



## Clinical trial results:

### A Randomized, Crossover Pharmacokinetic and Pharmacodynamic Study to Determine the Safety and Efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103), Compared to Cystagon® in Patients with Nephropathic Cystinosis

#### Summary

EudraCT number	2009-017882-42
Trial protocol	FR NL
Global end of trial date	03 June 2011

#### Results information

Result version number	v1 (current)
This version publication date	20 May 2017
First version publication date	20 May 2017

#### Trial information

##### Trial identification

Sponsor protocol code	RP103-03
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01000961
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Horizon Pharma USA, Inc.
Sponsor organisation address	150 S. Saunders Road, Lake Forest, Illinois, United States, 60045
Public contact	Evelyn Olson, BS, Horizon Pharma USA, Inc., clinicaltrials@horizonpharma.com
Scientific contact	Evelyn Olson, BS, 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	03 June 2011
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	03 June 2011
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Cystinosis is an inherited disease that if untreated, results in kidney failure as early as the first decade of life. The current marketed therapy is Cystagon® (cysteamine bitartrate) which must be taken every six hours for the rest of the patient's life to prevent complications of cystinosis. RP103 is a formulation of cysteamine bitartrate that is being studied to see if it may be able to be given less frequently, once every 12 hours, and have similar results to four times a day Cystagon®.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. The study was conducted in accordance with legal and regulatory requirements including Guidance for Good Clinical Practice (International Conference on Harmonization [ICH] 1996), and the Declaration of Helsinki (World Medical Association 2008). Only subjects who met the inclusion criteria and none of the exclusion criteria were enrolled to this study. Written informed consent was to be obtained from the subject's legally acceptable representative and assent by the minor subject, as applicable, before screening or baseline assessments. Instructions were given to the subject's legally acceptable representative in case of emergency or other questions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 June 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	France: 14
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	44
EEA total number of subjects	18

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)	24
Adolescents (12-17 years)	16
Adults (18-64 years)	4
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants randomized to each per sequence Arm are expected to remain in the same Arm throughout all intervention periods.

### Pre-assignment period milestones

Number of subjects started	44
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Number of subjects completed	43
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### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 1
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### Period 1

Period 1 title	Run-in Period of 2-3 weeks on Cystagon
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Is this the baseline period?	Yes
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Allocation method	Non-randomised - controlled
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Blinding used	Not blinded
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### Arms

Are arms mutually exclusive?	Yes
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Arm title	Cystagon first, then Cystagon, then RP103
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Arm description:

Cystagon® dose in 50 mg and 150 mg capsule formulations administered every 6 hours in first intervention (after Run-in period) and RP103 dose in 25 mg and 75 mg capsule formulations administered every 12 hours in second intervention period.

Arm type	Experimental
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Investigational medicinal product name	Cystagon®
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Capsule, hard
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Routes of administration	Oral use
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Dosage and administration details:

Prior to treatment, eligible subjects underwent a 2 to 3 week Run-in Period of their stable dose of Cystagon® administered every 6 hours.

Arm title	Cystagon first, then RP103, then Cystagon
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Arm description:

RP103 dose in 25 mg and 75 mg capsule formulations administered every 12 hours in first intervention (after Run-in period) and Cystagon® dose in 50 mg and 150 mg capsule formulations administered every 6 hours in second intervention period.

Arm type	Experimental
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Investigational medicinal product name	Cystagon®
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Capsule, hard
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Routes of administration	Oral use
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Dosage and administration details:

Prior to treatment, eligible subjects underwent a 2 to 3 week Run-in Period of their stable dose of

<b>Number of subjects in period 1<sup>[1]</sup></b>	Cystagon first, then Cystagon, then RP103	Cystagon first, then RP103, then Cystagon
Started	21	22
Completed	21	22

**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 was withdrawn prior to randomization, and is accounted for in the Pre-assignment Milestones table.

**Period 2**

Period 2 title	First Intervention (3 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Cystagon first, then Cystagon, then RP103

**Arm description:**

Cystagon® dose in 50 mg and 150 mg capsule formulations administered every 6 hours in first intervention (after Run-in period) and RP103 dose in 25 mg and 75 mg capsule formulations administered every 12 hours in second intervention period.

Arm type	Experimental
Investigational medicinal product name	Cystagon®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

**Dosage and administration details:**

3 weeks (±3 days) treatment with Cystagon® every 6 hours

<b>Arm title</b>	Cystagon first, then RP103, then Cystagon
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**Arm description:**

RP103 dose in 25 mg and 75 mg capsule formulations administered every 12 hours in first intervention (after Run-in period) and Cystagon® dose in 50 mg and 150 mg capsule formulations administered every 6 hours in second intervention period.

Arm type	Experimental
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Investigational medicinal product name	Cysteamine bitartrate
Investigational medicinal product code	RP103
Other name	PROCYSBI®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

3 weeks ( $\pm 3$  days) of RP103 administered every 12 hours

Number of subjects in period 2	Cystagon first, then Cystagon, then RP103	Cystagon first, then RP103, then Cystagon
Started	21	22
Completed	21	20
Not completed	0	2
Consent withdrawn by subject	-	1
Infection after pre-planned surgery	-	1

### Period 3

Period 3 title	Second Intervention (3 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Cystagon first, then Cystagon, then RP103

Arm description:

Cystagon® dose in 50 mg and 150 mg capsule formulations administered every 6 hours in first intervention (after Run-in period) and RP103 dose in 25 mg and 75 mg capsule formulations administered every 12 hours in second intervention period.

Arm type	Experimental
Investigational medicinal product name	Cysteamine bitartrate
Investigational medicinal product code	RP103
Other name	PROCYSBI®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

3 weeks ( $\pm 3$  days) of RP103 administered every 12 hours

<b>Arm title</b>	Cystagon first, then RP103, then Cystagon
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Arm description:

RP103 dose in 25 mg and 75 mg capsule formulations administered every 12 hours in first intervention (after Run-in period) and Cystagon® dose in 50 mg and 150 mg capsule formulations administered every 6 hours in second intervention period.

Arm type	Experimental
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Investigational medicinal product name	Cystagon®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

3 weeks ( $\pm 3$  days) treatment with Cystagon® every 6 hours

<b>Number of subjects in period 3</b>	Cystagon first, then Cystagon, then RP103	Cystagon first, then RP103, then Cystagon
Started	21	20
Completed	21	20

## Baseline characteristics

### Reporting groups

Reporting group title	Run-in Period of 2-3 weeks on Cystagon
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Reporting group description: -

Reporting group values	Run-in Period of 2-3 weeks on Cystagon	Total	
Number of subjects	43	43	
Age Categorical Units: Participants			
Age Continuous Units: years			
arithmetic mean	11.7		
standard deviation	± 4.19	-	
Gender, Male/Female Units: Participants			
Female	19	19	
Male	24	24	

## End points

### End points reporting groups

Reporting group title	Cystagon first, then Cystagon, then RP103
Reporting group description: Cystagon® dose in 50 mg and 150 mg capsule formulations administered every 6 hours in first intervention (after Run-in period) and RP103 dose in 25 mg and 75 mg capsule formulations administered every 12 hours in second intervention period.	
Reporting group title	Cystagon first, then RP103, then Cystagon
Reporting group description: RP103 dose in 25 mg and 75 mg capsule formulations administered every 12 hours in first intervention (after Run-in period) and Cystagon® dose in 50 mg and 150 mg capsule formulations administered every 6 hours in second intervention period.	
Reporting group title	Cystagon first, then Cystagon, then RP103
Reporting group description: Cystagon® dose in 50 mg and 150 mg capsule formulations administered every 6 hours in first intervention (after Run-in period) and RP103 dose in 25 mg and 75 mg capsule formulations administered every 12 hours in second intervention period.	
Reporting group title	Cystagon first, then RP103, then Cystagon
Reporting group description: RP103 dose in 25 mg and 75 mg capsule formulations administered every 12 hours in first intervention (after Run-in period) and Cystagon® dose in 50 mg and 150 mg capsule formulations administered every 6 hours in second intervention period.	
Reporting group title	Cystagon first, then Cystagon, then RP103
Reporting group description: Cystagon® dose in 50 mg and 150 mg capsule formulations administered every 6 hours in first intervention (after Run-in period) and RP103 dose in 25 mg and 75 mg capsule formulations administered every 12 hours in second intervention period.	
Reporting group title	Cystagon first, then RP103, then Cystagon
Reporting group description: RP103 dose in 25 mg and 75 mg capsule formulations administered every 12 hours in first intervention (after Run-in period) and Cystagon® dose in 50 mg and 150 mg capsule formulations administered every 6 hours in second intervention period.	
Subject analysis set title	RP103 and Cystagon® crossover
Subject analysis set type	Full analysis
Subject analysis set description: Per Protocol Population	
Subject analysis set title	RP103
Subject analysis set type	Per protocol
Subject analysis set description: Per Protocol Population	
Subject analysis set title	Cystagon®
Subject analysis set type	Per protocol
Subject analysis set description: Per Protocol Population	

### Primary: The Steady-State White Blood Cell Cystine Levels of RP103 Compared to Cystagon®

End point title	The Steady-State White Blood Cell Cystine Levels of RP103 Compared to Cystagon®
End point description:	
End point type	Primary

End point timeframe:

4 weeks after the last subject has completed the study

End point values	RP103	Cystagon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: nmol ½ Cystine / mg protein				
least squares mean (standard error)	0.5152 (± 0.05555)	0.4367 (± 0.05555)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

16-subject study will have 90% power to reject the null hypothesis of non-inferiority at the 0.025 level of significance with a non-inferiority margin of 0.3. Final analysis was performed at a nominal significance level of 0.02104.

Comparison groups	RP103 v Cystagon®
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[1]</sup>
P-value	= 0.0001
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.0785
Confidence interval	
level	95.8 %
sides	2-sided
lower limit	0.0107
upper limit	0.1464

Notes:

[1] - The non-inferiority endpoint of the clinical trial would be achieved if the upper limit of the 95.8% CI of the difference between RP103 and Cystagon® was less than the a-priori 0.3 non-inferiority margin, which would correspond to an observed p-value less than or equal to 0.02104

## Secondary: Comparison of Cysteamine PK Profiles, Steady State Cmax, Between RP103 and Cystagon®

End point title	Comparison of Cysteamine PK Profiles, Steady State Cmax, Between RP103 and Cystagon®
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End point description:

End point type	Secondary
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End point timeframe:

4 weeks after the last subject has completed the study

End point values	RP103	Cystagon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	39		
Units: Cmax (mg/L)				
least squares mean (standard deviation)	3.7 (± 1.72)	2.73 (± 1.36)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	RP103 v Cystagon®
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	1.67

## Secondary: Comparison of Cysteamine PK profiles, Steady State Tmax, Between RP103 and Cystagon®

End point title	Comparison of Cysteamine PK profiles, Steady State Tmax, Between RP103 and Cystagon®
End point description:	
End point type	Secondary
End point timeframe:	4 weeks after the last subject has completed the study

End point values	RP103	Cystagon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	39		
Units: Tmax (minute)				
least squares mean (standard deviation)	187 (± 89)	72 (± 31)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cystagon® v RP103

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	105
Confidence interval	
level	95 %
sides	2-sided
lower limit	90
upper limit	150

## Secondary: Comparison of Cysteamine PK Profiles, AUC(0-t), Between RP103 and Cystagon®

End point title	Comparison of Cysteamine PK Profiles, AUC(0-t), Between RP103 and Cystagon®
End point description:	
End point type	Secondary
End point timeframe:	6 hours post dosing for Cystagon®; 12 hours post dosing for RP103.

End point values	RP103	Cystagon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	39		
Units: AUC(0-t) (min*mg/L)				
least squares mean (standard deviation)	739 (± 334)	357 (± 150)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cystagon® v RP103
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	2.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.75
upper limit	2.39

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment periods

Adverse event reporting additional description:

Safety population AE reporting.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.0
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### Reporting groups

Reporting group title	Cystagon®
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Reporting group description:

Safety population during treatment periods

Reporting group title	RP103
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Reporting group description:

Safety Population during treatment periods

Serious adverse events	Cystagon®	RP103	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 41 (2.44%)	6 / 43 (13.95%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femur Fracture			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Discomfort	Additional description: possibly related to study drug		
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Knee deformity			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypovolaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
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: 5 %

<b>Non-serious adverse events</b>	Cystagon®	RP103	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 41 (12.20%)	16 / 43 (37.21%)	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 41 (7.32%)	5 / 43 (11.63%)	
occurrences (all)	5	8	
Nausea			
subjects affected / exposed	2 / 41 (4.88%)	5 / 43 (11.63%)	
occurrences (all)	3	7	
Abdominal Pain			
subjects affected / exposed	0 / 41 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	4	
Metabolism and nutrition disorders			

Hypokalaemia			
subjects affected / exposed	0 / 41 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 February 2010	Per the CSR, the rationale for Amendment 1 (21 February 2010) was to revise aspects of the protocol design to incorporate input from the FDA. The most significant of these was to update and clarify study endpoints and analysis plans, update and finalize sample size estimate, and add collection of PK data to the study design. In addition, the study schedule and procedures were changed to reduce discomfort and impact to the subject and their family. Minor editorial changes were made to clarify statements and instructions and correct typographical and formatting errors in the protocol.
03 May 2010	Per the CSR, as was the case for Amendment 1, Amendment 2 (03 May 2010) was intended to incorporate input from the FDA. The most significant revisions included the addition of a Run-in Period and randomized parallel crossover which allowed for Cystagon® dose adjustment. Inclusion and exclusion criteria were modified to establish entry criteria for subjects with low WBC cystine levels, specify subject age and weight restrictions, and provide specific parameters for clinically significant changes in liver and renal function. Study objectives, endpoints, and analysis plans were updated. Minor editorial changes were made to clarify statements and instructions and correct typographical and formatting errors in the protocol.
22 July 2010	Per the CSR, Amendment 3 (22 July 2010) was intended to incorporate input from the FDA. The most significant revisions included restricting study participation to those subjects with a 3-day average WBC cystine level $\leq 2$ nmol $\frac{1}{2}$ cystine/mg protein during Week 2 of the Run-in Period; adjustment of RP103 PD sampling timepoints to ensure appropriate collection; including stratification of subjects according to baseline WBC cystine levels; eliminating one week from the Run-in Period; and setting the minimum sample size to 30 subjects. Inclusion criteria were modified to include subjects with WBC cystine levels $\leq 2$ nmol $\frac{1}{2}$ cystine/mg protein. Minor editorial changes were made to clarify statements and instructions and correct typographical and formatting errors in the protocol.
22 October 2010	Per the CSR, Amendment 4 (22 October 2010) was intended primarily to change the starting total daily dose of RP103 from 70% to 80% at the end of the Run-in Period Cystagon® total daily dose and allow a maximum RP103 dose increase to 100% at the end of the Run-in Period Cystagon® total daily dose, with additional information on the background and rationale for the change in RP103 starting dose. Minor editorial changes were made to clarify statements and instructions and correct typographical and formatting errors in the protocol.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported