Clinical trial results:
A Randomized, Double blind, Active Control Study of the Safety and Efficacy of PRX-102 compared to Agalsidase Beta on Renal Function in Patients with Fabry Disease Previously Treated With Agalsidase Beta

Summary

EudraCT number	2016-000378-38
Trial protocol	GB HU ES CZ NO BE NL SI IT FI FR
Global end of trial date	12 October 2021

Results information

Result version number	v2 (current)
This version publication date	09 June 2023
First version publication date	16 March 2023
Version creation reason	• Correction of full data set No additional results have been added, the results for mean Lyso Gb3 and mean eGFR were removed, keeping median Lyso Gb3 and median eGFR

Trial information

Trial identification

Sponsor protocol code	PB-102-F20

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02795676
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Protalix Ltd.
Sponsor organisation address	2 Snunit Street, Carmiel, Israel, 2161401
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Scientific contact	Sari Alon, Protalix Ltd., +972 4-902-8100, sari@protalix.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 October 2021
Global end of trial reached?	Yes
Global end of trial date	12 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, efficacy, and pharmacokinetics (PK) of PRX-102 (pegunigalsidase alfa) compared to agalsidase beta in adult Fabry disease patients with impaired renal function

Protection of trial subjects:

The first infusions of agalsidase beta or PRX-102 were performed under controlled conditions at the investigation site.
Patients were allowed to receive subsequent infusions at home if the Investigator and the sponsor's Medical Monitor agreed that it was safe to do so, based on the patient's clinical condition and on local practices and regulations.
The administration of Agalsidase beta or PRX-102 was intravenously over 3 hours, every 2 weeks. After the first 3 months, infusion time was reduced gradually to 1.5 hours pending patient tolerability, per Principal Investigator (PI) evaluation, and Medical Monitor approval.
All patients and study staff were blind to the treatment given throughout the whole study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 August 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Regulatory reason
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 52
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 3

Worldwide total number of subjects	78
EEA total number of subjects	21

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	78
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Symptomatic adult Fabry patients who had been taking agalsidase beta for at least 1 year and on a stable dose for at least 6 months. No more than 50% could be female. Screening eGFR (CKD-EPI) 40 to 120 mL/min/1.73 m^2; Screening linear eGFR slope more negative than -2 mL/min/1.73 m^2/year based on at least 3 values over ~1 year.

Pre-assignment

Screening details:

Of the 78 randomized patients, 53 were assigned to the PRX-102 arm and 25 to the agalsidase beta arm. One PRX-102 patient withdrew consent before receiving the study product; accordingly, 77 patients were treated, 52 in PRX-102 arm and 25 in agalsidase beta arm.

Pre-assignment period milestones

Number of subjects started	78
Number of subjects completed	77

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

The infusions were prepared by an unblinded pharmacist or nurse at the site or at a central pharmacy (for home care), resulting in identical infusion bag appearance and blinded labelling prior to administration. Both the patients and the staff members administering the treatments were blinded as to what the infusion bag contained.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pegunigalsidase alfa ITT set

Arm description:

Pegunigalsidase alfa administered as an intravenous infusion every 2 weeks, at a dosage of 1 mg/kg

Arm type	Experimental
Investigational medicinal product name	Pegunigalsidase alfa
Investigational medicinal product code	
Other name	PRX-102
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 mg/kg administered as an intravenous infusion every 2 weeks for up to 24 months

Arm title	Agalsidase beta ITT set

Arm description:

Agalsidase beta administered as an intravenous infusion every 2 weeks, at a dosage of 1 mg/kg

Arm type	Active comparator

Investigational medicinal product name	agalsidase beta
Investigational medicinal product code	
Other name	Fabrazyme
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 mg/kg administered as an intravenous infusion every 2 weeks for up to 24 months

Number of subjects in period 1[1]	Pegunigalsidase alfa ITT set	Agalsidase beta ITT set
Started	52	25
Completed	48	24
Not completed	4	1
Consent withdrawn by subject	2	1
Adverse event, non-fatal	2	-

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: The number of subjects reported in the baseline period (77) are not the same as the worldwide number enrolled (78), since one enrolled patient withdrew consent before receiving study drug, and therefore is not counted in the baseline period

Baseline characteristics

Reporting groups	
Reporting group title	Pegunigalsidase alfa ITT set
Reporting group description:	
Pegunigalsidase alfa administered as an intravenous infusion every 2 weeks, at a dosage of 1 mg/kg	
Reporting group title	Agalsidase beta ITT set
Reporting group description:	
Agalsidase beta administered as an intravenous infusion every 2 weeks, at a dosage of 1 mg/kg	

Reporting group values	Pegunigalsidase alfa ITT set	Agalsidase beta ITT set	Total
Number of subjects	52	25	77
Age categorical Units: Subjects			
Adults (18-64 years)	52	25	77
Age continuous Units: years			
arithmetic mean	43.9	45.2	
standard deviation	± 10.2	± 9.6	-
Gender categorical Units: Subjects			
Female	23	7	30
Male	29	18	47

End points

End points reporting groups

Reporting group title	Pegunigalsidase alfa ITT set
Reporting group description:	
Pegunigalsidase alfa administered as an intravenous infusion every 2 weeks, at a dosage of 1 mg/kg	
Reporting group title	Agalsidase beta ITT set
Reporting group description:	
Agalsidase beta administered as an intravenous infusion every 2 weeks, at a dosage of 1 mg/kg	

Primary: Annualized change (slope) in estimated glomerular filtration rate (eGFR)

End point title	Annualized change (slope) in estimated glomerular filtration rate (eGFR)
End point description:	
The individual annualized mean change (slope) in eGFR (mL/min/1.73 m^2/year) is an estimate of the individual patient's annualized change in eGFR, which is derived from the eGFR (by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI formula, 2009] assessments over time, for up to 24 months.	
End point type	Primary
End point timeframe:	
24 Months	

End point values	Pegunigalsidase alfa ITT set	Agalsidase beta ITT set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	25		
Units: mL/min/1.73 m^2/year				
median (confidence interval 95%)	-2.514 (-3.788 to -1.240)	-2.155 (-3.805 to -0.505)		

Statistical analyses

Statistical analysis title	eGFR slope comparison
Statistical analysis description:	
The primary efficacy analysis compared eGFR slope between the treatment arms using a 2-stage model with quantile regression. At the 1st stage, the individual annualized change (slope) in eGFR was estimated for each patient using a linear regression model. At the 2nd stage, the annualized change (slope) of the eGFR between the two treatment arms were compared using quantile regression estimating the median slopes.	
Comparison groups	Pegunigalsidase alfa ITT set v Agalsidase beta ITT set

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Median difference (final values)
Point estimate	-0.359
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.444
upper limit	1.726

Notes:

[1] - The dependent variable was the slope of each individual patient and the model included intercept and treatment arm.
Non-inferiority was to be declared if the lower bound of the confidence interval for the treatment difference (PRX-102 minus agalsidase beta) was greater or equal to -3.0 mL/min/1.73 m^2/year.

Secondary: Estimated Glomerular Filtration rate (eGFR)

End point title	Estimated Glomerular Filtration rate (eGFR)
End point description:	
eGFR was calculated based on measured serum creatinine levels according to the CKD-EPI formula.	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Pegunigalsidase alfa ITT set	Agalsidase beta ITT set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	25		
Units: mL/min/1.73 m^2				
median (full range (min-max))				
Baseline	73.45 (30.2 to 125.9)	74.85 (34.1 to 107.6)		
Month 24	69.35 (27.6 to 113.7)	74.48 (24.4 to 114.8)		
Change from Baseline to Month 24	-2.39 (-36.9 to 21.8)	-3.20 (-18.0 to 16.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma lyso-Gb3

End point title	Plasma lyso-Gb3
End point description:	
Globotriaosylsphingosine (Lyso-Gb3) is Fabry disease specific biomarker measured in the plasma (nanomole/liter, nM).	
End point type	Secondary
End point timeframe:	
24 Months	

End point values	Pegunigalsidase alfa ITT set	Agalsidase beta ITT set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	25		
Units: nM				
median (full range (min-max))				
Baseline	15.20 (0.8 to 143.9)	17.60 (2.1 to 142.0)		
Month 24	18.80 (2.4 to 139.4)	15.30 (1.5 to 71.2)		
Change from Baseline to Month 24	1.15 (-32.2 to 32.7)	-1.50 (-102.3 to 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Short Form Brief Pain Inventory (BPI)

End point title	Short Form Brief Pain Inventory (BPI)

End point description:

The Short Form Brief Pain Inventory (BPI) questioner is self-completed by patients regarding pain severity and interference.
Descriptive statistics summarizes the findings for the change from baseline at Week 104 for "Pain at Its Worst in Last 24 Hours" .
The severity of various aspects of pain scored on a scale of 0 to 10 (no pain / pain as bad as you can imagine).

End point type	Secondary

End point timeframe:

24 Month

End point values	Pegunigalsidase alfa ITT set	Agalsidase beta ITT set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	25		
Units: score				
arithmetic mean (standard error)				
Baseline	3.5 (± 0.4)	2.6 (± 0.6)		
Month 24	3.3 (± 0.5)	3.0 (± 0.7)		
Change from Baseline to Month 24	-0.1 (± 0.5)	0.6 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mainz Severity Score Index (MSSI)

End point title	Mainz Severity Score Index (MSSI)

End point description:

The Mainz Severity Score Index (MSSI), is an instrument that is specifically designed to measure the severity of Fabry disease signs/symptoms and to monitor the clinical course of the disease. MSSI is administered by the investigator, yields scores for general, neurological, cardiovascular, renal, and overall assessments.
An overall score of less than 20 points is considered mild, 20 to 40 is considered moderate, and greater than 40 is considered severe signs and symptoms of Fabry disease.

End point type	Secondary

End point timeframe:

24 Month

End point values	Pegunigalsidase alfa ITT set	Agalsidase beta ITT set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	25		
Units: score				
arithmetic mean (standard error)				
Baseline	23.18 (± 1.42)	25.16 (± 2.14)		
Month 24	22.11 (± 1.80)	27.09 (± 2.30)		
Change from Baseline to Month 24	-2.07 (± 0.77)	2.04 (± 1.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Urine Protein/Creatinine Ratio (UPCR)

End point title	Urine Protein/Creatinine Ratio (UPCR)

End point description:

The UPCR provides an estimate of protein excretion in urine, is used as an indicator of the extent of chronic kidney disease, and was classified into three categories:
1) UPCR ≤ 0.5 gr/gr, 2) 0.5gr/gr < UPCR < 1gr/gr, 3) 1gr/gr ≤ UPCR. Presented as the percent of patients (%) in each category at baseline and Month 24.

End point type	Secondary

End point timeframe:

24 months

End point values	Pegunigalsidase alfa ITT set	Agalsidase beta ITT set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	25		
Units: percent of patients (%)				
Baseline: UPCR ≤ 0.5 gr/gr	69	80		
Month 24: UPCR ≤ 0.5 gr/gr	76	75		
Baseline: 0.5 < UPCR < 1 gr/gr	17	8		
Month 24: 0.5 < UPCR < 1 gr/gr	11	8		
Baseline: UPCR ≥ 1 gr/gr	14	12		
Month 24: UPCR ≥ 1 gr/gr	13	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Left Ventricular Mass Index (LVMI) with hypertrophy at baseline

End point title	Left Ventricular Mass Index (LVMI) with hypertrophy at baseline

End point description:

Left Ventricular Mass Index (LVMI) based on cardiac MRI for patients with hypertrophy at baseline (for males hypertrophy is above 91 g/m^2 and for females above 77 g/m^2).

End point type	Secondary

End point timeframe:

24 Months

End point values	Pegunigalsidase alfa ITT set	Agalsidase beta ITT set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: g/m^2				
median (full range (min-max))				
Baseline	108.005 (81.77 to 168.42)	103.030 (78.91 to 147.33)		
Month 24	118.130 (87.78 to 150.67)	121.380 (63.78 to 187.23)		
Change from Baseline to Month 24	-4.790 (-24.42 to 21.55)	4.120 (-28.41 to 41.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Left Ventricular Mass Index (LVMI) without hypertrophy at baseline

End point title	Left Ventricular Mass Index (LVMI) without hypertrophy at baseline

End point description:

Left Ventricular Mass Index (LVMI) based on cardiac MRI for patients without hypertrophy at baseline (for males hypertrophy is above 91 g/m^2 and for females above 77 g/m^2).

End point type	Secondary

End point timeframe:

24 Months

End point values	Pegunigalsidase alfa ITT set	Agalsidase beta ITT set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	13		
Units: g/m^2				
median (full range (min-max))				
Baseline	55.555 (33.81 to 89.24)	66.040 (35.74 to 86.92)		
Month 24	52.160 (35.80 to 100.01)	62.520 (35.38 to 88.48)		
Change from Baseline to Month 24	1.990 (-29.37 to 18.37)	0.515 (-13.69 to 11.15)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected at every visit.

Adverse event reporting additional description:

A treatment-emergent adverse event (TEAE) is defined as any AE occurring after the start of the first infusion.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Patients in the pegunigalsidase alfa arm

Reporting group description:

Events occurring from the start of the study treatment to the final dose were defined as treatment-emergent adverse events (TEAEs)

Reporting group title	Patients in the agalsidase beta arm

Reporting group description:

Events occurring from the start of the study treatment to the final dose were defined as treatment-emergent adverse events (TEAEs)

Serious adverse events	Patients in the pegunigalsidase alfa arm	Patients in the agalsidase beta arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 52 (15.38%)	6 / 25 (24.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Medical device battery replacement			

subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrectomy			
subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Hypothermia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 52 (0.00%)	2 / 25 (8.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 52 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 52 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			

subjects affected / exposed	0 / 52 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 52 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 52 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Protein-losing gastroenteropathy			
subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 52 (1.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Patients in the pegunigalsidase alfa arm	Patients in the agalsidase beta arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 52 (90.38%)	24 / 25 (96.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 52 (5.77%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Hypotension			
subjects affected / exposed	0 / 52 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 52 (17.31%)	4 / 25 (16.00%)	
occurrences (all)	10	6	
Pyrexia			
subjects affected / exposed	5 / 52 (9.62%)	3 / 25 (12.00%)	
occurrences (all)	5	4	
Oedema peripheral			
subjects affected / exposed	4 / 52 (7.69%)	3 / 25 (12.00%)	
occurrences (all)	9	3	
Infusion site extravasation			
subjects affected / exposed	3 / 52 (5.77%)	0 / 25 (0.00%)	
occurrences (all)	4	0	
Pain			
subjects affected / exposed	2 / 52 (3.85%)	3 / 25 (12.00%)	
occurrences (all)	3	5	
Chest pain			
subjects affected / exposed	1 / 52 (1.92%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
Influenza like illness			
subjects affected / exposed	1 / 52 (1.92%)	3 / 25 (12.00%)	
occurrences (all)	1	4	
Malaise			
subjects affected / exposed	1 / 52 (1.92%)	2 / 25 (8.00%)	
occurrences (all)	1	3	

Chest discomfort			
subjects affected / exposed	0 / 52 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	3	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	4 / 52 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	5	2	
Hypersensitivity			
subjects affected / exposed	2 / 52 (3.85%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 52 (11.54%)	5 / 25 (20.00%)	
occurrences (all)	7	7	
Upper respiratory tract congestion			
subjects affected / exposed	4 / 52 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	6	0	
Nasal congestion			
subjects affected / exposed	3 / 52 (5.77%)	1 / 25 (4.00%)	
occurrences (all)	3	1	
Oropharyngeal pain			
subjects affected / exposed	3 / 52 (5.77%)	3 / 25 (12.00%)	
occurrences (all)	4	3	
Rhinorrhoea			
subjects affected / exposed	1 / 52 (1.92%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 52 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Investigations			
Urine protein/creatinine ratio increased			
subjects affected / exposed	3 / 52 (5.77%)	0 / 25 (0.00%)	
occurrences (all)	5	0	
Blood creatine increased			

subjects affected / exposed	2 / 52 (3.85%)	4 / 25 (16.00%)	
occurrences (all)	5	5	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 52 (1.92%)	2 / 25 (8.00%)	
occurrences (all)	1	3	
Fall			
subjects affected / exposed	1 / 52 (1.92%)	3 / 25 (12.00%)	
occurrences (all)	1	4	
Thermal burn			
subjects affected / exposed	1 / 52 (1.92%)	2 / 25 (8.00%)	
occurrences (all)	1	4	
Wound			
subjects affected / exposed	0 / 52 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 52 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	5	3	
Palpitations			
subjects affected / exposed	3 / 52 (5.77%)	2 / 25 (8.00%)	
occurrences (all)	4	2	
Cardiomyopathy			
subjects affected / exposed	0 / 52 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 52 (21.15%)	5 / 25 (20.00%)	
occurrences (all)	19	9	
Dizziness			
subjects affected / exposed	6 / 52 (11.54%)	2 / 25 (8.00%)	
occurrences (all)	8	2	
Neuralgia			
subjects affected / exposed	4 / 52 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	5	0	
Neuropathy peripheral			

subjects affected / exposed	3 / 52 (5.77%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Sciatica			
subjects affected / exposed	3 / 52 (5.77%)	0 / 25 (0.00%)	
occurrences (all)	5	0	
Paraesthesia			
subjects affected / exposed	2 / 52 (3.85%)	4 / 25 (16.00%)	
occurrences (all)	2	8	
Cerebral infarction			
subjects affected / exposed	0 / 52 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Migraine			
subjects affected / exposed	0 / 52 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 52 (7.69%)	2 / 25 (8.00%)	
occurrences (all)	4	2	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 52 (5.77%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 52 (19.23%)	6 / 25 (24.00%)	
occurrences (all)	15	10	
Nausea			
subjects affected / exposed	9 / 52 (17.31%)	3 / 25 (12.00%)	
occurrences (all)	10	3	
Abdominal pain			
subjects affected / exposed	6 / 52 (11.54%)	0 / 25 (0.00%)	
occurrences (all)	6	0	
Vomiting			
subjects affected / exposed	6 / 52 (11.54%)	3 / 25 (12.00%)	
occurrences (all)	8	8	
Gastrooesophageal reflux disease			

subjects affected / exposed	3 / 52 (5.77%)	1 / 25 (4.00%)	
occurrences (all)	3	1	
Abdominal pain upper			
subjects affected / exposed	2 / 52 (3.85%)	4 / 25 (16.00%)	
occurrences (all)	2	7	
Abdominal discomfort			
subjects affected / exposed	1 / 52 (1.92%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 52 (9.62%)	2 / 25 (8.00%)	
occurrences (all)	5	3	
dermatitis contact			
subjects affected / exposed	1 / 52 (1.92%)	2 / 25 (8.00%)	
occurrences (all)	1	3	
Erythema			
subjects affected / exposed	1 / 52 (1.92%)	2 / 25 (8.00%)	
occurrences (all)	1	6	
Pruritus			
subjects affected / exposed	0 / 52 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	23	
Urticaria			
subjects affected / exposed	0 / 52 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	6 / 52 (11.54%)	0 / 25 (0.00%)	
occurrences (all)	7	0	
Haematuria			
subjects affected / exposed	3 / 52 (5.77%)	0 / 25 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 52 (15.38%)	5 / 25 (20.00%)	
occurrences (all)	12	6	
Pain in extremity			

subjects affected / exposed	8 / 52 (15.38%)	4 / 25 (16.00%)	
occurrences (all)	15	5	
Muscle spasms			
subjects affected / exposed	5 / 52 (9.62%)	3 / 25 (12.00%)	
occurrences (all)	6	3	
Arthralgia			
subjects affected / exposed	4 / 52 (7.69%)	2 / 25 (8.00%)	
occurrences (all)	4	4	
Musculoskeletal pain			
subjects affected / exposed	3 / 52 (5.77%)	2 / 25 (8.00%)	
occurrences (all)	3	2	
Arthritis			
subjects affected / exposed	1 / 52 (1.92%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Joint swelling			
subjects affected / exposed	0 / 52 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 52 (21.15%)	4 / 25 (16.00%)	
occurrences (all)	21	6	
Sinusitis			
subjects affected / exposed	8 / 52 (15.38%)	3 / 25 (12.00%)	
occurrences (all)	9	5	
Upper respiratory tract infection			
subjects affected / exposed	6 / 52 (11.54%)	4 / 25 (16.00%)	
occurrences (all)	12	7	
Urinary tract infection			
subjects affected / exposed	6 / 52 (11.54%)	3 / 25 (12.00%)	
occurrences (all)	6	4	
Bronchitis			
subjects affected / exposed	5 / 52 (9.62%)	5 / 25 (20.00%)	
occurrences (all)	6	7	
Respiratory tract infection			
subjects affected / exposed	3 / 52 (5.77%)	1 / 25 (4.00%)	
occurrences (all)	4	3	

Viral infection			
subjects affected / exposed	3 / 52 (5.77%)	3 / 25 (12.00%)	
occurrences (all)	3	5	
Pneumonia			
subjects affected / exposed	2 / 52 (3.85%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 52 (3.85%)	2 / 25 (8.00%)	
occurrences (all)	3	2	
Gastrointestinal viral infection			
subjects affected / exposed	1 / 52 (1.92%)	2 / 25 (8.00%)	
occurrences (all)	1	4	
Pharyngitis			
subjects affected / exposed	1 / 52 (1.92%)	4 / 25 (16.00%)	
occurrences (all)	1	4	
Gastroenteritis			
subjects affected / exposed	0 / 52 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported