Clinical trial results:
A Randomised, Controlled, Open-Label Parallel Arm Study of the Safety, Pharmacokinetics and Ammonia Control of RAVICTI® (Glycerol Phenylbutyrate [GPB]) Oral Liquid and Sodium Phenylbutyrate (NaPBA) in Phenylbutyrate Treatment Naïve Patients with Urea Cycle Disorders (UCDs)

Summary

EudraCT number	2015-000075-27
Trial protocol	BE GB AT IT ES
Global end of trial date	20 December 2022

Results information

Result version number	v2 (current)
This version publication date	05 August 2023
First version publication date	02 July 2023
Version creation reason	• Correction of full data set Endpoint title clarification

Trial information

Trial identification

Sponsor protocol code	HPN-100-021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03335488
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 073480

Notes:

Sponsors

Sponsor organisation name	Horizon Pharma USA, Inc.
Sponsor organisation address	150 S. Saunders Road, Lake Forest, Illinois, United States, 60045
Public contact	Director, Clinical Drug Development, Horizon Therapeutics, LLC, clinicaltrials@horizonpharma.com
Scientific contact	Director, Clinical Drug Development, Horizon Therapeutics, LLC, clinicaltrials@horizonpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety, tolerability, pharmacokinetics (PK) and ammonia control of RAVICTI and NaPBA in UCD subjects not currently treated with phenylacetic acid (also referred to as phenylacetate; PAA) prodrugs.

Protection of trial subjects:

The Investigator ensured that each parent/legal guardian was given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Parents/legal guardians were notified that the subjects were free to discontinue from the study at any time. Parents/legal guardians were given the opportunity to ask questions and allowed time to consider the information provided. Subjects or their caregiver/guardians were informed that medical records will be kept private and no information will be published without their permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 11
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	16
EEA total number of subjects	4

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	1

Infants and toddlers (28 days-23 months)	4
Children (2-11 years)	2
Adolescents (12-17 years)	2
Adults (18-64 years)	6
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In the Initial Treatment Period (approximately 28 days), eligible participants were randomized to one of two treatment arms: RAVICTI or NaPBA. For all Initial Treatment Period NaPBA participants and RAVICTI participants who were treatment failures, a Transition Period (7 days ± 2 days) with RAVICTI followed.

Pre-assignment

Screening details:

Screening assessments were performed within 30 days of Baseline.

All participants received RAVICTI in the Maintenance Period (8 Weeks) and the Safety Extension Period (12 Weeks).

Period 1

Period 1 title	Initial Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Randomized, Controlled, Open-Label Parallel Arm study

Arms

Are arms mutually exclusive?	Yes
Arm title	RAVICTI -> RAVICTI

Arm description:

Initial Treatment, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Arm type	Experimental
Investigational medicinal product name	RAVICTI
Investigational medicinal product code	HPN-100
Other name	glycerol phenylbutyrate, GPB
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Administered orally three or more times daily with meals.

Arm title	NaPBA -> RAVICTI

Arm description:

Initial Treatment Period: NaPBA dosing based on participants disease and treatment status at entry to the study:
• NaPBA in patients weighing < 20 Kg - 600 mg/Kg, maximum total daily dose
• NaPBA in patients weighing > 20 Kg - 13 g/m2, maximum total daily dose.
Transition, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Arm type	Active comparator
Investigational medicinal product name	NaPBA
Investigational medicinal product code	
Other name	Sodium phenylbutyrate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally three or more times daily with meals.

Number of subjects in period 1	RAVICTI -> RAVICTI	NaPBA -> RAVICTI
Started	11	5
Completed	11	5

Period 2

Period 2 title	Transition Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	NaPBA -> RAVICTI

Arm description:

Initial Treatment Period: NaPBA dosing based on participants disease and treatment status at entry to the study:
• NaPBA in patients weighing < 20 Kg - 600 mg/Kg, maximum total daily dose
• NaPBA in patients weighing > 20 Kg - 13 g/m2, maximum total daily dose.
Transition, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Arm type	Active comparator
Investigational medicinal product name	RAVICTI
Investigational medicinal product code	HPN-100
Other name	glycerol phenylbutyrate, GPB
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Administered orally three or more times daily with meals.

Arm title	RAVICTI -> RAVICTI

Arm description:

Initial Treatment, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	NaPBA -> RAVICTI	RAVICTI -> RAVICTI
Started	5	11
Completed	5	11

Period 3

Period 3 title	Maintenance Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	RAVICTI -> RAVICTI

Arm description:

Initial Treatment, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Arm type	Experimental
Investigational medicinal product name	RAVICTI
Investigational medicinal product code	HPN-100
Other name	glycerol phenylbutyrate, GPB
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Administered orally three or more times daily with meals.

Arm title	NaPBA -> RAVICTI

Arm description:

Initial Treatment Period: NaPBA dosing based on participants disease and treatment status at entry to the study:
• NaPBA in patients weighing < 20 Kg - 600 mg/Kg, maximum total daily dose
• NaPBA in patients weighing > 20 Kg - 13 g/m2, maximum total daily dose.
Transition, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Arm type	Active comparator
Investigational medicinal product name	RAVICTI
Investigational medicinal product code	HPN-100
Other name	glycerol phenylbutyrate, GPB
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Administered orally three or more times daily with meals.

Number of subjects in period 3	RAVICTI -> RAVICTI	NaPBA -> RAVICTI
Started	11	5
Completed	10	5
Not completed	1	0
Withdrawn by parent/guardian	1	-

Period 4

Period 4 title	Safety Extension Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	RAVICTI -> RAVICTI

Arm description:

Initial Treatment, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Arm type	Experimental
Investigational medicinal product name	RAVICTI
Investigational medicinal product code	HPN-100
Other name	glycerol phenylbutyrate, GPB
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Administered orally three or more times daily with meals.

Arm title	NaPBA -> RAVICTI

Arm description:

Initial Treatment Period: NaPBA dosing based on participants disease and treatment status at entry to the study:
• NaPBA in patients weighing < 20 Kg - 600 mg/Kg, maximum total daily dose
• NaPBA in patients weighing > 20 Kg - 13 g/m2, maximum total daily dose.
Transition, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Arm type	Active comparator
Investigational medicinal product name	RAVICTI
Investigational medicinal product code	HPN-100
Other name	glycerol phenylbutyrate, GPB
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Administered orally three or more times daily with meals.

Number of subjects in period 4	RAVICTI -> RAVICTI	NaPBA -> RAVICTI
Started	10	5
Completed	8	5
Not completed	2	0
Did not return to study visit	1	-
Adverse event	1	-

Baseline characteristics

Reporting groups	
Reporting group title	RAVICTI -> RAVICTI
Reporting group description:	
Initial Treatment, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.	
Reporting group title	NaPBA -> RAVICTI
Reporting group description:	
Initial Treatment Period: NaPBA dosing based on participants disease and treatment status at entry to the study: • NaPBA in patients weighing < 20 Kg - 600 mg/Kg, maximum total daily dose • NaPBA in patients weighing > 20 Kg - 13 g/m2, maximum total daily dose. Transition, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.	

Reporting group values	RAVICTI -> RAVICTI	NaPBA -> RAVICTI	Total
Number of subjects	11	5	16
Age categorical Units: Subjects			
< 2 months	1	0	1
2 months - < 2 years	4	0	4
2 years - 12 years	1	3	4
> 12 - 16 years	0	0	0
>= 17 years	5	2	7
Gender categorical Units: Subjects			
Female	4	3	7
Male	7	2	9
Ethnicity Units: Subjects			
Hispanic or Latino	4	2	6
Not Hispanic or Latino	7	3	10
Race Units: Subjects			
White	10	5	15
More than one race	1	0	1

End points

End points reporting groups

Reporting group title	RAVICTI -> RAVICTI

Reporting group description:

Initial Treatment, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Reporting group title	NaPBA -> RAVICTI

Reporting group description:

Initial Treatment Period: NaPBA dosing based on participants disease and treatment status at entry to the study:
• NaPBA in patients weighing < 20 Kg - 600 mg/Kg, maximum total daily dose
• NaPBA in patients weighing > 20 Kg - 13 g/m2, maximum total daily dose.
Transition, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Reporting group title	NaPBA -> RAVICTI

Reporting group description:

Initial Treatment Period: NaPBA dosing based on participants disease and treatment status at entry to the study:
• NaPBA in patients weighing < 20 Kg - 600 mg/Kg, maximum total daily dose
• NaPBA in patients weighing > 20 Kg - 13 g/m2, maximum total daily dose.
Transition, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Reporting group title	RAVICTI -> RAVICTI

Reporting group description:

Initial Treatment, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Reporting group title	RAVICTI -> RAVICTI

Reporting group description:

Initial Treatment, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Reporting group title	NaPBA -> RAVICTI

Reporting group description:

Initial Treatment Period: NaPBA dosing based on participants disease and treatment status at entry to the study:
• NaPBA in patients weighing < 20 Kg - 600 mg/Kg, maximum total daily dose
• NaPBA in patients weighing > 20 Kg - 13 g/m2, maximum total daily dose.
Transition, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Reporting group title	RAVICTI -> RAVICTI

Reporting group description:

Initial Treatment, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Reporting group title	NaPBA -> RAVICTI

Reporting group description:

Initial Treatment Period: NaPBA dosing based on participants disease and treatment status at entry to the study:
• NaPBA in patients weighing < 20 Kg - 600 mg/Kg, maximum total daily dose
• NaPBA in patients weighing > 20 Kg - 13 g/m2, maximum total daily dose.
Transition, Maintenance, Safety Extension Periods: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Subject analysis set title	RAVICTI
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Initial Treatment Period: RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose. Dosing will be based on participants disease and treatment status at entry to the study.

Subject analysis set title	NaPBA
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Initial Treatment Period: NaPBA dosing based on participants disease and treatment status at entry to the study:
NaPBA in patients weighing < 20 Kg - 600 mg/Kg, maximum total daily dose NaPBA in patients weighing > 20 Kg - 13 g/m2, maximum total daily dose.

Primary: Rate of Treatment Success (Percentage of Participants Defined as Treatment Success at Week 4) During the Initial Treatment Period

End point title	Rate of Treatment Success (Percentage of Participants Defined as Treatment Success at Week 4) During the Initial Treatment Period

End point description:

A participant was considered a Treatment Success for the assigned treatment arm if the participant had not experienced an unprovoked hyperammonemic crisis (HAC) (i.e., a HAC that cannot be attributed to one or more specific precipitating factors such as infection, intercurrent illness, diet noncompliance, treatment noncompliance, etc.) on the assigned treatment and had met at least 2 of the following 3 criteria:
• Had absolute values at the 3 time points (pre-dose, after dose at 4 hours and 8 hours) of plasma ammonia levels which do not exceed ULN at the Week 4(End of Initial Treatment Period visit)
• Had normal (≤ ULN) glutamine levels at the Week 4 (End of Initial Treatment Period visit at the time point Zero Hour.
• Had normal (≤ ULN) essential amino acids including branched chain amino acid levels (threonine, phenylalanine, methionine, lysine, leucine, isoleucine, histidine, valine) at the End of Initial Treatment Period visit at time point Zero Hour.

Modified Intent-to-Trea

End point type	Primary

End point timeframe:

Week 4

End point values	RAVICTI	NaPBA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	5		
Units: percentage of participants				
number (not applicable)	81.8	80.0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	RAVICTI v NaPBA
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	28.1

Secondary: Rate of Drug Discontinuations (Percentage of Participants Who Discontinued Study Drug) Due to Any Reason in the Initial Treatment Period

End point title	Rate of Drug Discontinuations (Percentage of Participants Who Discontinued Study Drug) Due to Any Reason in the Initial Treatment Period

End point description:

Modified Intent-to-Treat Population: all participants from the Safety population with no major eligibility violations and participants who had ammonia data post-randomization.

End point type	Secondary

End point timeframe:

Baseline through Week 4

End point values	RAVICTI	NaPBA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	5		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fasting Plasma Ammonia Levels During the Initial Treatment Period

End point title	Change From Baseline in Fasting Plasma Ammonia Levels During the Initial Treatment Period

End point description:

mITT Population: all participants from the Safety population with no major eligibility violations and participants who had ammonia data post-randomization.

End point type	Secondary

End point timeframe:

Baseline, Initial Treatment Period Week 1, Week 2, Week 3, Week 4 (0, 4, 8 hours post dose)

End point values	RAVICTI	NaPBA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	5		
Units: µmol*h/L				
arithmetic mean (standard deviation)				
Week 1; n=11, 5	6.5 (± 21.16)	0.0 (± 10.12)		
Week 2; n=11, 4	25.5 (± 59.88)	-10.4 (± 10.17)		
Week 3; n=10, 4	7.4 (± 35.91)	-10.9 (± 6.40)		
Week 4: 0 hour; n=11, 5	2.1 (± 15.52)	-0.3 (± 8.49)		
Week 4: 4 hours postdose; n=8, 5	2.6 (± 23.49)	-1.1 (± 8.68)		
Week 4: 8 hours postdose; n=10, 5	23.4 (± 62.09)	-0.7 (± 7.37)		

Attachments (see zip file)	Statistical Analysis for Change From Baseline in Fasting

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Ammonia Area Under the Curve (AUC) 0 to 8h at the End of the Initial Treatment Period

End point title	Plasma Ammonia Area Under the Curve (AUC) 0 to 8h at the End of the Initial Treatment Period

End point description:

mITT Population: all participants from the Safety population with no major eligibility violations and participants who had ammonia data post-randomization.

End point type	Secondary

End point timeframe:

Week 4: hour 0 (predose), and hours 4 and 8 postdose

End point values	RAVICTI	NaPBA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10[1]	5[2]		
Units: µmol*h/L				
arithmetic mean (standard deviation)	331.8 (± 342.79)	258.9 (± 153.35)		

Notes:

[1] - Participants with an assessment at given time point.

[2] - Participants with an assessment at given time point.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	RAVICTI v NaPBA

Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8579 [3]
Method	t-test

Notes:

[3] - P-value is from a t-test comparing log-transformed RAVICTI vs NaPBA values.

Secondary: Peak Plasma Concentration (Cmax) of Ammonia at the End of the Initial Treatment Period

End point title	Peak Plasma Concentration (Cmax) of Ammonia at the End of the Initial Treatment Period

End point description:

mITT Population: all participants from the Safety population with no major eligibility violations and participants who had ammonia data post-randomization.

End point type	Secondary

End point timeframe:

Week 4: hour 0 (predose), and hours 4 and 8 postdose

End point values	RAVICTI	NaPBA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	5		
Units: µmol/L				
arithmetic mean (standard deviation)	60.2 (± 78.47)	38.1 (± 18.91)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	RAVICTI v NaPBA
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7155 [4]
Method	t-test

Notes:

[4] - P-value is from a t-test comparing log-transformed RAVICTI vs NaPBA values.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events: from the first dose through the last dose of study drug in a given period, plus 30 days from the last dose taken, regardless of period.

Adverse event reporting additional description:

Overall mean time on treatment for the Initial Treatment Period was 30.7 days (RAVICTI) and 26.0 days (NaPBA), for the Transition Period was 8.0 days, for the Maintenance Period was 54.4 days, and for the Safety Extension Period was 84.6 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Initial Treatment Period: RAVICTI

Reporting group description:

RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose for up to 28 days.

Reporting group title	Initial Treatment Period: NaPBA

Reporting group description:

Initial Treatment Period: NaPBA for up to 28 days dosing based on participants disease and treatment status at entry to the study:
NaPBA in patients weighing < 20 Kg - 600 mg/kg, maximum total daily dose NaPBA in patients weighing > 20 kg - 13 g/m^2, maximum total daily dose.

Reporting group title	Transition Period: RAVICTI

Reporting group description:

RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose for 7 days ± 2 days.

Reporting group title	Maintenance and Safety Periods Combined

Reporting group description:

RAVICTI, Oral Liquid Product 17.5 mL maximum total daily dose in the Maintenance Period (8 Weeks) and the
Safety Extension Period (12 Weeks)

Serious adverse events	Initial Treatment Period: RAVICTI	Initial Treatment Period: NaPBA	Transition Period: RAVICTI
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 11 (18.18%)	0 / 5 (0.00%)	1 / 5 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			

subjects affected / exposed	0 / 11 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperammonaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperammonaemic crisis			
subjects affected / exposed	2 / 11 (18.18%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Maintenance and Safety Periods Combined		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 16 (18.75%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bone marrow failure			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperammonaemia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperammonaemic crisis			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Initial Treatment Period: RAVICTI	Initial Treatment Period: NaPBA	Transition Period: RAVICTI
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 11 (54.55%)	2 / 5 (40.00%)	1 / 5 (20.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Fibula fracture			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Middle ear effusion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Dacryostenosis acquired			
subjects affected / exposed	0 / 11 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 11 (18.18%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Dysphagia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	0 / 11 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Maintenance and Safety Periods Combined		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 16 (50.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Fibula fracture			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Lymphadenopathy			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Middle ear effusion			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Hypoacusis			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Eye disorders			
Dacryostenosis acquired			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		

Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0 1 / 16 (6.25%) 1 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0		
Skin and subcutaneous tissue disorders Dermatitis diaper subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Otitis media subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1 0 / 16 (0.00%) 2 1 / 16 (6.25%) 1 0 / 16 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2014	(continued) - Added: If pregnancy occurs at any time during the Crossover Period in which the subject receives NaPBA (Section 7.1.8) - Added: The use of corticosteroids, valproic acid, or haloperidol may increase plasma ammonia level. Therefore, ammonia levels should be monitored closely, as deemed appropriate by the Investigator, if the subject is on one of these medications. Probenecid may inhibit the renal excretion of metabolites of RAVICTI, including PAGN and PAA, and therefore this potential should be considered when assessing PK results. - Added: NaPBA is contraindicated for use during pregnancy. Therefore, if a subject is pregnant at any time during the Crossover Period in which they receive NaPBA, the subject must be withdrawn from the study - Deleted: The Clinical Global Impression - Efficacy Index is a 4 point rating scale that assesses the therapeutic effect of the treatment by the Investigator and subject as: • 1 unchanged to worse • 2 minimal effect • 3 moderate effect • 4 marked effect And the side effects rated by the Investigator and subject as: • None • Some but do not significantly interfere with patient's functioning • Significantly interferes with patient's functioning and outweighs therapeutic effect - Deleted: 1Assess compliance and/or method of drug administration if the following below range U-PAGN concentrations from morning spot urine samples are observed, based on patient’s body surface area (BSA) - Updated SCHEDULE OF ASSESSMENTS

04 June 2014	Added: - Treatment options for subjects following completion of the Protocol: European Sites: After completion of the Safety Extension, subjects at European sites will be given the option to consent and enroll in a long term study and receive study drug until it becomes commercially available in European countries. US Sites (as applicable): After completion of the Safety Extension and at the discretion of the Investigator, subjects at US sites may, if eligible, receive RAVICTI using commercial supply. Added: - 8-hour amino acid sampling at Hour 0 (pre-dose) and Hour 8 (post-dose) - For subjects taking NaBz at study entry who had NaBz treatment withdrawn during Crossover Period 1, the NaBz treatment may be resumed during the Safety Extension Period at the discretion of the Investigator. The dose of NaBz cannot be greater than the equivalent dose of RAVICTI. Please see protocol Section 5.2.2.1 for dose equivalents of RAVICTI. Added: - All females of childbearing potential and all sexually active males must agree to use an acceptable method of contraception throughout the study. Appropriate contraceptive methods include hormonal contraceptives (oral, injected, implanted, or transdermal), tubal ligation, intrauterine device, hysterectomy, vasectomy, or double barrier methods. Abstinence is an acceptable form of birth control, though appropriate contraception must be used if the subject becomes sexually active. Edited: - Subject has received chronic treatment with RAVICTI® (glycerol phenylbutyrate) Oral Liquid or NaPBA longer than 14 days before within one year prior to enrollment o Temporary use of NaPBA for acute management of a hyperammonemic crisis in the past is acceptable. Added: - Pregnant or breast-feeding patients. Women of childbearing potential must have a pregnancy test performed at the Baseline Visit prior to the start of study drug.

04 June 2014	(continued) - Added: Only at Baseline Visit (for subjects on NaBz only), Day 7 and 14, eight (8)-hour amino acid panel testing will occur at the following timepoints: Hour 0 (just before the first main meal after an overnight fasting or after 4-6 hours without high calorie and protein intake: i.e., 08:00 [8:00 am]); Hour 8 (~2–4 hours after lunch or the after second main meal: i.e. ~16:00 [4:00 pm] - Deleted: The Clinical Global Impression - Efficacy (CGI-E) Index is a 4 point rating scale that assesses the therapeutic effect of the treatment by the investigator and subject. - Deleted: • Rate of adverse events • Drug discontinuation due to adverse events • Subject preference for Study drug after completing Crossover Period 2 (Day14) • Palatability of Study drug (Hedonic Scale) - Deleted: • Changes in clinical global impression (CGI) scales (Investigator and Patient) • Rate of adverse events • Drug discontinuation due to adverse events • Neuropsychological assessments: Child Behavior Checklist (CBCL) or Adult Behavior Checklist (ABCL)/Adult Self Report (ASR) • EQ-5D-5L health status quality of life assessment - Deleted: • Drug preference - Added: • Subject preference for study drug after completing Crossover Period 2 (Day 14) • Palatability of study drug (Hedonic Scale) • Changes in clinical global impression (CGI) scales (Investigator and Patient) • Neuropsychological assessments: Child Behavior Checklist (CBCL) or Adult Behavior Checklist (ABCL) or Adult Self Report (ASR) • EQ-5D-5L health status quality of life assessment - Deleted: Based on analysis of all available data from clinical trials of RAVICTI using the lower 25 percentile as a cutoff, the Investigator should assess compliance and/or effectiveness of drug administration if the U-PAGN concentration is <8300 µg/mL for patients whose body surface area is at or less than 1.3 m2 and <5200 µg/mL if the BSA is greater than 1.3.
17 December 2014	- Updates the sponsor from Hyperion Therapeutics to Horizon Therapeutics - Updates the names and contact information to reflect Horizon's responsible study personnel -Clarifies that adequate contraception methods must be used from the signing of informed consent until 30 days after the last dose of study drug - Adds known hypersensitivity to PBA or any of the excipients of the NaPBA/PBA formulations to the exclusion criteria - Adds an optional Long-Term Safety Extension (LTE) period to allow European subjects the option t remain on RAVICTI until it is available commercially - Provides additional details concerning the LTE period and adds the assessments for this period to the schedule of assessments in Appendix A - Adds the criteria for premature termination or suspension of the study - Clarifies that adverse events will be collected from the time of signing of the informed consent - Clarifies the sponsor's responsibility with regard to reporting SAEs/SUSARs in accordance with the European Directive 2001/20/EC

07 August 2015	- Updates all sections related o the optional LTE to define it as a one year period of continued dosing for the purpose of ongoing collection of safety data for subjects who continue to derive benefit as determined by the investigator - Removes all references to the use of flavors with RAVICTI - Corrects minor typographical and formatting errors
23 September 2015	- Changes the design for the initial dosing period from a crossover to a parallel arm - Adds information on the EMA approval of RAVICTI - Replaces Crossover Periods 1 and 2 with a single parallel arm Initial Treatment Period (4 weeks) - Adds a RAVICTI only Transition Period (1 week) - Adds a RAVICTI only Maintenance Period (8 weeks) - Changes the duration of the Safety Extension Period to 12 weeks - Removes the Optional Long Term Safety Extension Period - Removes pharmacokinetic (PK) analyses for sodium benzoate (NaBz) - Removes inclusion criterion of weight > 15 Kg - Limits analysis of serum phenylbutyric acid (PBA), phenylacetatic acid (PAA), and (phenylacetylglutamine) PAGN, as well as, urine PAGN to the End of Initial Treatment Period (EITP) visit - Modifies the definition of Treatment Success - Adjusts the PBA starting dose based on disease and treatment status at study entry - Adds a dose adjustment algorithm - Adds a process for product complaints - Changes the entity responsible for receiving SAE reports - Adds the maximum daily dose of study drug to all relevant sections - Adds a contact at 30 days post study to check for SAEs and pregnancy
22 June 2016	- Corrects the prior summary of changes to include removal of the inclusion criterion of weight > 15 Kg - Clarifies that “normal” as used in the definition of Treatment Success means < the upper limit of normal (ULN) - Adds collection of plasma and urine for pharmacokinetic (PK) assessments whenever a subject presents at the study center with hyperammonemic crisis (HAC) or potential phenylacetic acid (PAA) toxicity and as feasible when subjects present at other health care facilities - Adds the signs and symptoms of PAA toxicity to section 1.2.1 - Revises the dose adjustment algorithm in section 3.8 to: o Add specificity regarding plasma ammonia > ULN when the subject is asymptomatic o Include the maximum daily doses of study drugs o Provide definitions of terms used in the algorithm - Adds dietary protein adjustment guidelines to section 5.6 and capture of dietary changes to each relevant visit - Corrects typographical and formatting errors
27 October 2016	- Revises the inclusion criteria to allow subjects ≥ 2 months of age and older - Updates the age range for measurement of head circumference - Updates the age range for administration of CBCL - Includes a recommendation for step-wise reduction of the dose of phenylbutyric acid (PBA) - Adds stopping rule relating to adverse clinical and laboratory parameters - Adds stopping rule relating to pregnancy - Removes the statement in section 5.7 “The randomisation will be stratified by NaBz use at study entry” - Adds an anticipated dropout rate and rationale for sample size calculations
19 January 2017	- Clarifies that NaPBA powder and NaPBA granules are the same product - Adds requirement to collect AST, ALT and total bilirubin at Unscheduled visits throughout the study when subjects experience hyperammonemia, HAC or PAA toxicity and when PK sampling occurs at unscheduled visits due to signs and symptoms of HAC or PAA toxicity - Corrects the prior summary of changes, protocol version 4 to protocol version 5 to include: Removal of the requirement for the subject to complete the Clinical Global Impression scale

31 May 2017	- Updated Horizon signature page in line with Horizon internal procedures - Synopsis Study Procedures section, Protocol Sections 3.2.1, 6.1.3, 15.4.2, and Appendix A, Schedule of Assessments, updated to clarify the timing of randomisation ie. Following baseline assessments and confirmation of eligibility, up to and including Initial Treatment Period Day 1, subjects will be randomised - Amino Acid Panel for analysis at study visits has been updated - Treatment Success clarified to include: - specific timepoint (Hour 0) to assess glutamine levels - specific timepoint (Hour 0) to assess amino acids - specific Amino Acids which contribute to Treatment Success are listed: Essential amino acids and branch chain amino acids: threonine, phenylalanine, methionine, lysine, leucine, isoleucine, histidine, valine - Study Endpoints in Protocol Synopsis, Protocol section 2.2 and Protocol section 15.3 have been revised for consistency. - Section 15.4.2 mITT population has been updated per SAP - Updated sponsor contact for SAE reporting - Section 7: Updated SAE reporting process - Section 8: corrected order of priority for blood samples - Administrative Changes as appropriate
15 June 2018	- Synopsis Dosage and Regimen Transition Period, Protocol Sections 3.4, 5.2.2.3, 6.1.4: Provides a visit window of 2 days from End of Initial Treatment Period (EITP) visit to assignment to the next study period in order to evaluate ammonia and amino acid results from EITP, for subjects in Treatment Arm 1 - Appendix A, Schedule of Assessments: added footnote #22 to EITP visit
28 August 2018	- Administrative changes on pages 1 and 2 of this protocol document - Protocol Section 1, Prior studies with RAVICTI text replaced with the Benefit Risk Analysis from the EU PBRER (DL31Jan2019) section 18.2 - Protocol list of abbreviations, VHP removed - Synopsis, Protocol Section 3.3, 5.2.2.1: Clarifies the requirement to assign the initial dose of study drug according to the disease/treatment status on entry as set out in protocol section 3.3 - Synopsis, Protocol Section 15.1: Reduces the Number of Subjects to 18 - Protocol section 15.4: Removes age range for sub-groups, these will be defined in the Statistical Analysis Plan. - Synopsis, Protocol Section 4.1, 6, 9, 15.4, Reduces age at entry to Birth
12 November 2019	- Administrative changes on pages 1, 2, 4 of this protocol document - Section 7.1.5.1. Added the fax and email address for reporting SAE
22 April 2022	- Synopsis: Number of Subjects, Study Rationale: Updated to: 16 subjects - Synopsis; Sample Size and Statistical Considerations and Protocol Section 15.1: A sample size of 16 subjects rather than 18 will be enrolled. Approximately 12 subjects will complete the study - Administrative changes on pages 1, 2, 3, 4 - Protocol Section 15.2 Interim Analysis: updated to read: There will be no formal interim analysis. - Protocol Section 20: References; Lee 2015, corrected to Lee 2014

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported