number of Crises	3			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Quality of life assessed by the SF-15 questionnaire

End point title	Quality of life assessed by the SF-15 questionnaire
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End point description:

Change from baseline to Month 12.

The SF 15 questionnaire consists of 15 questions that assess the following:

- Physical functioning (5 questions)
- Emotional functioning (4 questions)
- Social functioning (3 questions)
- School functioning (3 questions)

Items were scored on a 5-point Likert scale from 0 (never) to 4 (almost always) or a 3-point scale (0 [not at all], 2 [sometimes], or 4 [a lot] for the young child self-report). Items were reverse-scored and linearly transformed to a 0–100 scale as follows: 0=100, 1=75, 2=50, 3=25, and 4=0. Total score was 0–100 scale (averaged from each functional areas). In the 0–100 scale, 0 is the worst score and 100 is best score.

Improved quality of life was shown by increased total score from baseline to Month 12.

End point type	Secondary
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End point timeframe:

1 year



<b>End point values</b>	HPN-100			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: score on a scale				
arithmetic mean (standard deviation)	4 ( $\pm$ 10.67)			

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Safety Extension period only (from Day 15 to 1 year)

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:

HPN-100: Patient treated with HPN-100

Serious adverse events	HPN-100		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 17 (17.65%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
gastroenteritis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
hyperammonemia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	HPN-100		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 17 (23.53%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Catheter site erythema			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Asthma			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Psychiatric disorders			
Food aversion			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Insomnia			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Intentional self-injury			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Aggression			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Investigations			
ALT increased			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
AST increased			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Anion gap increased			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood potassium decreased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Body temperature increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Electrocardiogram abnormal			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Vitamin D decreased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

White blood cell count increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Injury, poisoning and procedural complications Excoriation subjects affected / exposed occurrences (all)  Hand fracture subjects affected / exposed occurrences (all)  Joint sprain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1  1 / 17 (5.88%) 1  1 / 17 (5.88%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)  Migraine subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2  1 / 17 (5.88%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)  Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1  1 / 17 (5.88%) 1		
Eye disorders Blepharospasm subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)  Abdominal pain upper	4 / 17 (23.53%) 4		

subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Chapped lips			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin odour abnormal			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Dermatitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Psoriasis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal mass			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 17 (23.53%) 4		
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Sinusitis subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Body tinea subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Bronchitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Conjunctivitis infective subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Ear Infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Pharyngitis streptococcal subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Viral infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Hyperammonemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hypokalemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		



## 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

None reported

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### Online references

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