



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 |
|-----------------------|-------------|

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 |
| Arm title | 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/m²/day in heavier subjects (equivalent to 13 g/m²/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.

| | |
|------------------|-------|
| Arm title | NaPBA |
|------------------|-------|

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/m² 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.

| Number of subjects in period 1 | HPN-100 | NaPBA |
|---------------------------------------|---------|-------|
| Started | 15 | 15 |
| Completed | 15 | 15 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

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 ^[2] | 15 ^[3] | | |
| 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 |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 12.1 |
|--------------------|------|

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.

| 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

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.

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|---|
| 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: