



## Clinical trial results:

### An Open Label Study of the Safety, Efficacy and Pharmacokinetics of Glycerol Phenylbutyrate (GPB; RAVICTI®) in Pediatric Subjects under Two Years of Age with Urea Cycle Disorders (UCDs)

#### Summary

EudraCT number	2016-003460-38
Trial protocol	Outside EU/EEA
Global end of trial date	17 July 2017

#### Results information

Result version number	v1 (current)
This version publication date	24 February 2018
First version publication date	24 February 2018

#### Trial information

##### Trial identification

Sponsor protocol code	HPN-100-009
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02246218
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Horizon Therapeutics, LLC
Sponsor organisation address	150 South Saunders Rd , Lake Forest, IL, United States, 60045
Public contact	Brenda Ranchino, Horizon Therapeutics, LLC, clinicaltrials@horizonpharma.com
Scientific contact	Tom Vescio, MD, Horizon Therapeutics, LLC, 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	17 July 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 July 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

This is an open-label study consisting of a transition period to RAVICTI, followed by a safety extension period for at least 6 months and up to 24 months of treatment with RAVICTI, depending on age at enrollment. It is designed to capture information important for evaluating safety, pharmacokinetics and efficacy in young children.

Subjects who are followed by or referred to the Investigator for management of their UCD. Subjects eligible for this study will include patients ranging from newborn to < 2 years of age with either a diagnosed or clinically suspected UCD.

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	31 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	27
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)	11
Infants and toddlers (28 days-23	16

months)	
Children (2-11 years)	0
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: -

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

Number of subjects started	27
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Number of subjects completed	26
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### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Enrolled, not dosed: 1
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### Period 1

Period 1 title	Overall Study (overall period)
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Is this the baseline period?	Yes
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Allocation method	Not applicable
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Blinding used	Not blinded
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### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	RAVICTI: Age 2 Months to <2 Years
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Arm description:

Subjects age 2 months to < 2 years received RAVICTI Oral Liquid administered just prior to breastfeeding or intake of formula or food. The recommended dosing regimen is 3-6 times per day depending on feeding schedule and at the discretion of the Investigator.

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

The starting dose of RAVICTI is based on UCD status (newly diagnosed, or already stable on sodium phenylbutyrate [NaPBA] and/or sodium benzoate [NaBz]) and whether a hyperammonemic crisis is present. Subsequently, the dose may be adjusted based on clinical and/or ammonia results, according to an algorithm provided in the protocol.

<b>Arm title</b>	RAVICTI: Age 0 to <2 Months
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Arm description:

Subjects age 0 to < 2 months received RAVICTI Oral Liquid administered just prior to breastfeeding or intake of formula or food. The recommended dosing regimen is 3-6 times per day depending on feeding schedule and at the discretion of the Investigator.

Arm type	Experimental
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Investigational medicinal product name	RAVICTI
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Investigational medicinal product code	HPN-100
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Other name	glycerol phenylbutyrate, GPB
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Pharmaceutical forms	Oral liquid
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Dosage and administration details:

The starting dose of RAVICTI is based on UCD status (newly diagnosed, or already stable on sodium phenylbutyrate [NaPBA] and/or sodium benzoate [NaBz]) and whether a hyperammonemic crisis is

present. Subsequently, the dose may be adjusted based on clinical and/or ammonia results, according to an algorithm provided in the protocol.

<b>Number of subjects in period 1<sup>[1]</sup></b>	RAVICTI: Age 2 Months to <2 Years	RAVICTI: Age 0 to <2 Months
Started	10	16
Completed	6	10
Not completed	4	6
Stopping Rule: Liver Transplant	2	4
Adverse event	1	1
Lost to follow-up	1	-
Withdrawal by parent/guardian	-	1

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One subject enrolled in the study and prior to taking study drug the parents decided not to be dosed.

## Baseline characteristics

### Reporting groups

Reporting group title	RAVICTI: Age 2 Months to <2 Years
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Reporting group description:

Subjects age 2 months to < 2 years received RAVICTI Oral Liquid administered just prior to breastfeeding or intake of formula or food. The recommended dosing regimen is 3-6 times per day depending on feeding schedule and at the discretion of the Investigator.

Reporting group title	RAVICTI: Age 0 to <2 Months
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Reporting group description:

Subjects age 0 to < 2 months received RAVICTI Oral Liquid administered just prior to breastfeeding or intake of formula or food. The recommended dosing regimen is 3-6 times per day depending on feeding schedule and at the discretion of the Investigator.

Reporting group values	RAVICTI: Age 2 Months to <2 Years	RAVICTI: Age 0 to <2 Months	Total
Number of subjects	10	16	26
Age categorical Units: Subjects			

Age Continuous Units: months arithmetic mean standard deviation	9.87 ± 5.529	0.83 ± 0.697	-
Gender categorical Units: Subjects			
Female	5	7	12
Male	5	9	14

## End points

### End points reporting groups

Reporting group title	RAVICTI: Age 2 Months to <2 Years
Reporting group description: Subjects age 2 months to < 2 years received RAVICTI Oral Liquid administered just prior to breastfeeding or intake of formula or food. The recommended dosing regimen is 3-6 times per day depending on feeding schedule and at the discretion of the Investigator.	
Reporting group title	RAVICTI: Age 0 to <2 Months
Reporting group description: Subjects age 0 to < 2 months received RAVICTI Oral Liquid administered just prior to breastfeeding or intake of formula or food. The recommended dosing regimen is 3-6 times per day depending on feeding schedule and at the discretion of the Investigator.	

### Primary: Percentage of Subjects With Successful Transition to RAVICTI With Controlled Ammonia (i.e. No Clinical Symptoms and Ammonia < 100 µmol/L): Cohort of 2 Months to <2 Years Subjects

End point title	Percentage of Subjects With Successful Transition to RAVICTI With Controlled Ammonia (i.e. No Clinical Symptoms and Ammonia < 100 µmol/L): Cohort of 2 Months to <2 Years Subjects <sup>[1][2]</sup>
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#### End point description:

The percentage of subjects with successful transition is based on Investigator response to the question, "Has transition to 100% RAVICTI been successful with controlled ammonia?" For subjects 2 months of age and older, after a minimum of 24 hours of ammonia monitoring following the first full dose of RAVICTI alone, the subject was effectively transitioned when following conditions were met: no signs and symptoms of hyperammonemia; ammonia level less than 100 µmol/L (without normalization of ammonia, ie, without conversion of values from local laboratories with varying normal ranges to standardized values); and eligible for discharge per Investigator judgment.

Safety Population: all enrolled subjects who received any amount of study medication.

End point type	Primary
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#### End point timeframe:

Up to Day 4

#### 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: Descriptive statistics are presented, per protocol.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of subjects				
number (not applicable)	100			

## Statistical analyses

**Primary: Percentage of Subjects With Successful Transition to RAVICTI With Controlled Ammonia (i.e. No Clinical Symptoms and Ammonia < 100 µmol/L): Cohort of 0 Months to <2 Months Subjects**

End point title	Percentage of Subjects With Successful Transition to RAVICTI With Controlled Ammonia (i.e. No Clinical Symptoms and Ammonia < 100 µmol/L): Cohort of 0 Months to <2 Months Subjects <sup>[3]</sup> <sup>[4]</sup>
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## End point description:

The percentage of subjects with successful transition is based on Investigator response to the question, "Has transition to 100% RAVICTI been successful with controlled ammonia?" For subjects 0 to <2 months of age, after a minimum of 24 hours of ammonia monitoring following the first full dose of RAVICTI alone, the subject was effectively transitioned when following conditions were met: no signs and symptoms of hyperammonemia; ammonia level less than 100 µmol/L (without normalization of ammonia, ie, without conversion of values from local laboratories with varying normal ranges to standardized values); and eligible for discharge per Investigator judgment.

Safety Population: all enrolled subjects who received any amount of study medication.

End point type	Primary
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## End point timeframe:

Up to Day 4

## Notes:

[3] - 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: Descriptive statistics are presented, per protocol.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percentage of subjects				
number (not applicable)	100			

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Rate of Hyperammonemic Crises (HACs): Cohort of 2 Months to <2 Years Subjects**

End point title	Rate of Hyperammonemic Crises (HACs): Cohort of 2 Months to <2 Years Subjects <sup>[5]</sup>
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## End point description:

HAC is defined as having signs and symptoms consistent with hyperammonemia (such as but not limited to frequent vomiting, nausea, headache, lethargy, irritability, combativeness, and/or somnolence) associated with high blood ammonia and requiring medical intervention. Rate of HACs per 6 months during the safety extension was calculated as sum of (number of HAC) / sum of (days during first 6 months starting on Day 8 or number days on RAVICTI, whichever is less) across all subjects in the corresponding group.

Safety Population: all enrolled subjects who received any amount of study medication.

End point type	Secondary
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End point timeframe:

Day 8 through up to Month 6

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	9 <sup>[6]</sup>			
Units: rate ratio				
number (not applicable)	0.005			

Notes:

[6] - subjects with an assessment

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, Deaths, and Discontinuations Due to TEAEs: Cohort of 2 Months to <2 Years Subjects

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, Deaths, and Discontinuations Due to TEAEs: Cohort of 2 Months to <2 Years Subjects <sup>[7]</sup>
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End point description:

An adverse event (AE) is any untoward medical occurrence, whether or not the event is considered related to the study drug. A serious AE is any AE that: results in death; is life threatening; requires hospitalization or prolongation of existing hospitalization; results in disability/incapacity; is a congenital anomaly/birth defect; is an important medical event. TEAEs are defined as AEs with an onset date on or after the first dose of study medication until study discontinuation. The Investigator assessed the causal relationship of each TEAE to the study drug as not related, possibly related, or probably related.

Safety Population: all enrolled subjects who received any amount of study medication.

End point type	Secondary
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End point timeframe:

From the first dose of study treatment through 30 days after the final dose (mean [SD] duration of treatment was 9.13 [6.838] months).

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: subjects				
≥ 1 TEAE	10			
≥ 1 Related TEAE	4			
≥ 1 Serious TEAE	6			
≥ 1 Serious Related TEAE	0			
Fatal Outcome TEAE	1			

≥ 1 TEAE Leading to Study Discontinuation	1			
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## Statistical analyses

No statistical analyses for this end point

### Secondary: Amino Acid Assessment: Baseline and Change from Baseline in Glutamate Up to Month 24: Cohort of 2 Months to <2 Years Subjects

End point title	Amino Acid Assessment: Baseline and Change from Baseline in Glutamate Up to Month 24: Cohort of 2 Months to <2 Years Subjects <sup>[8]</sup>
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End point description:

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Day 7, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 24

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[9]</sup>			
Units: µmol/L				
arithmetic mean (standard deviation)				
Baseline; n=7	122.43 (± 118.620)			
Day 7 change from Baseline; n=6	-54.50 (± 92.626)			
Month 2 change from Baseline; n=5	7.80 (± 25.646)			
Month 3 change from Baseline; n=3	-16.33 (± 39.209)			
Month 4 change from Baseline; n=4	-13.00 (± 39.590)			
Month 5 change from Baseline; n=4	0.25 (± 13.426)			
Month 6 change from Baseline; n=5	-2.20 (± 34.463)			
Month 9 change from Baseline; n=3	30.80 (± 17.092)			
Month 12 change from Baseline; n=3	22.20 (± 23.506)			
Month 15 change from Baseline; n=1	39.00 (± 00000)			
Month 24 change from Baseline; n=2	48.00 (± 53.740)			

Notes:

[9] - n=subjects with an assessment at given time point; 00000=not applicable (1 subject assessed).

## Statistical analyses

No statistical analyses for this end point

### Secondary: Amino Acid Assessment: Baseline and Change from Baseline in Glutamine Up to Month 24: Cohort of 2 Months to <2 Years Subjects

End point title	Amino Acid Assessment: Baseline and Change from Baseline in Glutamine Up to Month 24: Cohort of 2 Months to <2 Years Subjects <sup>[10]</sup>
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End point description:

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment at given time point.

End point type	Secondary
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End point timeframe:

Baseline, Day 7, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 24

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[11]</sup>			
Units: µmol/L				
arithmetic mean (standard deviation)				
Baseline; n=7	750.43 (± 309.000)			
Day 7 change from Baseline; n=6	-184.33 (± 168.657)			
Month 2 change from Baseline; n=5	-174.60 (± 318.249)			
Month 3 change from Baseline; n=3	-374.00 (± 425.903)			
Month 4 change from Baseline; n=4	-252.75 (± 323.852)			
Month 5 change from Baseline; n=4	-370.25 (± 377.222)			
Month 6 change from Baseline; n=5	-113.20 (± 519.710)			
Month 9 change from Baseline; n=3	-446.53 (± 360.457)			
Month 12 change from Baseline; n=3	-450.50 (± 386.699)			
Month 15 change from Baseline; n=1	-149.00 (± 00000)			
Month 24 change from Baseline; n=2	195.00 (± 554.372)			

Notes:

[11] - n=subjects with an assessment at given time point; 00000=not applicable (1 subject assessed).

## Statistical analyses

No statistical analyses for this end point

### Secondary: Amino Acid Assessment: Baseline and Change from Baseline in Sum of Glutamine and Glutamate Up to Month 24: Cohort of 2 Months to <2 Years Subjects

End point title	Amino Acid Assessment: Baseline and Change from Baseline in Sum of Glutamine and Glutamate Up to Month 24: Cohort of 2 Months to <2 Years Subjects <sup>[12]</sup>
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End point description:

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Day 7, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 24

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[13]</sup>			
Units: µmol/L				
arithmetic mean (standard deviation)				
Baseline; n=7	872.86 (± 381.005)			
Day 7 change from Baseline; n=6	-238.83 (± 203.567)			
Month 2 change from Baseline; n=5	-166.80 (± 332.421)			
Month 3 change from Baseline; n=3	-390.33 (± 462.292)			
Month 4 change from Baseline; n=4	-265.75 (± 339.015)			
Month 5 change from Baseline; n=4	-370.00 (± 379.884)			
Month 6 change from Baseline; n=5	-115.40 (± 546.796)			
Month 9 change from Baseline; n=3	-415.73 (± 365.419)			
Month 12 change from Baseline; n=3	-428.30 (± 404.351)			
Month 15 change from Baseline; n=1	-110.00 (± 00000)			
Month 24 change from Baseline; n=2	243.00 (± 608.112)			

Notes:

[13] - n=subjects with an assessment at given time point; 00000=not applicable (1 subject assessed).

## Statistical analyses

No statistical analyses for this end point

### Secondary: Amino Acid Assessment: Baseline and Change from Baseline in Isoleucine Up to Month 24: Cohort of 2 Months to <2 Years Subjects

End point title	Amino Acid Assessment: Baseline and Change from Baseline in Isoleucine Up to Month 24: Cohort of 2 Months to <2 Years Subjects <sup>[14]</sup>
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End point description:

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Day 7, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 24

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[15]</sup>			
Units: µmol/L				
arithmetic mean (standard deviation)				
Baseline; n=7	54.86 (± 19.497)			
Day 7 change from Baseline; n=6	2.67 (± 19.159)			
Month 2 change from Baseline; n=5	4.20 (± 45.861)			
Month 3 change from Baseline; n=3	-25.67 (± 16.743)			
Month 4 change from Baseline; n=4	-20.25 (± 20.353)			
Month 5 change from Baseline; n=4	-20.00 (± 36.341)			
Month 6 change from Baseline; n=5	-16.40 (± 12.137)			
Month 9 change from Baseline; n=3	-6.73 (± 13.342)			
Month 12 change from Baseline; n=3	-13.33 (± 15.885)			
Month 15 change from Baseline; n=1	-18.00 (± 00000)			
Month 24 change from Baseline; n=2	1.50 (± 10.607)			

Notes:

[15] - n=subjects with an assessment at given time point; 00000=not applicable (1 subject assessed).

## Statistical analyses

No statistical analyses for this end point

### Secondary: Amino Acid Assessment: Baseline and Change from Baseline in Leucine Up to Month 24: Cohort of 2 Months to <2 Years Subjects

End point title	Amino Acid Assessment: Baseline and Change from Baseline in Leucine Up to Month 24: Cohort of 2 Months to <2 Years Subjects <sup>[16]</sup>
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End point description:

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Day 7, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 24

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[17]</sup>			
Units: µmol/L				
arithmetic mean (standard deviation)				
Baseline; n=7	90.86 (± 29.249)			
Day 7 change from Baseline; n=6	-0.83 (± 32.762)			
Month 2 change from Baseline; n=5	9.80 (± 65.975)			
Month 3 change from Baseline; n=3	-33.00 (± 25.239)			
Month 4 change from Baseline; n=4	-31.25 (± 24.771)			
Month 5 change from Baseline; n=4	-39.50 (± 61.136)			
Month 6 change from Baseline; n=5	-25.40 (± 13.594)			
Month 9 change from Baseline; n=3	-19.13 (± 39.322)			
Month 12 change from Baseline; n=3	-34.37 (± 23.283)			
Month 15 change from Baseline; n=1	-40.00 (± 00000)			
Month 24 change from Baseline; n=2	-1.50 (± 31.820)			

Notes:

[17] - n=subjects with an assessment at given time point; 00000=not applicable (1 subject assessed).

## Statistical analyses

No statistical analyses for this end point

### Secondary: Amino Acid Assessment: Baseline and Change from Baseline in Valine Up to Month 24: Cohort of 2 Months to <2 Years Subjects

End point title	Amino Acid Assessment: Baseline and Change from Baseline in Valine Up to Month 24: Cohort of 2 Months to <2 Years Subjects <sup>[18]</sup>
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End point description:

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Day 7, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 24

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[19]</sup>			
Units: µmol/L				
arithmetic mean (standard deviation)				
Baseline; n=7	171.43 (± 42.887)			
Day 7 change from Baseline; n=6	4.00 (± 24.133)			
Month 2 change from Baseline; n=5	40.60 (± 90.057)			
Month 3 change from Baseline; n=3	-27.33 (± 37.018)			
Month 4 change from Baseline; n=4	-31.50 (± 29.760)			
Month 5 change from Baseline; n=4	-56.00 (± 75.939)			
Month 6 change from Baseline; n=5	-21.60 (± 18.202)			
Month 9 change from Baseline; n=3	-11.90 (± 71.753)			
Month 12 change from Baseline; n=3	-48.87 (± 51.644)			
Month 15 change from Baseline; n=1	-46.00 (± 0000)			
Month 24 change from Baseline; n=2	5.00 (± 55.154)			

Notes:

[19] - n=subjects with an assessment at given time point; 00000=not applicable (1 subject assessed).

## Statistical analyses

No statistical analyses for this end point

### Secondary: Assessment of Growth and Development: Baseline and Change from Baseline in Body Mass Index (BMI) Z-Score Up to Month 24: Cohort of 2 Months to <2 Years Subjects

End point title	Assessment of Growth and Development: Baseline and Change from Baseline in Body Mass Index (BMI) Z-Score Up to Month 24: Cohort of 2 Months to <2 Years Subjects <sup>[20]</sup>
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End point description:

To assess any effect of study drug treatment on growth, Z-scores were calculated to express the deviation from a reference population for BMI. The Z-scores are based on the World Health Organization's Child Growth Standards charts. Negative Z-scores indicate lower than typical for age and gender while positive scores indicate higher than typical for age and gender.

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 18, Month 24

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[21]</sup>			
Units: z-score				
arithmetic mean (standard deviation)				
Baseline; n=10	0.8107 (± 2.17017)			
Month 1 change from Baseline; n=9	-0.2385 (± 0.77830)			
Month 2 change from Baseline; n=7	-0.0249 (± 0.74861)			
Month 3 change from Baseline; n=7	0.1815 (± 0.86056)			
Month 4 change from Baseline; n=7	0.4434 (± 0.94854)			
Month 5 change from Baseline; n=6	0.1484 (± 0.76293)			
Month 6 change from Baseline; n=7	0.2497 (± 0.80923)			
Month 9 change from Baseline; n=5	0.6407 (± 0.98695)			



Month 12 change from Baseline; n=4	0.4164 ( $\pm$ 0.80674)			
Month 15 change from Baseline; n=2	-0.2997 ( $\pm$ 0.16959)			
Month 18 change from Baseline; n=1	-0.2038 ( $\pm$ 00000)			
Month 24 change from Baseline; n=4	0.5581 ( $\pm$ 1.23993)			

Notes:

[21] - n=subjects with an assessment at given time point; 00000=not applicable (1 subject assessed).

## Statistical analyses

No statistical analyses for this end point

### Secondary: Assessment of Growth and Development: Baseline and Change from Baseline in Body Surface Area (BSA) Z-Score Up to Month 24: Cohort of 2 Months to <2 Years Subjects

End point title	Assessment of Growth and Development: Baseline and Change from Baseline in Body Surface Area (BSA) Z-Score Up to Month 24: Cohort of 2 Months to <2 Years Subjects <sup>[22]</sup>
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End point description:

To assess any effect of study drug treatment on growth, Z-scores were calculated to express the deviation from a reference population for BSA. The Z-scores are based on weight-for-length charts. Negative Z-scores indicate lower than typical for age and gender while positive scores indicate higher than typical for age and gender.

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 18, Month 24

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[23]</sup>			
Units: z-score				
arithmetic mean (standard deviation)				
Baseline; n=10	0.7143 ( $\pm$ 2.14922)			
Month 1 change from Baseline; n=9	-0.2105 ( $\pm$ 0.74135)			
Month 2 change from Baseline; n=7	-0.0704 ( $\pm$ 0.70393)			
Month 3 change from Baseline; n=7	0.1065 ( $\pm$ 0.70165)			
Month 4 change from Baseline; n=7	0.3365 ( $\pm$ 0.77672)			
Month 5 change from Baseline; n=6	0.1043 ( $\pm$ 0.56747)			

Month 6 change from Baseline; n=7	0.1842 ( $\pm$ 0.62205)			
Month 9 change from Baseline; n=5	0.4875 ( $\pm$ 0.86137)			
Month 12 change from Baseline; n=4	0.2944 ( $\pm$ 0.75133)			
Month 15 change from Baseline; n=2	-0.3661 ( $\pm$ 0.00932)			
Month 18 change from Baseline; n=1	-0.2214 ( $\pm$ 00000)			
Month 24 change from Baseline; n=4	0.4310 ( $\pm$ 1.13140)			

Notes:

[23] - n=subjects with an assessment at given time point; 00000=not applicable (1 subject assessed).

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Phenylbutyrate/Phenylbutyric Acid (PBA) Maximum Plasma Concentration (C<sub>max</sub>) on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects

End point title	Plasma Phenylbutyrate/Phenylbutyric Acid (PBA) Maximum Plasma Concentration (C <sub>max</sub> ) on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[24]</sup>
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End point description:

Pharmacokinetic (PK) Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg/mL				
arithmetic mean (standard deviation)	42.44 ( $\pm$ 36.715)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma PBA Minimum Plasma Concentration (C<sub>min</sub>) on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects

End point title	Plasma PBA Minimum Plasma Concentration (C <sub>min</sub> ) on the First
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg/mL				
arithmetic mean (standard deviation)	1.697 (± 2.254)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma PBA Area Under the Curve From Time Zero to the Time of Last Quantifiable Concentration (AUC[0-last]) on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects

End point title	Plasma PBA Area Under the Curve From Time Zero to the Time of Last Quantifiable Concentration (AUC[0-last]) on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[26]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg*hr/mL				
arithmetic mean (standard deviation)	280.936 (± 293.553)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma PBA Time to Cmax (Tmax) on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects

End point title	Plasma PBA Time to Cmax (Tmax) on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[27]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: hours				
arithmetic mean (standard deviation)	8.383 (± 4.564)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Phenylacetate/Phenylacetic Acid (PAA) Cmax on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects

End point title	Plasma Phenylacetate/Phenylacetic Acid (PAA) Cmax on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[28]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg/mL				
arithmetic mean (standard deviation)	36.52 (± 31.784)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma PAA Cmin on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects

End point title	Plasma PAA Cmin on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[29]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg/mL				
arithmetic mean (standard deviation)	4.197 (± 6.434)			

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Plasma PAA AUC(0-last) on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects**

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End point title	Plasma PAA AUC(0-last) on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[30]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg*hr/mL				
arithmetic mean (standard deviation)	246.126 (± 238.547)			

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Plasma PAA Tmax on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects**

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End point title	Plasma PAA Tmax on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[31]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: hours				
arithmetic mean (standard deviation)	7.422 (± 7.351)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma phenylacetylglutamine (PAGN) Cmax on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects

End point title	Plasma phenylacetylglutamine (PAGN) Cmax on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[32]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg/mL				
arithmetic mean (standard deviation)	62.45 (± 27.281)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma PAGN Cmin on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects

End point title	Plasma PAGN Cmin on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[33]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg/mL				
arithmetic mean (standard deviation)	20.62 (± 14.529)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma PAGN AUC(0-last) on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects

End point title	Plasma PAGN AUC(0-last) on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[34]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg*hr/mL				
arithmetic mean (standard deviation)	583.835 (± 285.241)			

## Statistical analyses



No statistical analyses for this end point

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**Secondary: Plasma PAGN Tmax on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects**

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End point title	Plasma PAGN Tmax on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[35]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: hours				
arithmetic mean (standard deviation)	6.573 (± 7.181)			

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Assessment of Urinary PAGN Concentrations on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects**

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End point title	Assessment of Urinary PAGN Concentrations on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[36]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 0.5 and 1.5 hours, 1.5 and 2.5 hours, 4 and 6 hours, 7.5 and 8.5 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[37]</sup>			
Units: µg/mL				
arithmetic mean (standard deviation)				
Hour 0; n=6	3273 (± 1993)			
0.5 to 1.5 hours; n=6	4140 (± 4399)			
1.5 to 2.5 hours; n=9	3145 (± 5045)			
4 to 6 hours; n=9	5202 (± 4547)			
7.5 to 8.5 hours; n=8	3950 (± 3068)			
12 to 24 hours; n=9	7561 (± 6956)			

Notes:

[37] - n=subjects with an assessment at given time point

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of Urinary PAGN Concentrations Up to End of Trial: Cohort of 2 Months to <2 Years Subjects

End point title	Assessment of Urinary PAGN Concentrations Up to End of Trial: Cohort of 2 Months to <2 Years Subjects <sup>[38]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Day 7, Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 18, End of Trial

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 7; n=8	8859 (± 10500)			
Month 1; n=8	6274 (± 4802)			
Month 2; n=5	7386 (± 6419)			
Month 3; n=6	11456 (± 14471)			
Month 4; n=3	21416 (± 33695)			
Month 5; n=5	6129 (± 8024)			
Month 6; n=3	5347 (± 3153)			
Month 9; n=3	9357 (± 7286)			

Month 12; n=3	2580 (± 286)			
Month 15; n=1	6400 (± 00000)			
Month 18; n=1	5250 (± 00000)			
End of trial; n=3	25333 (± 21324)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of Urinary PAA Concentrations on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects

End point title	Assessment of Urinary PAA Concentrations on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[39]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 0.5 and 1.5 hours, 1.5 and 2.5 hours, 4 and 6 hours, 7.5 and 8.5 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg/mL				
arithmetic mean (standard deviation)				
Hour 0; n=3	18.78 (± 27.33)			
0.5 to 1.5 hours; n=4	6.50 (± 3.39)			
1.5 to 2.5 hours; n=4	7.29 (± 4.10)			
4 to 6 hours; n=6	2.60 (± 2.18)			
7.5 to 8.5 hours; n=4	4.48 (± 4.38)			
12 to 24 hours; n=4	4.31 (± 2.33)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of Urinary PAA Concentrations Up to End of Trial: Cohort of 2 Months to <2 Years Subjects

End point title	Assessment of Urinary PAA Concentrations Up to End of Trial: Cohort of 2 Months to <2 Years Subjects <sup>[40]</sup>
End point description: PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.	
End point type	Secondary
End point timeframe: Day 7, Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 15, Month 18, End of Trial	
Notes: [40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for each cohort are presented as separate endpoints.	

End point values	RAVICTI: Age 2 Months to <2 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 7; n=2	5.82 (± 2.21)			
Month 1; n=6	4.44 (± 4.61)			
Month 2; n=3	3.69 (± 1.82)			
Month 3; n=2	4.65 (± 0.49)			
Month 4; n=1	7.14 (± 00000)			
Month 5; n=2	3.27 (± 1.96)			
Month 6; n=1	1.59 (± 00000)			
Month 9; n=3	4.10 (± 1.65)			
Month 15; n=1	2.04 (± 00000)			
Month 18; n=1	1.64 (± 00000)			
End of trial; n=3	7.0 (± 5.16)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Rate of HACs: Cohort of 0 Months to <2 Months Subjects

End point title	Rate of HACs: Cohort of 0 Months to <2 Months Subjects <sup>[41]</sup>
End point description: HAC is defined as having signs and symptoms consistent with hyperammonemia (such as but not limited to frequent vomiting, nausea, headache, lethargy, irritability, combativeness, and/or somnolence) associated with high blood ammonia and requiring medical intervention. Rate of HACs per 6 months during the safety extension was calculated as sum of (number of HAC) / sum of (days during first 6 months starting on Day 8 or number days on RAVICTI, whichever is less) across all subjects in the corresponding group.	
Safety Population: all enrolled subjects who received any amount of study medication.	
End point type	Secondary
End point timeframe: Day 8 through up to Month 6	

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: rate ratio				
number (not applicable)	0.003			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With TEAEs, Serious TEAEs, Deaths, and Discontinuations Due to TEAEs: Cohort of 0 Months to <2 Months Subjects

End point title	Number of Subjects With TEAEs, Serious TEAEs, Deaths, and Discontinuations Due to TEAEs: Cohort of 0 Months to <2 Months Subjects <sup>[42]</sup>
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End point description:

An AE is any untoward medical occurrence, whether or not the event is considered related to the study drug. A serious AE is any AE that: results in death; is life threatening; requires hospitalization or prolongation of existing hospitalization; results in disability/incapacity; is a congenital anomaly/birth defect; is an important medical event. TEAEs are defined as AEs with an onset date on or after the first dose of study medication until study discontinuation. The Investigator assessed the causal relationship of each TEAE to the study drug as not related, possibly related, or probably related.

Safety Population: all enrolled subjects who received any amount of study medication.

End point type	Secondary
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End point timeframe:

From the first dose of study treatment through 30 days after the final dose (mean [SD] duration of treatment was 10.67 [6.142] months).

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: subjects				
≥ 1 TEAE	16			
≥ 1 Related TEAE	10			
≥ 1 Serious TEAE	11			
≥ 1 Serious Related TEAE	0			
Fatal Outcome TEAE	0			
≥ 1 TEAE Leading to Study Discontinuation	1			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Amino Acid Assessment: Baseline and Change from Baseline in Glutamate Up to Month 24: Cohort of 0 Months to <2 Months Subjects

End point title	Amino Acid Assessment: Baseline and Change from Baseline in Glutamate Up to Month 24: Cohort of 0 Months to <2 Months Subjects <sup>[43]</sup>
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End point description:

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Day 7, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 18, Month 24

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[44]</sup>			
Units: µmol/L				
arithmetic mean (standard deviation)				
Baseline; n=15	84.97 (± 52.086)			
Day 7 change from Baseline; n=14	26.81 (± 76.417)			
Month 2 change from Baseline; n=14	25.16 (± 64.474)			
Month 3 change from Baseline; n=14	50.05 (± 73.988)			
Month 4 change from Baseline; n=11	18.77 (± 67.561)			
Month 5 change from Baseline; n=10	57.43 (± 98.550)			
Month 6 change from Baseline; n=8	43.65 (± 140.985)			
Month 9 change from Baseline; n=8	33.41 (± 150.273)			
Month 12 change from Baseline; n=4	8.75 (± 97.329)			
Month 15 change from Baseline; n=4	25.75 (± 62.660)			
Month 18 change from Baseline; n=2	2.50 (± 21.920)			

Month 24 change from Baseline; n=8	16.10 ( $\pm$ 95.461)			
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Notes:

[44] - n=subjects with an assessment at given time point.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Amino Acid Assessment: Baseline and Change from Baseline in Glutamine Up to Month 24: Cohort of 0 Months to <2 Months Subjects

End point title	Amino Acid Assessment: Baseline and Change from Baseline in Glutamine Up to Month 24: Cohort of 0 Months to <2 Months Subjects <sup>[45]</sup>
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End point description:

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment at given time point.

End point type	Secondary
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End point timeframe:

Baseline, Day 7, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 18, Month 24

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[46]</sup>			
Units: $\mu\text{mol/L}$				
arithmetic mean (standard deviation)				
Baseline; n=15	508.83 ( $\pm$ 337.175)			
Day 7 change from Baseline; n=14	21.04 ( $\pm$ 260.500)			
Month 2 change from Baseline; n=14	-27.62 ( $\pm$ 379.796)			
Month 3 change from Baseline; n=14	-15.09 ( $\pm$ 352.471)			
Month 4 change from Baseline; n=11	-113.98 ( $\pm$ 230.855)			
Month 5 change from Baseline; n=10	-99.82 ( $\pm$ 305.674)			
Month 6 change from Baseline; n=8	-138.16 ( $\pm$ 349.269)			
Month 9 change from Baseline; n=8	-56.08 ( $\pm$ 269.288)			
Month 12 change from Baseline; n=4	-181.50 ( $\pm$ 118.604)			
Month 15 change from Baseline; n=4	-103.75 ( $\pm$ 328.583)			
Month 18 change from Baseline; n=2	-184.00 ( $\pm$ 80.610)			

Month 24 change from Baseline; n=8	-219.93 ( $\pm$ 279.815)			
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Notes:

[46] - n=subjects with an assessment at given time point

## Statistical analyses

No statistical analyses for this end point

### Secondary: Amino Acid Assessment: Baseline and Change from Baseline in Sum of Glutamine and Glutamate Up to Month 24: Cohort of 0 Months to <2 Months Subjects

End point title	Amino Acid Assessment: Baseline and Change from Baseline in Sum of Glutamine and Glutamate Up to Month 24: Cohort of 0 Months to <2 Months Subjects <sup>[47]</sup>
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End point description:

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Day 7, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 18, Month 24

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[48]</sup>			
Units: $\mu\text{mol/L}$				
arithmetic mean (standard deviation)				
Baseline; n=15	593.80 ( $\pm$ 333.657)			
Day 7 change from Baseline; n=14	47.85 ( $\pm$ 230.343)			
Month 2 change from Baseline; n=14	-2.46 ( $\pm$ 402.919)			
Month 3 change from Baseline; n=14	34.96 ( $\pm$ 371.522)			
Month 4 change from Baseline; n=11	-95.21 ( $\pm$ 238.136)			
Month 5 change from Baseline; n=10	-42.39 ( $\pm$ 288.782)			
Month 6 change from Baseline; n=8	-94.51 ( $\pm$ 297.378)			
Month 9 change from Baseline; n=8	-22.66 ( $\pm$ 318.034)			
Month 12 change from Baseline; n=4	-172.75 ( $\pm$ 210.202)			
Month 15 change from Baseline; n=4	-78.00 ( $\pm$ 297.410)			
Month 18 change from Baseline; n=2	-181.50 ( $\pm$ 102.530)			



Month 24 change from Baseline; n=8	-203.83 (± 255.810)			
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Notes:

[48] - n=subjects with an assessment at given time point

## Statistical analyses

No statistical analyses for this end point

### Secondary: Amino Acid Assessment: Baseline and Change from Baseline in Isoleucine Up to Month 24: Cohort of 0 Months to <2 Month Subjects

End point title	Amino Acid Assessment: Baseline and Change from Baseline in Isoleucine Up to Month 24: Cohort of 0 Months to <2 Month Subjects <sup>[49]</sup>
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End point description:

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Day 7, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 18, Month 24

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[50]</sup>			
Units: µmol/L				
arithmetic mean (standard deviation)				
Baseline; n=15	142.68 (± 222.694)			
Day 7 change from Baseline; n=14	-49.09 (± 198.730)			
Month 2 change from Baseline; n=14	-1.62 (± 233.754)			
Month 3 change from Baseline; n=14	-20.46 (± 216.885)			
Month 4 change from Baseline; n=11	-67.32 (± 173.564)			
Month 5 change from Baseline; n=10	-75.45 (± 221.845)			
Month 6 change from Baseline; n=8	-35.94 (± 78.367)			
Month 9 change from Baseline; n=8	-73.09 (± 245.051)			
Month 12 change from Baseline; n=4	-178.50 (± 335.538)			
Month 15 change from Baseline; n=4	-139.50 (± 359.287)			
Month 18 change from Baseline; n=2	1.00 (± 45.255)			

Month 24 change from Baseline; n=8	-55.31 ( $\pm$ 217.209)			
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Notes:

[50] - n=subjects with an assessment at given time point

## Statistical analyses

No statistical analyses for this end point

## Secondary: Amino Acid Assessment: Baseline and Change from Baseline in Leucine Up to Month 24: Cohort of 0 Months to <2 Months Subjects

End point title	Amino Acid Assessment: Baseline and Change from Baseline in Leucine Up to Month 24: Cohort of 0 Months to <2 Months Subjects <sup>[51]</sup>
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End point description:

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Day 7, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 18, Month 24

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[52]</sup>			
Units: $\mu\text{mol/L}$				
arithmetic mean (standard deviation)				
Baseline; n=15	133.67 ( $\pm$ 253.829)			
Day 7 change from Baseline; n=14	-81.91 ( $\pm$ 273.127)			
Month 2 change from Baseline; n=14	-60.80 ( $\pm$ 278.083)			
Month 3 change from Baseline; n=14	-51.66 ( $\pm$ 269.558)			
Month 4 change from Baseline; n=11	-82.82 ( $\pm$ 224.269)			
Month 5 change from Baseline; n=10	-118.55 ( $\pm$ 311.125)			
Month 6 change from Baseline; n=8	-11.85 ( $\pm$ 40.693)			
Month 9 change from Baseline; n=8	-115.09 ( $\pm$ 338.186)			
Month 12 change from Baseline; n=4	-249.50 ( $\pm$ 483.776)			
Month 15 change from Baseline; n=4	-195.75 ( $\pm$ 496.313)			
Month 18 change from Baseline; n=2	6.00 ( $\pm$ 62.225)			

Month 24 change from Baseline; n=8	-82.54 ( $\pm$ 228.107)			
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Notes:

[52] - n=subjects with an assessment at given time point

## Statistical analyses

No statistical analyses for this end point

## Secondary: Amino Acid Assessment: Baseline and Change from Baseline in Valine Up to Month 24: Cohort of 0 Months to <2 Months Subjects

End point title	Amino Acid Assessment: Baseline and Change from Baseline in Valine Up to Month 24: Cohort of 0 Months to <2 Months Subjects <sup>[53]</sup>
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End point description:

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Day 7, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 18, Month 24

Notes:

[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[54]</sup>			
Units: $\mu\text{mol/L}$				
arithmetic mean (standard deviation)				
Baseline; n=15	181.49 ( $\pm$ 257.948)			
Day 7 change from Baseline; n=14	-63.96 ( $\pm$ 290.312)			
Month 2 change from Baseline; n=14	-39.04 ( $\pm$ 297.634)			
Month 3 change from Baseline; n=14	-23.86 ( $\pm$ 290.128)			
Month 4 change from Baseline; n=11	-74.41 ( $\pm$ 233.538)			
Month 5 change from Baseline; n=10	-98.67 ( $\pm$ 326.300)			
Month 6 change from Baseline; n=8	2.64 ( $\pm$ 77.843)			
Month 9 change from Baseline; n=8	-90.40 ( $\pm$ 355.316)			
Month 12 change from Baseline; n=4	-238.25 ( $\pm$ 506.435)			
Month 15 change from Baseline; n=4	-137.00 ( $\pm$ 519.042)			
Month 18 change from Baseline; n=2	38.00 ( $\pm$ 67.882)			

Month 24 change from Baseline; n=8	-72.78 ( $\pm$ 258.710)			
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Notes:

[54] - n=subjects with an assessment at given time point

## Statistical analyses

No statistical analyses for this end point

### Secondary: Assessment of Growth and Development: Baseline and Change from Baseline in BMI Z-Score Up to Month 24: Cohort of 0 Months to <2 Months Subjects

End point title	Assessment of Growth and Development: Baseline and Change from Baseline in BMI Z-Score Up to Month 24: Cohort of 0 Months to <2 Months Subjects <sup>[55]</sup>
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End point description:

To assess any effect of study drug treatment on growth, Z-scores were calculated to express the deviation from a reference population for BMI. The Z-scores are based on the World Health Organization's Child Growth Standards charts. Negative Z-scores indicate lower than typical for age and gender while positive scores indicate higher than typical for age and gender.

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 18, Month 24

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[56]</sup>			
Units: z-score				
arithmetic mean (standard deviation)				
Baseline; n=16	-0.0544 ( $\pm$ 1.26821)			
Month 1 change from Baseline; n=16	-0.2158 ( $\pm$ 1.35960)			
Month 2 change from Baseline; n=15	-0.2598 ( $\pm$ 1.19544)			
Month 3 change from Baseline; n=15	-0.1617 ( $\pm$ 1.02572)			
Month 4 change from Baseline; n=12	-0.0264 ( $\pm$ 1.68215)			
Month 5 change from Baseline; n=11	0.0828 ( $\pm$ 1.14206)			
Month 6 change from Baseline; n=10	0.0136 ( $\pm$ 1.72106)			
Month 9 change from Baseline; n=9	0.4614 ( $\pm$ 1.25343)			
Month 12 change from Baseline; n=6	0.6646 ( $\pm$ 0.95334)			

Month 15 change from Baseline; n=4	0.6830 ( $\pm$ 0.55703)			
Month 18 change from Baseline; n=3	0.3308 ( $\pm$ 0.27572)			
Month 24 change from Baseline; n=10	0.7743 ( $\pm$ 0.64962)			

Notes:

[56] - n=subjects with an assessment at given time point

## Statistical analyses

No statistical analyses for this end point

### Secondary: Assessment of Growth and Development: Baseline and Change from Baseline in BSA Z-Score Up to Month 24: Cohort of 0 Months to <2 Months Subjects

End point title	Assessment of Growth and Development: Baseline and Change from Baseline in BSA Z-Score Up to Month 24: Cohort of 0 Months to <2 Months Subjects <sup>[57]</sup>
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End point description:

To assess any effect of study drug treatment on growth, Z-scores were calculated to express the deviation from a reference population for BSA. The Z-scores are based on weight-for-length charts. Negative Z-scores indicate lower than typical for age and gender while positive scores indicate higher than typical for age and gender.

Safety Population: all enrolled subjects who received any amount of study medication and had an assessment.

End point type	Secondary
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End point timeframe:

Baseline, Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 18, Month 24

Notes:

[57] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[58]</sup>			
Units: z-score				
arithmetic mean (standard deviation)				
Baseline; n=16	-0.1980 ( $\pm$ 2.11774)			
Month 1 change from Baseline; n=16	0.2336 ( $\pm$ 1.95603)			
Month 2 change from Baseline; n=15	0.2006 ( $\pm$ 1.72135)			
Month 3 change from Baseline; n=15	0.2684 ( $\pm$ 1.37517)			
Month 4 change from Baseline; n=12	0.2372 ( $\pm$ 2.30831)			
Month 5 change from Baseline; n=11	0.1810 ( $\pm$ 1.70024)			
Month 6 change from Baseline; n=10	0.2902 ( $\pm$ 2.05956)			
Month 9 change from Baseline; n=9	0.1679 ( $\pm$ 1.32407)			

Month 12 change from Baseline; n=6	0.1308 ( $\pm$ 0.50371)			
Month 15 change from Baseline; n=4	0.1595 ( $\pm$ 0.75833)			
Month 18 change from Baseline; n=3	0.1050 ( $\pm$ 0.73521)			
Month 24 change from Baseline; n=10	0.7341 ( $\pm$ 1.35582)			

Notes:

[58] - n=subjects with an assessment at given time point

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma PBA Cmax on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects

End point title	Plasma PBA Cmax on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects <sup>[59]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[59] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: µg/mL				
arithmetic mean (standard deviation)	46.2 ( $\pm$ 49.8)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma PBA Cmin on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects

End point title	Plasma PBA Cmin on the First Full Day of RAVICTI Dosing: Cohort of 2 Months to <2 Years Subjects <sup>[60]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the

day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	7 <sup>[61]</sup>			
Units: µg/mL				
arithmetic mean (standard deviation)	4.8 (± 4.2)			

Notes:

[61] - subjects with an evaluable assessment

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma PBA AUC(0-last) on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects

End point title	Plasma PBA AUC(0-last) on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects <sup>[62]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: µg*hr/mL				
arithmetic mean (standard deviation)	374.53 (± 390.48)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma PBA Tmax on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects

End point title	Plasma PBA Tmax on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects <sup>[63]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[63] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
arithmetic mean (standard deviation)	9.39 (± 7.41)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma PAA Cmax on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects

End point title	Plasma PAA Cmax on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects <sup>[64]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: µg/mL				
arithmetic mean (standard deviation)	115.3 (± 102.0)			

## Statistical analyses



No statistical analyses for this end point

### Secondary: Plasma PAA Cmin on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects

End point title	Plasma PAA Cmin on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects <sup>[65]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[65] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[66]</sup>			
Units: µg/mL				
arithmetic mean (standard deviation)	98.98 (± 122.07)			

Notes:

[66] - subjects with an evaluable assessment

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma PAA AUC(0-last) on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects

End point title	Plasma PAA AUC(0-last) on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects <sup>[67]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[67] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: µg*hr/mL				
arithmetic mean (standard deviation)	1321.18 (± 1220.52)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma PAA Tmax on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects

End point title	Plasma PAA Tmax on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects <sup>[68]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
arithmetic mean (standard deviation)	9.85 (± 9.26)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma PAGN Cmax on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects

End point title	Plasma PAGN Cmax on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects <sup>[69]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the

day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[69] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: µg/mL				
arithmetic mean (standard deviation)	102.1 (± 48.6)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma PAGN Cmin on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects

End point title	Plasma PAGN Cmin on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects <sup>[70]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	13 <sup>[71]</sup>			
Units: µg/mL				
arithmetic mean (standard deviation)	69.39 (± 54.03)			

Notes:

[71] - subjects with an evaluable assessment

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma PAGN AUC(0-last) on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects

End point title	Plasma PAGN AUC(0-last) on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects <sup>[72]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[72] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: µg*hr/mL				
arithmetic mean (standard deviation)	1384.12 (± 1141.03)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma PAGN Tmax on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects

End point title	Plasma PAGN Tmax on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects <sup>[73]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 4 and 6 hours, 8 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[73] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
arithmetic mean (standard deviation)	11.72 (± 8.24)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Assessment of Urinary PAGN Concentrations on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects

End point title	Assessment of Urinary PAGN Concentrations on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects <sup>[74]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 0.5 and 1.5 hours, 1.5 and 2.5 hours, 4 and 6 hours, 7.5 and 8.5 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[74] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[75]</sup>			
Units: µg/mL				
arithmetic mean (standard deviation)				
Hour 0; n=6	3530.43 (± 3600.4)			
0.5 to 1.5 hours; n=8	1828 (± 2862)			
1.5 to 2.5 hours; n=9	1746 (± 1464)			
4 to 6 hours; n=11	2260 (± 1472)			
7.5 to 8.5 hours; n=14	3530.43 (± 3600.4)			
12 to 24 hours; n=16	4404 (± 3766)			

Notes:

[75] - n=subjects with an assessment at given time point

### Statistical analyses

No statistical analyses for this end point

### Secondary: Assessment of Urinary PAGN Concentrations Up to End of Trial: Cohort of 0 Months to <2 Months Subjects

End point title	Assessment of Urinary PAGN Concentrations Up to End of Trial: Cohort of 0 Months to <2 Months Subjects <sup>[76]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Day 7, Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, End of Trial

Notes:

[76] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

End point values	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[77]</sup>			
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 7; n=10	4643 (± 2506)			
Month 1; n=11	4517 (± 2485)			
Month 2; n=12	4116 (± 3137)			
Month 3; n=9	7037 (± 4493)			
Month 4; n=9	2826 (± 1543)			
Month 5; n=8	6973 (± 3682)			
Month 6; n=3	5883 (± 3128)			
Month 9; n=7	7006 (± 4289)			
Month 12; n=3	5847 (± 2992)			
Month 15; n=4	3915 (± 2584)			
End of trial; n=8	6939 (± 6581)			

Notes:

[77] - n=subjects with an assessment at given time point

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of Urinary PAA Concentrations on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects

End point title	Assessment of Urinary PAA Concentrations on the First Full Day of RAVICTI Dosing: Cohort of 0 Months to <2 Months Subjects <sup>[78]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Hour 0 and between 0.5 and 1.5 hours, 1.5 and 2.5 hours, 4 and 6 hours, 7.5 and 8.5 hours, and between 12 and 24 hours after the first dose of the day on Day 1 for stable subjects and on Day 2 for subjects in HAC

Notes:

[78] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[79]</sup>			
Units: µg/mL				
arithmetic mean (standard deviation)				
Hour 0; n=3	11.1 (± 10.4)			
0.5 to 1.5 hours; n=4	46.2 (± 58.6)			
1.5 to 2.5 hours; n=4	62.5 (± 42.8)			
4 to 6 hours; n=9	34.6 (± 56.2)			
7.5 to 8.5 hours; n=11	22.8 (± 25.3)			
12 to 24 hours; n=12	35.2 (± 51.0)			

Notes:

[79] - n=subjects with an assessment at given time point

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of Urinary PAA Concentrations Up to End of Trial: Cohort of 0 Months to <2 Months Subjects

End point title	Assessment of Urinary PAA Concentrations Up to End of Trial: Cohort of 0 Months to <2 Months Subjects <sup>[80]</sup>
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End point description:

PK Evaluable Population: all subjects from the safety population with individual concentration-time profiles that allow computation of meaningful PK parameter values.

End point type	Secondary
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End point timeframe:

Day 7, Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, End of Trial

Notes:

[80] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for each cohort are presented as separate endpoints.

<b>End point values</b>	RAVICTI: Age 0 to <2 Months			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[81]</sup>			
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 7; n=9	23.7 (± 31.2)			
Month 1; n=8	14.6 (± 17.2)			
Month 2; n=8	12.3 (± 13.3)			
Month 3; n=7	14.4 (± 10.7)			
Month 4; n=6	6.4 (± 7.1)			
Month 5; n=6	13.2 (± 14.0)			
Month 6; n=1	5.5 (± 00000)			
Month 9; n=7	11.8 (± 8.5)			
Month 12; n=3	6.0 (± 3.8)			
Month 15; n=2	4.9 (± 0.3)			
End of trial; n=5	11.6 (± 9.0)			

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Notes:

[81] - n=subjects with an assessment at given time point; 00000=not applicable (1 subject assessed).

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### **Statistical analyses**

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of study treatment through 30 days after the final dose (mean [SD] duration of treatment was 9.13 [6.838] months for Cohort of 2 Months to <2 Years Subjects and 10.67 [6.142] months for Cohort of 0 Months to <2 Months Subjects).

Adverse event reporting additional description:

TEAEs (defined as AEs with an onset date on or after the first dose of study medication until study discontinuation) are presented.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	RAVICTI: Age 2 Months to <2 Years
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Reporting group description:

Subjects age 2 months to < 2 years received RAVICTI Oral Liquid administered just prior to breastfeeding or intake of formula or food. The recommended dosing regimen is 3-6 times per day depending on feeding schedule and at the discretion of the Investigator.

Reporting group title	RAVICTI: Age 0 to <2 Months
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Reporting group description:

Subjects age 0 to < 2 months received RAVICTI Oral Liquid administered just prior to breastfeeding or intake of formula or food. The recommended dosing regimen is 3-6 times per day depending on feeding schedule and at the discretion of the Investigator.

Serious adverse events	RAVICTI: Age 2 Months to <2 Years	RAVICTI: Age 0 to <2 Months	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)	11 / 16 (68.75%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Investigations			
Ammonia increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cyanosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Lethargy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pneumatosis intestinalis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	2 / 16 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apnoeic attack			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status asthmaticus			

subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Croup infectious			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	2 / 10 (20.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rhinovirus infection			

subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			

subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperammonaemia			
subjects affected / exposed	3 / 10 (30.00%)	5 / 16 (31.25%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	RAVICTI: Age 2 Months to <2 Years	RAVICTI: Age 0 to <2 Months	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)	16 / 16 (100.00%)	
Vascular disorders			
Venous thrombosis limb			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 16 (12.50%)	
occurrences (all)	2	3	

Catheter site rash subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Device occlusion subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Drug withdrawal syndrome subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Medical device site haemorrhage subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	4 / 16 (25.00%) 5	
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Apnoea subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Nasal congestion subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 16 (12.50%) 2	
Respiratory disorder subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 16 (12.50%) 2	
Pneumothorax			

subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Tachypnoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Use of accessory respiratory muscles			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Irritability			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Investigations			
Amino acid level decreased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Ammonia increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Carbon dioxide decreased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	
occurrences (all)	1	2	
Hepatic enzyme increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Amino acid level increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Anion gap increased			

subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Blood bicarbonate decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Blood urea decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Body height below normal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Platelet count increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Transaminases increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Stoma site reaction			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Tibia fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Arthropod bite			



subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Congenital, familial and genetic disorders			
Dacryostenosis congenital subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Plagiocephaly subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 16 (12.50%) 2	
Cardiac disorders			
Tachycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Nervous system disorders			
Gross motor delay subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Lethargy subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Tremor subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	3 / 16 (18.75%) 3	
Neutropenia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 16 (12.50%) 2	
Thrombocytosis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 16 (12.50%) 2	

Leukocytosis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Lymphocytosis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Microcytic anaemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Ear and labyrinth disorders Excessive cerumen production subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Eye disorders Eye discharge subjects affected / exposed occurrences (all)  Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0  0 / 10 (0.00%) 0	1 / 16 (6.25%) 1  1 / 16 (6.25%) 1	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Teething subjects affected / exposed occurrences (all)  Constipation subjects affected / exposed occurrences (all)  Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)  Flatulence	4 / 10 (40.00%) 5  1 / 10 (10.00%) 1  1 / 10 (10.00%) 1  2 / 10 (20.00%) 2  0 / 10 (0.00%) 0	5 / 16 (31.25%) 12  5 / 16 (31.25%) 6  3 / 16 (18.75%) 3  2 / 16 (12.50%) 2  6 / 16 (37.50%) 6	

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	3 / 16 (18.75%) 3	
Dysphagia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Post-tussive vomiting subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 2	
Hepatobiliary disorders Hepatic calcification subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3	5 / 16 (31.25%) 6	
Nail ridging subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Dermatitis diaper subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	6 / 16 (37.50%) 6	
Eczema subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 16 (6.25%) 2	
Red man syndrome subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Seborrhoeic dermatitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 2	
Renal and urinary disorders Vesicoureteric reflux subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Nephrolithiasis			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Musculoskeletal and connective tissue disorders Torticollis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 6	5 / 16 (31.25%) 7	
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	1 / 16 (6.25%) 2	
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 16 (12.50%) 2	
Viral infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 16 (6.25%) 1	
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	4 / 16 (25.00%) 7	
Croup infectious subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 16 (6.25%) 2	
Otitis media subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	1 / 16 (6.25%) 1	
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Pharyngitis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Pneumonia			

subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Ear infection			
subjects affected / exposed	0 / 10 (0.00%)	3 / 16 (18.75%)	
occurrences (all)	0	3	
Oral candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Angular cheilitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Candida infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Lower respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Otitis media acute			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Rhinovirus infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypophagia			
subjects affected / exposed	2 / 10 (20.00%)	1 / 16 (6.25%)	
occurrences (all)	3	1	

Metabolic acidosis			
subjects affected / exposed	2 / 10 (20.00%)	2 / 16 (12.50%)	
occurrences (all)	2	2	
Hyperammonaemia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	3	
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	4	
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Feeding disorder of infancy or early childhood			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Protein deficiency			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2015	<ul style="list-style-type: none"><li>• It was clarified that the total daily RAVICTI dose should remain the same when making changes to dose or dosing regimen.</li><li>• The section describing how urine PAGN measurements could be used to help guide RAVICTI dose adjustment was updated to reflect that the final analysis of urine PAGN concentration data was to be based on age and BSA, rather than RAVICTI dose.</li><li>• The density of RAVICTI Oral Liquid used in the study was corrected from 1.1 g/L to 1.1 g/mL.</li><li>• It was indicated that at early termination, a PK sample was to be collected as close to the last dose of RAVICTI as possible and that the Medical Monitor was to be contacted for guidance when early termination procedures could not be conducted as scheduled.</li><li>• It was clarified that liver transplantation was not to be considered an AE when performed for the treatment of stable underlying UCDs.</li><li>• It was clarified that the DSMB met at least every 6 months, beginning 6 months after the first subject was enrolled, rather than every 6 to 8 months as previously stated.</li><li>• It was clarified that single blood samples were used for PK PBA analysis in addition to PAA and PAGN, and added a Day 3 collection time for subjects &lt;2 months of age presenting in hyperammonemic crisis.</li><li>• It was clarified that single urine samples were used for urinary creatinine PK analysis, in addition to PAA and PAGN, and added a Day 3 collection time for subjects &lt;2 months of age presenting in hyperammonemic crisis.</li><li>• It was added that the single PK urine and blood samples were analyzed as outlined in the dosing algorithm guidance in Appendix B of the protocol, and that the results of all PK samples may have been provided to the DSMB, Sponsor, and Investigators when available.</li><li>• A planned analysis when the database was locked for the 2 months to &lt;2 years old cohort was added, in order to meet the PMR requirement.</li></ul>
13 July 2015	<p>(continued)</p> <ul style="list-style-type: none"><li>• It was added that the Investigator must maintain adequate and accurate records of study data and provide a list of such source data.</li><li>• It was clarified that although an algorithm was provided as guidance to the Investigator for the use of ammonia and PK in future dose adjustment, the algorithm was not intended to be used in lieu of clinical judgment, i.e., Investigators was not to defer clinical decision making until the PK results were received.</li><li>• Administrative changes were made related to the change in ownership from Hyperion Therapeutics, Inc. to Horizon Therapeutics, Inc. throughout the protocol (subsequently became Horizon Therapeutics, LLC).</li></ul>

23 August 2016	<ul style="list-style-type: none"> <li>• Because samples could not be consistently obtained when dose adjustments were needed on an outpatient basis, and the PK results could not be delivered in a timely manner to guide dosing, the following changes were made: <ul style="list-style-type: none"> <li>o The objectives of characterizing the PK of RAVICTI were revised to omit examining the utility of ammonia, urinary PAGN, and plasma PAA and PAGN as dosing biomarkers.</li> <li>o It was clarified that the PK results would be used to examine the study drug absorption and metabolism but would not be used to provide information on management of individualized dosing. Additionally, Investigators were to use their clinical judgment and consider the subject's status if the allowable blood volume limit was reached per their institutional guideline.</li> <li>o It was specified that blood and urinary metabolite levels would not be used to guide dose adjustments. Rather, dose adjustment would be individualized at the discretion of the Investigator and according to the needs of each subject and accounting for the subject's expected level of growth and development, BSA, and ammonia control.</li> <li>o All language that PAA, PAGN, and/or urinary PAGN were to be used to help guide study drug dosing was removed.</li> <li>o It was specified that the dose adjustment algorithm was to be driven by ammonia control and other clinical considerations.</li> <li>o Language regarding PK sample collection prior to dose adjustment was removed.</li> </ul> </li> <li>• Outpatient ammonia monitoring after 48 hours inpatient following the first study drug dose was allowed. At least 48 hours monitoring after the first full dose of RAVICTI had to occur in an inpatient setting, and if the subject was discharged after 48 hours but prior to 72 hours of monitoring, the subject was to return at approximately the 60- and 72-hour mark for evaluation and plasma ammonia measurement.</li> </ul>
23 August 2016	<p>(continued)</p> <ul style="list-style-type: none"> <li>• It was clarified that although it was preferred to measure height (length), weight, and head circumference twice (and an average calculated), failure to obtain second value would not constitute a protocol deviation.</li> <li>• Collection of the date and time of PK sample collection was added to ensure the most informative analysis of PK results.</li> <li>• All GPB sample collection was removed because these samples were obtained for select sites only and in less than a third of subjects prior to the amendment. It was unlikely that the subjects yet to enroll, who all would be less than 2 months of age, would yield additional samples.</li> <li>• A section was added that specified any of remaining subjects enrolled who entered the study at age birth to &lt;1 month of age (rather than 1 month to &lt;2 months of age as originally planned) would undergo thorough PK assessment when they were age 1 month to &lt;2 months, as well as in the transition period, to facilitate completion of the study. Enrollment of additional subjects between 1-2 months of age could have been challenging because it may have required the subject to switch therapies or delay treatment. Therefore the remaining enrollment included any otherwise eligible subject &lt;2 months of age at the time of consent.</li> <li>• A section was added that a product complaint form would be provided to each site, and any product complaint would be reported to the Sponsor using the form.</li> <li>• The total enrollment was increased from 24 to 26 subjects based on over enrollment of the 2 months to 2 years cohort by 2 subjects. Information on enrollment to date was added, and allowed completion of enrollment with any mix of subjects &lt;2 months of age without losing the opportunity to get the needed data from 1 month to &lt;2 months of age.</li> </ul>
23 August 2016	<p>(continued)</p> <ul style="list-style-type: none"> <li>• The Per-Protocol population (all subjects from the Safety population with at least 80% compliance with study drug and no major protocol violations) was removed from the analysis plans because it was not possible to precisely determine compliance in the study.</li> <li>• It was clarified that the planned interim analysis for the 2 months to 2 years old cohort conducted to meet the PMR milestone from FDA was completed prior to Protocol Amendment 2. The interim analysis was conducted after the subjects in this cohort completed the Month 3 assessments, the data for that age group were locked, and a CSR was generated. Data subsequently gathered from this age group was included in an addendum to that CSR. There were no other planned interim analyses.</li> </ul>



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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported