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

Summary

EudraCT number	2012-002773-64
Trial protocol	GB BE NL IT FR
Global end of trial date	10 July 2017

Results information

Result version number	v1 (current)
This version publication date	26 January 2018
First version publication date	26 January 2018

Trial information

Trial identification

Sponsor protocol code	RP103-07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01733316
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	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	10 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective:
To demonstrate superiority of RP103 versus Cystagon® in controlling white blood cell cystine (WBC) levels over 24 hours in patients with cystinosis and to assess long-term safety and tolerability of RP103

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). 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	31 January 2013
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: 5
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	41
EEA total number of subjects	25

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	2
Adolescents (12-17 years)	14
Adults (18-64 years)	25
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A Screening Visit occurred up to 7 days prior to Day 1. Subjects were to continue with Cystagon® treatment.

Period 1

Period 1 title	Cystagon® Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All Subjects: Cystagon® Phase

Arm description:

From Screening and during Months 1, 2, 3: subjects received their usual dose of Cystagon® Q6H.

Arm type	Experimental
Investigational medicinal product name	Cystagon® Q6H
Investigational medicinal product code	
Other name	cysteamine bitartrate
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

From Screening and during Months 1, 2, 3: subjects receive their usual dose of Cystagon® every 6 hours (Q6H).

Number of subjects in period 1	All Subjects: Cystagon® Phase
Started	41
Completed	41

Period 2

Period 2 title	RP103 Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All Subjects: RP103 Phase

Arm description:

During Months 3.5, 4, 5, 6, 7: subjects received RP103 Q12H.

Arm type	Experimental
Investigational medicinal product name	RP103 Q12H
Investigational medicinal product code	RP103
Other name	cysteamine bitartrate delayed-release capsules; PROCYSBI®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

From Months 3.5, 4, 5, 6, 7 and the remainder of study participation: RP103 every 12 hours (Q12H) started at a total daily dose of 70% of subjects' Cystagon® dose.

Number of subjects in period 2	All Subjects: RP103 Phase
Started	41
Completed	40
Not completed	1
Non-compliance	1

Period 3

Period 3 title	Long Term Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All Subjects: Long Term Phase

Arm description:

On or after Month 7, for the remainder of study: subjects received RP103 Q12H.

Arm type	Experimental
Investigational medicinal product name	RP103 Q12H
Investigational medicinal product code	RP103
Other name	cysteamine bitartrate delayed-release capsules; PROCYSBI®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

From Months 3.5, 4, 5, 6, 7 and the remainder of study participation: RP103 every 12 hours (Q12H) started at a total daily dose of 70% of subjects' Cystagon® dose.

Number of subjects in period 3[1]	All Subjects: Long Term Phase
Started	38
Completed	33
Not completed	5
Consent withdrawn by subject	2
Adverse event	1
Sponsor decision	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Two subjects did not enter the long term follow up period.

Baseline characteristics

Reporting groups	
Reporting group title	Cystagon® Phase

Reporting group description: -

Reporting group values	Cystagon® Phase	Total	
Number of subjects	41	41	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 24.5 ± 11.56	 -	
Gender categorical Units: Subjects			
Female	21	21	
Male	20	20	

End points

End points reporting groups

Reporting group title	All Subjects: Cystagon® Phase
Reporting group description:	
From Screening and during Months 1, 2, 3: subjects received their usual dose of Cystagon® Q6H.	
Reporting group title	All Subjects: RP103 Phase
Reporting group description:	
During Months 3.5, 4, 5, 6, 7: subjects received RP103 Q12H.	
Reporting group title	All Subjects: Long Term Phase
Reporting group description:	
On or after Month 7, for the remainder of study: subjects received RP103 Q12H.	
Subject analysis set title	Pharmacokinetic Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects who report halitosis (“bad breath”) as a side effect while receiving Cystagon®.	

Primary: Average Difference Between Morning and Non-Morning Log WBC Cystine Values

End point title	Average Difference Between Morning and Non-Morning Log WBC Cystine Values

End point description:

The primary analysis of WBC cystine was performed using the natural log transformed WBC cystine level; the log transformation is a normalizing transformation. For each subject, the difference between the morning and corresponding non-morning log WBC cystine value (non-morning minus morning) at each monthly visit during the Cystagon® phase (Months 1, 2, and 3) was computed and these differences were averaged. The average difference between morning and non-morning log WBC cystine value was similarly computed for each subject during the RP103 phase (Months 5, 6, and 7). The primary analysis compared within-subject pairs (Cystagon® phase paired with RP103 phase) of non-morning minus morning average differences of log WBC cystine level.

Pharmacodynamic (PD) Analysis Set: All subjects who received at least one treatment of Cystagon® and RP103 and who had at least one WBC cystine level recorded after each of Cystagon® treatment and RP103 treatment.

End point type	Primary

End point timeframe:

While taking Cystagon® (Months 1, 2, 3): within 15 minutes pre-AM and pre-non AM dose. During 3 months of RP103 (Months 5, 6, 7): 30 minutes post-AM and post-PM dose.

End point values	All Subjects: Cystagon® Phase	All Subjects: RP103 Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[1]	40[2]		
Units: log [nmol ½ cystine/mg protein]				
arithmetic mean (standard deviation)	-0.229 (± 0.5027)	0.080 (± 0.3939)		

Notes:

[1] - Only subjects with an average difference during both the Cystagon and RP103 phases were included.

[2] - Only subjects with an average difference during both the Cystagon and RP103 phases were included.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Note: Number of subjects in this analysis is 40, not 80. The EudraCT system's limitations double-counted these subjects erroneously.

Comparison groups	All Subjects: RP103 Phase v All Subjects: Cystagon® Phase
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0048 [3]
Method	t-test, 2-sided

Notes:

[3] - Paired t-test testing the null hypothesis that the population average difference during the Cystagon phase is equal to the population average difference during the RP103 phase.

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs), Serious Adverse Events (SAEs), and Discontinuations Due to AEs

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs), Serious Adverse Events (SAEs), and Discontinuations Due to AEs

End point description:

AE: any untoward medical occurrence that does not necessarily have a causal relationship with study drug. SAE: any untoward medical occurrence that at any dose: results in death; is life threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; or is medically significant, and though not included in the above list, is an important medical event, according to the Investigator. Treatment-emergent adverse events (TEAEs) occurred after first dose of study drug. Observations from Day 1 Cystagon® dosing up to the first dose of RP103 were attributed to the Cystagon® Phase; those on or after the first dose of RP103 up to Month 7 or study termination visit (which ever occurred first) were attributed to the RP103 Phase. All observations on or after the Month 7 visit through study termination were attributed to the Long-Term RP103 Phase.

End point type	Secondary

End point timeframe:

From first dose of study drug to 7 days after last dose. Median duration of exposure was 91 days (range 82-108) for Cystagon® phase, 119 days (range 98-137) for the RP103 phase, and 861 days (range 30 - 1350) during the long-term RP-103 phase.

End point values	All Subjects: Cystagon® Phase	All Subjects: RP103 Phase	All Subjects: Long Term Phase	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	41	38	
Units: subjects				
At least 1 TEAE	31	38	32	
At least 1 TEAE-related to study drug	4	20	18	
At least 1 grade ≥ 3 TEAE	5	4	13	
At least 1 serious TEAE	5	6	13	
At least 1 TEAE leading to discontinuation	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Halitosis Substudy: Maximum Plasma Concentration (Cmax) for Plasma Cysteamine

End point title	Halitosis Substudy: Maximum Plasma Concentration (Cmax) for Plasma Cysteamine

End point description:

Subjects who reported halitosis ("bad breath") as a side effect while receiving Cystagon® were asked to participate in a substudy to investigate the concentration of dimethylsulfide (DMS) in expired air after the administration of study medication. To assess halitosis during study medication treatment, the steady state pharmacokinetic (PK) samples of cysteamine and DMS were collected over a 6 hour period when Cystagon® was administered and over a 12 hour period when RP103 was administered.

PK Analysis Set: All participants who received at least one dose of RP103 and had available PK data.

End point type	Secondary

End point timeframe:

While taking Cystagon® (Month 1, 2 or 3): Within 15 minutes prior to morning dose, 30 minutes post-dose, 1, 2, 4 and 6 hours post-dose. While taking RP103 (Month 5, 6, or 7): 30 minutes after morning dose and 1, 2, 3, 4, 6, 8, 10, 12 hours post-dose

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	20[4]			
Units: mg/L				
arithmetic mean (standard deviation)				
Cystagon® dosing period; n=19	3.5 (± 1.87)			
RP103 dosing period; n=20	2.9 (± 1.65)			

Notes:

[4] - n=Halitosis substudy subjects with data at given timepoint

Statistical analyses

No statistical analyses for this end point

Secondary: Halitosis Substudy: Time to Cmax (Tmax) for Plasma Cysteamine

End point title	Halitosis Substudy: Time to Cmax (Tmax) for Plasma Cysteamine

End point description:

Subjects who reported halitosis ("bad breath") as a side effect while receiving Cystagon® were asked to participate in a substudy to investigate the concentration of DMS in expired air after the administration of study medication. To assess halitosis during study medication treatment, the steady state PK samples of cysteamine and DMS were collected over a 6 hour period when Cystagon® was administered and over a 12 hour period when RP103 was administered.

PK Analysis Set: All participants who received at least one dose of RP103 and had available PK data.

End point type	Secondary

End point timeframe:

While taking Cystagon® (Month 1, 2 or 3): Within 15 minutes prior to morning dose, 30 minutes post-dose, 1, 2, 4 and 6 hours post-dose. While taking RP103 (Month 5, 6, or 7): 30 minutes after morning dose and 1, 2, 3, 4, 6, 8, 10, 12 hours post-dose

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	20[5]			
Units: hour				
arithmetic mean (standard deviation)				
Cystagon® dosing period; n=19	1.2 (± 0.87)			
RP103 dosing period; n=20	3.2 (± 1.30)			

Notes:

[5] - n=Halitosis substudy subjects with data at given timepoint

Statistical analyses

No statistical analyses for this end point

Secondary: Halitosis Substudy: Area Under the Plasma Concentration Time Curve From Time Point 0 Through the Last Measurable Point (AUC0-t) for Plasma Cysteamine

End point title	Halitosis Substudy: Area Under the Plasma Concentration Time Curve From Time Point 0 Through the Last Measurable Point (AUC0-t) for Plasma Cysteamine

End point description:

Subjects who reported halitosis (“bad breath”) as a side effect while receiving Cystagon® were asked to participate in a substudy to investigate the concentration of DMS in expired air after the administration of study medication. To assess halitosis during study medication treatment, the steady state PK samples of cysteamine and DMS were collected over a 6 hour period when Cystagon® was administered and over a 12 hour period when RP103 was administered.

PK Analysis Set: All participants who received at least one dose of RP103 and had available PK data.

End point type	Secondary

End point timeframe:

While taking Cystagon® (Month 1, 2 or 3): Within 15 minutes prior to morning dose, 30 minutes post-dose, 1, 2, 4 and 6 hours post-dose. While taking RP103 (Month 5, 6, or 7): 30 minutes after morning dose and 1, 2, 3, 4, 6, 8, 10, 12 hours post-dose

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	20[6]			
Units: hr*mg/L				
arithmetic mean (standard deviation)				
Cystagon® dosing period; n=19	7.8 (± 5.18)			
RP103 dosing period; n=20	9.4 (± 4.86)			

Notes:

[6] - n=Halitosis substudy subjects with data at given timepoint

Statistical analyses

No statistical analyses for this end point

Secondary: Halitosis Substudy: Expired Air DMS Concentrations

End point title	Halitosis Substudy: Expired Air DMS Concentrations

End point description:

Subjects who reported halitosis ("bad breath") as a side effect while receiving Cystagon® were asked to participate in a substudy to investigate the concentration of DMS in expired air after the administration of study medication. To assess halitosis during study medication treatment, the steady state PK samples of cysteamine and DMS will
be collected over a 6 hour period when Cystagon® is administered and over a 12 hour period when RP103 is administered. Data will be summarized in final analysis.

PK Analysis Set: All participants who received at least one dose of RP103 and had available PK data.

End point type	Secondary

End point timeframe:

Visit 1: up to 6 hours hours post-dose; Visit 2: 12 hours post-morning dose

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	20[7]			
Units: nmol/L				
arithmetic mean (standard deviation)				
Cystagon®, within 15 minutes prior to dose; n=18	4.7 (± 5.54)			
Cystagon®, 30 minutes post dose; n=18	4.7 (± 4.75)			
Cystagon®, 1 hour post morning dose; n=18	6.9 (± 6.75)			
Cystagon®, 2 hours post morning dose; n=18	11.9 (± 11.26)			
Cystagon®, 3 hours post morning dose; n=18	11.2 (± 13.32)			
Cystagon®, 4 hours post morning dose; n=18	8.8 (± 12.05)			
Cystagon®, 6 hours post morning dose; n=18	4.4 (± 3.77)			
RP103, within 15 minutes prior to dose; n=20	4.6 (± 6.05)			
RP103, 1 hour post morning dose; n=20	5.4 (± 7.71)			
RP103, 2 hours post morning dose; n=20	5.1 (± 6.28)			
RP103, 3 hours post morning dose; n=20	7.7 (± 8.53)			
RP103, 4 hours post morning dose; n=20	8.6 (± 11.22)			
RP103, 5 hours post morning dose; n=20	11.2 (± 15.86)			
RP103, 6 hours post morning dose; n=20	8.5 (± 13.87)			
RP103, 8 hours post morning dose; n=20	5.7 (± 10.76)			
RP103, 10 hours post morning dose; n=20	5.2 (± 8.13)			
RP103, 12 hours post morning dose; n=20	4.3 (± 5.32)			

Notes:
[7] - n=Halitosis substudy subjects with a value at given time point

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 exposure was 91 days (range 82-108) for Cystagon® phase, 119 days (range 98-137) for the RP103 phase, and 861 days (range 30 - 1350) during the long term RP-103 phase.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	All Subjects: Cystagon® Phase

Reporting group description:

From Screening and during Months 1, 2, 3: subjects received their usual dose of Cystagon® Q6H.

Reporting group title	All Subjects: RP103 Phase

Reporting group description:

During Months 3.5, 4, 5, 6, 7: subjects received RP103 Q12H.

Reporting group title	All Subjects: Long Term Phase

Reporting group description:

On or after Month 7, for the remainder of study: subjects received RP103 Q12H.

Serious adverse events	All Subjects: Cystagon® Phase	All Subjects: RP103 Phase	All Subjects: Long Term Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 41 (12.20%)	6 / 41 (14.63%)	13 / 38 (34.21%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			

subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Arteriovenous fistula operation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ossiculoplasty			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal transplant			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	2 / 38 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Fatigue			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	2 / 38 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arteriovenous fistula aneurysm			

subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula site complication			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	2 / 38 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural hypotension			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			

subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine with aura			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	2 / 38 (5.26%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	2 / 38 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Renal failure acute			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	2 / 38 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis norovirus			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Graft infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Onychomycosis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 41 (2.44%)	1 / 41 (2.44%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	4 / 38 (10.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	All Subjects: Cystagon® Phase	All Subjects: RP103 Phase	All Subjects: Long Term Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 41 (68.29%)	33 / 41 (80.49%)	32 / 38 (84.21%)
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	4 / 38 (10.53%)
occurrences (all)	0	0	4
Malaise			
subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	1 / 38 (2.63%)
occurrences (all)	3	2	1
Pyrexia			
subjects affected / exposed	2 / 41 (4.88%)	2 / 41 (4.88%)	2 / 38 (5.26%)
occurrences (all)	2	3	2
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	2 / 38 (5.26%)
occurrences (all)	0	1	2
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 41 (4.88%)	1 / 41 (2.44%)	3 / 38 (7.89%)
occurrences (all)	3	1	3
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	2 / 38 (5.26%)
occurrences (all)	0	1	3
Hepatic enzyme increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	2
Weight decreased			
subjects affected / exposed	1 / 41 (2.44%)	1 / 41 (2.44%)	3 / 38 (7.89%)
occurrences (all)	1	1	4
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 41 (19.51%)	6 / 41 (14.63%)	7 / 38 (18.42%)
occurrences (all)	8	9	15
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	4 / 38 (10.53%)
occurrences (all)	0	1	4
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	3 / 38 (7.89%)
occurrences (all)	0	2	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 41 (2.44%)	3 / 41 (7.32%)	5 / 38 (13.16%)
occurrences (all)	1	3	10
Abdominal pain upper			
subjects affected / exposed	2 / 41 (4.88%)	6 / 41 (14.63%)	3 / 38 (7.89%)
occurrences (all)	2	6	4
Constipation			
subjects affected / exposed	0 / 41 (0.00%)	2 / 41 (4.88%)	3 / 38 (7.89%)
occurrences (all)	0	2	3
Diarrhoea			

subjects affected / exposed	4 / 41 (9.76%)	9 / 41 (21.95%)	7 / 38 (18.42%)
occurrences (all)	4	10	10
Nausea			
subjects affected / exposed	4 / 41 (9.76%)	15 / 41 (36.59%)	5 / 38 (13.16%)
occurrences (all)	5	22	7
Vomiting			
subjects affected / exposed	2 / 41 (4.88%)	11 / 41 (26.83%)	7 / 38 (18.42%)
occurrences (all)	2	15	10
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	3
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	2 / 38 (5.26%)
occurrences (all)	0	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	2
Knee deformity			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	4
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	2 / 38 (5.26%)
occurrences (all)	0	1	2
Candidiasis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	2 / 38 (5.26%)
occurrences (all)	0	1	2
Ear infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	3 / 38 (7.89%)
occurrences (all)	0	0	4
Gastroenteritis			
subjects affected / exposed	1 / 41 (2.44%)	4 / 41 (9.76%)	4 / 38 (10.53%)
occurrences (all)	1	4	4

Influenza			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	4 / 38 (10.53%)
occurrences (all)	0	0	6
Nasopharyngitis			
subjects affected / exposed	8 / 41 (19.51%)	5 / 41 (12.20%)	6 / 38 (15.79%)
occurrences (all)	8	5	8
Respiratory tract infection			
subjects affected / exposed	1 / 41 (2.44%)	2 / 41 (4.88%)	2 / 38 (5.26%)
occurrences (all)	1	2	2
Upper respiratory tract infection			
subjects affected / exposed	3 / 41 (7.32%)	0 / 41 (0.00%)	6 / 38 (15.79%)
occurrences (all)	4	0	9
Urinary tract infection			
subjects affected / exposed	2 / 41 (4.88%)	3 / 41 (7.32%)	4 / 38 (10.53%)
occurrences (all)	2	4	5
Viral infection			
subjects affected / exposed	1 / 41 (2.44%)	2 / 41 (4.88%)	2 / 38 (5.26%)
occurrences (all)	1	2	6
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	2 / 38 (5.26%)
occurrences (all)	1	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2016	Drug product storage condition was revised as follows: - From: Should be stored at controlled room temperature (maintained at 20-25°C, mean temperature not more than 25°C, with excursions permitted from 15 to 30°C) - To: Before opening, the bottle should be stored in a refrigerator (at 2°C - 8°C / 36°F 46°F), and after opening, the bottle should not be stored above 25°C (77°F)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported