Clinical trial results:
A Long-Term, Open-Label, Safety and Efficacy Study of Cysteamine Bitartrate Delayed-release Capsules (RP103) in Patients with Nephropathic Cystinosis

Summary

EudraCT number	2010-018365-34
Trial protocol	FR NL
Global end of trial date	26 June 2017

Results information

Result version number	v1 (current)
This version publication date	05 January 2018
First version publication date	05 January 2018

Trial information

Trial identification

Sponsor protocol code	RP103-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01197378
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Horizon Pharma USA, Inc.
Sponsor organisation address	150 S. Saunders Road, Lake Forest, United States, 60045
Public contact	Evelyn Olson, Horizon Pharma USA, Inc., clinicaltrials@horizonpharma.com
Scientific contact	Maria Pecoraro, MD, Horizon Pharma USA, Inc., clinicaltrials@horizonpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the safety and tolerability of long-term repeat dosing of RP103 in patients with nephropathic cystinosis.

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice (GCP).
The protocol, Informed Consent Form (ICF) and assents were reviewed and approved by the Institutional Review Board (IRB) or Ethics Committee (EC).
Written informed assent for the study was obtained from all pediatric subjects and from each pediatric subject's parent or legal guardian before protocol-specific procedures were carried out. For adults above the age of 18 years, written informed consent for the study was obtained before protocol-specific procedures were carried out.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 August 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	United States: 33
Worldwide total number of subjects	60
EEA total number of subjects	27

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	37
Adolescents (12-17 years)	17

Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Initially, only subjects who completed the previous Phase III Study RP103-03 were enrolled in this extension study. As of 27 September 2011, enrollment was opened up to additional subjects, including subjects who were less than 6 years of age and kidney transplant subjects who qualified based on the inclusion/exclusion criteria.

Pre-assignment

Screening details:

Of the 60 subjects who were screened for participation in the RP103-04 study, all 60 were eligible and subsequently enrolled.

Period 1

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

Arms

Arm title	Cysteamine bitartrate

Arm description:

Cysteamine bitartrate delayed-release capsules were administered twice daily.

Arm type	Experimental
Investigational medicinal product name	Cysteamine Bitartrate Delayed-Release
Investigational medicinal product code	RP103
Other name	mercaptamine bitartrate, PROCYSBI
Pharmaceutical forms	Gastro-resistant capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects who entered the trial from the RP103-03 study continued treatment with RP103 Q12H at the last dose level prescribed during their participation in the study.
Subjects not entering the trial from RP103-03 study were started on twice a day administration of RP103, where the total daily RP103 dose was 70% of their pre-study total daily stable Cystagon® dose.

Number of subjects in period 1	Cysteamine bitartrate
Started	60
Received treatment	59
Completed	53
Not completed	7
Physician decision	1
Consent withdrawn by subject	1
Adverse event, non-fatal	3
Other	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	60	60	
Age categorical Units: Subjects			
Children (2-11 years)	37	37	
Adolescent (12-17 years)	17	17	
18-64 years	6	6	
Age continuous Units: years			
arithmetic mean	10.7		
standard deviation	± 6.10	-	
Gender categorical Units: Subjects			
Female	23	23	
Male	37	37	
Race Units: Subjects			
White	59	59	
Other	1	1	
Ethnicity Units: Subjects			
Hispanic/Latino	3	3	
Not Hispanic/Latino	57	57	

End points

End points reporting groups

Reporting group title	Cysteamine bitartrate

Reporting group description:

Cysteamine bitartrate delayed-release capsules were administered twice daily.

Primary: Number of Participants with Treatment-emergent Adverse Events

End point title	Number of Participants with Treatment-emergent Adverse Events[1]

End point description:

Drug-related includes adverse events with investigator-assessed relation to drug of: 'possibly', 'probably' or 'definitely'.
The severity of AEs was categorized according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 as follows:
- MILD (Grade 1): experience is minor and does not cause significant discomfort to subject or change in activities of daily living (ADL); subject is aware of symptoms but symptoms are easily tolerated;
- MODERATE (Grade 2): experience is an inconvenience or concern to the subject and causes interference with ADL, but the subject is able to continue with ADL.
- SEVERE (Grade 3): experience significantly interferes with ADL and the subject is incapacitated and/or unable to continue with ADL
- LIFE THREATENING (Grade 4): experience that, in the view of the Investigator, places the subject at immediate risk of death from the event as it occurred.

End point type	Primary

End point timeframe:

From first dose of study drug to 7 days after the last dose; median duration of treatment was 1461 days.

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: No statistical analyses were performed in this open-label extension study.

End point values	Cysteamine bitartrate			
Subject group type	Reporting group			
Number of subjects analysed	59[2]			
Units: participants				
All adverse events	58			
Adverse events related to study drug	37			
Adverse events ≥ Grade 3	24			
Serious adverse events	32			
Adverse events leading to discontinuation	3			

Notes:

[2] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Cysteamine Concentration

End point title	Trough Plasma Cysteamine Concentration

End point description:

Plasma cysteamine concentration was determined using methods employing Hydrophilic Interaction Liquid Chromatography (HILC) high pressure liquid chromatography (HPLC) tandem mass spectrometry (HPLC-MS/MS).
The Pharmacokinetic/Pharmacodynamic (PK/PD) Population includes all subjects who had at least one PK/PD measurement. Day 1 results only include subjects who did not complete Study RP103-03. Month 1 results only available for subjects who did complete Study RP103-03.

End point type	Secondary

End point timeframe:

Day 1 (predose) and Month 6, Years 1, 1.5, 2, 3, 4 and 5 at 0.5 hours post-dose

End point values	Cysteamine bitartrate			
Subject group type	Reporting group			
Number of subjects analysed	59[3]			
Units: mg/L				
arithmetic mean (standard deviation)				
Day 1 (N = 19)	0.17 (± 0.093)			
Month 6 (N = 56)	0.29 (± 0.613)			
Year 1 (N = 56)	0.37 (± 0.513)			
Year 1.5 (N = 55)	0.48 (± 0.718)			
Year 2 (N = 45)	0.36 (± 0.412)			
Year 3 (N = 28)	0.34 (± 0.659)			
Year 4 (N = 38)	0.47 (± 0.708)			
Year 5 (N = 26)	0.40 (± 0.399)			

Notes:

[3] - PK/PD Population

Statistical analyses

No statistical analyses for this end point

Secondary: White Blood Cell Cystine Concentration

End point title	White Blood Cell Cystine Concentration

End point description:

White blood cell (WBC) cystine concentration was determined using high performance liquid chromatography-electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS).
The Pharmacokinetic/Pharmacodynamic (PK/PD) Population includes all subjects who had at least one PK/PD measurement. Day 1 results only include subjects who did not complete Study RP103-03. Month 1 results only available for subjects who did complete Study RP103-03.

End point type	Secondary

End point timeframe:

Day 1 (predose) and Month 6, Years 1, 1.5, 2, 3, 4 and 5 at 0.5 hours post-dose

End point values	Cysteamine bitartrate			
Subject group type	Reporting group			
Number of subjects analysed	59[4]			
Units: nmol 1/2 Cystine/mg protein				
arithmetic mean (standard deviation)				
Day 1 (N = 18)	1.68 (± 1.275)			
Month 6 (N = 56)	0.93 (± 1.174)			
Year 1 (N = 55)	0.65 (± 0.569)			
Year 1.5 (N = 54)	0.75 (± 0.852)			
Year 2 (N = 44)	0.65 (± 0.851)			
Year 3 (N = 28)	0.66 (± 0.575)			
Year 4 (N = 28)	1.38 (± 1.672)			
Year 5 (N = 24)	1.17 (± 2.117)			

Notes:

[4] - PK/PD Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to 7 days after last dose; median duration of treatment was 1461 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Cysteamine bitartrate

Reporting group description:

Cysteamine bitartrate delayed-release capsules were administered twice daily.

Serious adverse events	Cysteamine bitartrate		
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 59 (54.24%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Nephrectomy			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative care			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Kidney transplant rejection			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Tonsillar hypertrophy			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Impaired self-care			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental disorder			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Biopsy kidney			

subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Investigation			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Graft dysfunction			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Arnold-chiari malformation			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cryptorchism			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Congestive cardiomyopathy			

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudoparalysis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Constipation				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric fistula				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal failure chronic				
subjects affected / exposed	4 / 59 (6.78%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	3 / 59 (5.08%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal tubular acidosis				

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Knee deformity			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences causally related to treatment / all	1 / 15		
deaths causally related to treatment / all	0 / 0		
Appendicitis perforated			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial diarrhoea			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media chronic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pyelonephritis				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection viral				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Salpingitis				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth abscess				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urethritis				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	5 / 59 (8.47%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	4 / 59 (6.78%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Acidosis				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Electrolyte imbalance				

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cysteamine bitartrate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 59 (98.31%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	7		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 59 (16.95%)		
occurrences (all)	11		
Pyrexia			
subjects affected / exposed	8 / 59 (13.56%)		
occurrences (all)	14		
Asthenia			

subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Influenza like illness			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	6		
Oedema peripheral			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	7		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	5		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	39		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 59 (16.95%)		
occurrences (all)	14		
Epistaxis			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	7		
Oropharyngeal pain			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	8		
Psychiatric disorders			
Depression			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
Investigations			
Blood creatinine increased			

subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
Injury, poisoning and procedural complications			
Joint sprain			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Arthropod bite			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Cardiac disorders			
Left ventricular hypertrophy			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 59 (37.29%)		
occurrences (all)	69		
Syncope			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
Lethargy			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	14 / 59 (23.73%)		
occurrences (all)	16		
Photophobia			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	40 / 59 (67.80%)		
occurrences (all)	129		
Diarrhoea			
subjects affected / exposed	17 / 59 (28.81%)		
occurrences (all)	32		
Nausea			
subjects affected / exposed	16 / 59 (27.12%)		
occurrences (all)	21		
Abdominal pain			
subjects affected / exposed	12 / 59 (20.34%)		
occurrences (all)	19		
Breath odour			
subjects affected / exposed	8 / 59 (13.56%)		
occurrences (all)	8		
Abdominal pain upper			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	15		
Constipation			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	9		
Abdominal discomfort			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	4		
Flatulence			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Skin odour abnormal			

subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	6		
Acne			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	5		
Rash			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 59 (16.95%)		
occurrences (all)	13		
Pain in extremity			
subjects affected / exposed	9 / 59 (15.25%)		
occurrences (all)	15		
Back pain			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	8		
Muscle spasms			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Infections and infestations			
Influenza			
subjects affected / exposed	14 / 59 (23.73%)		
occurrences (all)	22		
Nasopharyngitis			
subjects affected / exposed	13 / 59 (22.03%)		
occurrences (all)	19		
Gastroenteritis			
subjects affected / exposed	11 / 59 (18.64%)		
occurrences (all)	25		
Ear infection			
subjects affected / exposed	10 / 59 (16.95%)		
occurrences (all)	10		
Upper respiratory tract infection			

subjects affected / exposed	10 / 59 (16.95%)		
occurrences (all)	24		
Sinusitis			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	9		
Urinary tract infection			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	7		
Bronchitis			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	8		
Otitis media			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	6		
Molluscum contagiosum			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Pharyngitis			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	4		
Pharyngitis streptococcal			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Rhinitis			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	5		
Tonsillitis			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Varicella			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	4		
Viral infection			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	7		
Decreased appetite			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	6		
Hypokalaemia			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2010	The objectives for Amendment 1 were: 1. To update the Background Information based on the final results obtained from the RP103-01 pilot study. 2. To revise the protocol design of version 1.1 to incorporate the following changes: - Monthly visits for at least six (6) months for each subject followed by synchronized quarterly visits. - Modify and clarify inclusion and exclusion criteria. - Eliminate the GSRS from the study. - Utilize the self-report PedsQL QoL instrument instead of the parent proxy report. - Addition of safety and PK/PD data reviews, during or prior to, each study visit to allow for greater subject oversight for dose adjustments. 3. To update the bioanalytical laboratory information. - Provide specific information concerning where samples are to be sent in the US and Europe. - To update the plasma cysteamine and WBC processing instructions. 4. To update the list of abbreviations. 5. To clarify statements and instructions concerning protocol specified procedures. 6. To update administrative information. 7. To update the reference list. 8. To correct typographical and formatting errors.
20 May 2010	The objectives for Amendment 2 were: 1. To update the protocol to synchronize with changes incorporated in the precursor pivotal study RP103-03 Amendment 2, which included: - Allowance for subjects that are receiving Cystagon® at the conclusion of study RP103-03 to roll over into this study without the need for a Day 1 study visit. - Clarification that WBC cystine values <1 nmol ½ cystine/mg protein represented a meaningful reduction in WBC cystine levels. - Changing the time for RP103 trough sampling (i.e., 1 hour changed to 0.5 hours post RP103 dose administration). 2. To update and correct the inclusion and exclusion criteria. 3. To update the list of abbreviations. 4. To correct and update the total amount of blood collected over the study duration. 5. To correct typographical and formatting errors.
09 August 2010	The objectives for Amendment 3 were: 1. To revise the protocol to restrict enrollment for subjects that did not participate in the precursor study (RP103-03) to occur only after all subjects enrolled in Study RP103-03 have completed their participation in that study and the data analyzed. 2. To add stopping criteria consistent with Study no. RP103-03. 3. To correct the list of safety endpoints. 4. To update the list of abbreviations. 5. To update the responsible party for medical monitoring. 6. To clarify inclusion criteria language. 7. To make language consistency changes between protocols RP103-03 and RP103-04. 8. To correct typographical and formatting errors.

02 May 2011	The objectives for Amendment 4 were: 1. To change the regular daily dose of Cystagon® to 80% (instead of 70% previously)and a dose adjustment to 100% of their regular daily dose of Cystagon® (instead of 20to 25% of the dose of RP103). 2. To clarify instructions for subjects not entering the RP103-04 trial from Study RP103-03. 3. To describe a food effect on cysteamine absorption. 4. To include total protein test method comparison and describe the correction factor. 5. To include the updated prefigured guideline for the dosage of the subjects. 6. To update one table and include two new figures. 7. To update the List of Abbreviations. 8. To clarify statements and instructions. 9. To correct formatting errors.
27 September 2011	The objectives for Amendment 5 were: 1. To include published results of recently completed clinical trials: - Bioequivalence studies RP103-02 and RP103-05, in healthy volunteers. - Pivotal Phase 3 study RP103-03, in cystinosis subjects. 2. To provide final data and guidance in the following areas, which in the previous protocol amendment were based on interim results of the recently completed clinical trials: - Starting total daily dose of RP103 changed to 70% of the stable baseline - Cystagon® dose and subsequent dose adjustment increased to 100% of that stable Cystagon® dose. - Food effect on cysteamine absorption has been detailed. - RP103 dosing recommendations with respect to food intake and timing have been updated. 3. To expand enrollment to subjects unable or unwilling to take intact capsules, the following areas were revised: - Total number of expected study participants has been increased. - Inclusion and Exclusion criteria were updated to permit enrollment of subjects who do not receive their cysteamine dose as intact capsules, and those who receive it via gastric tube. 4. To change the Schedule of Events for subjects not entering the trial from Study RP103-03, adding a Dose Confirmation Period which includes study visits on Day 4 and Day 5. 5. To change all references to “nephropathic cystinosis” to simply “cystinosis” 6. To clarify statements and instructions. 7. To correct formatting and typographical errors.
26 September 2012	The objectives for Amendment 6 were: 1. To insert a minimum required age for study participants; 2. To increase maximum study duration from 24 to 36 months; 3. To revise investigational product description to reflect currently manufactured lots; 4. To revise maximum blood volume to be collected from subjects, reflecting the change in maximum study duration to 36 months and to include the optional PK substudy; 5. To insert an optional PK substudy visit for all subjects 6 years old and younger; 6. To insert a newly published reference (previously reported as “submitted for publication”); 7. To update the bioanalytical laboratory contact details to reflect that all PK-PD samples were to be shipped to the US location (because the EU laboratory had closed); 8. To clarify statements and instructions, specifically pertaining to RP103 dosing; 9. To correct formatting and typographical errors.

04 November 2013	The objectives for Amendment 7 were: 1. To insert changes to Sponsor company name and contact details; 2. To insert a change in Institution and contact details for the Lead Investigator; 3. To increase the maximum study duration to 48 months; 4. To provide updated information regarding the acceptable storage temperature of the investigational product, RP103; 5. To revise maximum blood volume to be collected from subjects, reflecting the change in maximum study duration to 48 months; 6. To remove references to the specific central bioanalytical laboratory "BASi" in the event that a different laboratory would be utilized in future (in which case the site laboratory instructions would be updated); 7. To clarify statements and instructions, specifically pertaining to RP103 dosing; 8. To correct minor formatting and typographical errors.
25 November 2014	The objectives for Amendment 8 were: 1. To document a change in Sponsor Medical Officer; 2. To document a change in the Sponsor medical representative responsible for receipt of serious adverse event (SAE) reports; 3. To insert changes to Sponsor physical address; 4. To increase the maximum study duration to 60 months; 5. To insert the EudraCT number associated with the trial; 6. To revise maximum blood volume to be collected from subjects, reflecting the change in maximum study duration to 60 months; 7. To correct minor formatting and typographical errors.
18 November 2015	The purpose of RP103-04 Protocol Amendment 9 were as follows: - To update Raptor Chief Medical Officer; - To clarify study duration; - To update anticipated blood collection volumes for the entire study based on clarification to study duration; - To clarify Adverse Event reporting; - Update reference to Storage Conditions and Identity of Investigational Product (RP103); - To correct formatting and typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported