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	2014-003246-26
Trial protocol	Outside EU/EEA
Global end of trial date	01 August 2011

Results information

Result version number	v1 (current)
This version publication date	09 June 2016
First version publication date	09 June 2016

Trial information

Trial identification

Sponsor protocol code	HPN-100-005

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, 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)	EMEA-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	01 March 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 August 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. The extension part of the study was a separate study (HPN-100-005SE). 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 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 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	United States: 10
Country: Number of subjects enrolled	Canada: 1
Worldwide total number of subjects	11
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 months)	0
Children (2-11 years)	7
Adolescents (12-17 years)	4
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.

Period 1

Period 1 title	Switch-Over Period (2 weeks) (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	HPN-100 and NaPBA

Arm description:

1 week of NaPBA treatment followed by 1 week of HPN -100 treatment.

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) millitre 3 teaspoons of HPN-100 (approximately 17.4mL). Subjects dosed three times daily with meals during the first week and the same PBA mole-equivalent dose of HPN-100 during the second week.

Investigational medicinal product name	NaPBA
Investigational medicinal product code	sodium phenylbutyrate
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 as either tablets or powder. The dosing was in grams. Subjects dosed three times daily with meals. The dose level recommended by the investigator for each individual subject was not to exceed 20 g per day as recommended in the approved product labeling.

Number of subjects in period 1	HPN-100 and NaPBA
Started	11
Completed	11

Baseline characteristics

Reporting groups	
Reporting group title	HPN-100 and NaPBA
Reporting group description:	
1 week of NaPBA treatment followed by 1 week of HPN -100 treatment.	

Reporting group values	HPN-100 and NaPBA	Total	
Number of subjects	11	11	
Age Categorical Units: participants			
<=18 years	11	11	
Between 18 and 65 years	0	0	
>=65 years	0	0	
Age Continuous Units: years			
arithmetic mean	10.2		
standard deviation	± 3.95	-	
Gender, Male/Female Units: participants			
Female	10	10	
Male	1	1	
Region of Enrollment Units: Subjects			
United States	10	10	
Canada	1	1	

End points

End points reporting groups

Reporting group title	HPN-100 and NaPBA
Reporting group description:	
1 week of NaPBA treatment followed by 1 week of HPN -100 treatment.	
Subject analysis set title	HPN-100
Subject analysis set type	Full analysis
Subject analysis set description:	
HPN-100: Subjects treated with HPN-100	
Subject analysis set title	NaPBA
Subject analysis set type	Full analysis
Subject analysis set description:	
NaPBA: Subjects treated with NaPBA	

Primary: Rate of Adverse Events during the switchover part (number of participants showing Adverse Events)

End point title	Rate of Adverse Events during the switchover part (number of participants showing Adverse Events)[1]
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:	
1 week on each treatment for a total of 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	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	11		
Units: participants				
number (not applicable)	4	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood ammonia control

End point title	Blood ammonia control
End point description:	
To evaluate control of blood ammonia by HPN-100 compared with NaPBA in pediatric patients with urea cycle disorders. Results are for 24 hour ammonia levels.	
End point type	Secondary
End point timeframe:	
Day 7 (NaPBA) and Day 14 (HPN-100)	

End point values	HPN-100	NaPBA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	11		
Units: µmol·h/L				
arithmetic mean (standard deviation)	603.83 (± 187.92)	814.62 (± 322.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: NH3 Cmax on NaPBA vs. HPN-100 on the last day of treatment with each drug

End point title	NH3 Cmax on NaPBA vs. HPN-100 on the last day of treatment with each drug

End point description:

Blood samples were collected at pre-dose, 4, 8, 12, 16, 20, and 24 hour post dose on both Day 7 (NaPBA) and Day 14 (HPN-100).

End point type	Secondary

End point timeframe:

Day 7 (NaPBA) and Day 14 (HPN-100)

End point values	HPN-100	NaPBA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	11		
Units: subjects				
arithmetic mean (standard deviation)	47.77 (± 12.8)	55.66 (± 21.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate (percentage) of ammonia values above upper limit of normal (ULN) on NaPBA vs. HPN-100

End point title	Rate (percentage) of ammonia values above upper limit of normal (ULN) on NaPBA vs. HPN-100

End point description:

Blood samples were collected at pre-dose, 4, 8, 12, 16, 20, and 24 hour post dose on both Day 7 (NaPBA) and Day 14 (HPN-100). The percentages are the number of ammonia values above the upper limit of normal/ the total number of ammonia samples (76).

End point type	Secondary

End point timeframe:

Day 7 (NaPBA) and Day 14 (HPN-100)

End point values	HPN-100	NaPBA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	11		
Units: percentage of sample				
number (not applicable)	18.4	31.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Average ammonia values on NaPBA vs. HPN-100 on the last day of treatment with each drug (switch over)

End point title	Average ammonia values on NaPBA vs. HPN-100 on the last day of treatment with each drug (switch over)

End point description:

Blood samples were collected at pre-dose, 4, 8, 12, 16, 20, and 24 hour post dose on both Day 7 (NaPBA) and Day 14 (HPN-100).

End point type	Secondary

End point timeframe:

Day 7 (NaPBA) and Day 14 (HPN-100)

End point values	HPN-100	NaPBA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	11		
Units: µmol/L				
arithmetic mean (standard deviation)	28.68 (± 14.867)	37.75 (± 20.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Urinary PAGN 24-hour excretion values on NaPBA vs. HPN-100 (switch over)

End point title	Urinary PAGN 24-hour excretion values on NaPBA vs. HPN-100 (switch over)

End point description:

Urinary PAGN (phenylacetylglutamine) 24-hour excretion. Urine was collected during 0-12 hrs and 12-24 hrs.

End point type	Secondary

End point timeframe:

Day 7 (NaPBA) and Day 14 (HPN-100)

End point values	HPN-100	NaPBA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	11		
Units: µg				
arithmetic mean (standard deviation)	12501037 (± 56.9)	12512426 (± 51.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma PAA (phenylacetate) AUC0-24 values on NaPBA vs. HPN-100 on on the last day of treatment with each drug

End point title	Plasma PAA (phenylacetate) AUC0-24 values on NaPBA vs. HPN-100 on on the last day of treatment with each drug

End point description:

Blood samples were collected at pre-dose, 4, 8, 12, 16, 20, and 24 hour post dose on both Day 7 (NaPBA) and Day 14 (HPN-100).

End point type	Secondary

End point timeframe:

Day 7 (NaPBA) and Day 14 (HPN-100)

End point values	HPN-100	NaPBA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	11		
Units: µg•h/mL AUC 0-24				
arithmetic mean (standard deviation)	964 (± 63.6)	773 (± 73.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma PBA (phenylbutyrate) AUC0-24 values on NaPBA vs. HPN-100 on on the last day of treatment with each drug

End point title	Plasma PBA (phenylbutyrate) AUC0-24 values on NaPBA vs. HPN-100 on on the last day of treatment with each drug

End point description:

Blood samples were collected at pre-dose, 4, 8, 12, 16, 20, and 24 hour post dose on both Day 7

(NaPBA) and Day 14 (HPN-100).

End point type	Secondary

End point timeframe:

Day 7 (NaPBA) and Day 14 (HPN-100)

End point values	HPN-100	NaPBA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	11		
Units: µg*h/ml AUC 0-24				
arithmetic mean (standard deviation)	631 (± 44.9)	236 (± 105.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma PAGN AUC0-24 values on NaPBA vs. HPN-100 on on the last day of treatment with each drug

End point title	Plasma PAGN AUC0-24 values on NaPBA vs. HPN-100 on on the last day of treatment with each drug

End point description:

Blood samples were collected at pre-dose, 4, 8, 12, 16, 20, and 24 hour post dose on both Day 7 (NaPBA) and Day 14 (HPN-100).

End point type	Secondary

End point timeframe:

Day 7 (NaPBA) and Day 14 (HPN-100)

End point values	HPN-100	NaPBA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	11		
Units: µg*h/mL AUC 0-24				
arithmetic mean (standard deviation)	1378 (± 40.2)	1015 (± 44.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All treatment emergent adverse events (TEAE) were defined as an AE that began (or a pre-existing AE that worsened) after receiving study drug on Day 1 and at any time through 7 days after the last dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	HPN-100 and NaPBA

Reporting group description:

HPN-100: Patient treated with HPN-100

Serious adverse events	HPN-100 and NaPBA		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	HPN-100 and NaPBA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 11 (54.55%)		
Investigations			
Cardiac murmur			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphadenopathy			

subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 2 / 11 (18.18%) 2 1 / 11 (9.09%) 1		
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Ear infection subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

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