



## 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 |
|-----------------------|-------------|

##### 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.,<br>clinicaltrials@horizonpharma.com |
| Scientific contact           | Tom Vescio, MD, Horizon Therapeutics Inc.,<br>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 |
|-----------|---------|

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

Reporting group description: -

| Reporting group values  | Overall Study  | Total |  |
|---|----------------|-------|--|
| Number of subjects  | 23             | 23    |  |
| Age Categorical<br>Units: participants                                  |                |       |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 2.7<br>± 1.845 | -     |  |
| Gender, Male/Female<br>Units: participants                              |                |       |  |
| Female  | 12             | 12    |  |
| Male  | 11             | 11    |  |

## End points

### End points reporting groups

|   |                 |
|---|-----------------|
| Reporting group title   | HPN-100         |
| Reporting group description:<br>12-month long-term treatment with HPN-100.  |                 |
| Subject analysis set title  | Pre-enrollment  |
| Subject analysis set type   | Full analysis   |
| Subject analysis set description:<br>12-months preceding the study  |                 |
| Subject analysis set title  | Long-term Phase |
| Subject analysis set type   | Full analysis   |
| Subject analysis set description:<br>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:<br>Number of subjects with treatment-emergent adverse events during the safety extension portion of the protocol.  |  |
| End point type  | Primary  |
| End point timeframe:<br>12 months   |  |
| Notes:<br>[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.<br>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:<br>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:<br>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 |
|-----------------|--|

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:

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) |
|-----------------|---------------------------------------|

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

### Dictionary used

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

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

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | HPN-100 |
|-----------------------|---------|

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

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

Notes:

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### Online references

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

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