Clinical trial results:
This is a combined clinical report for PB-102-F01 study (EudraCT number 2012-004786-40) and its extension study PB-102-F02 (2013-002554-78) of a Phase 1/2, Open-Label, Dose Ranging Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Exploratory Efficacy Parameters of pegunigalsidase alfa (PRX-102) administered by Intravenous Infusion every 2 weeks for a total of 12 Months [divided into 12 weeks (PB-102-F01 study) followed by 38 weeks (PB-102-F02 study)] to Adult Fabry Patients.

Summary

EudraCT number	2013-002554-78
Trial protocol	GB ES
Global end of trial date	06 March 2016

Results information

Result version number	v1 (current)
This version publication date	03 January 2018
First version publication date	03 January 2018
Summary attachment (see zip file)	CSR Synopsis (CSR PB-102-F01-F02-Synopsis- for upload.pdf)

Trial information

Trial identification

Sponsor protocol code	PB-102-F02 / PB-102-F01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01769001
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Protalix Ltd.
Sponsor organisation address	2 Snunit St, Carmiel, Israel, 20100
Public contact	Rainer Schuckelt, CATO Europe GmbH, 49 2234379440, r.schuckelt@cato-europe.com
Scientific contact	Raul Chertkoff, Protalix Ltd., 972 49028100, raul@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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 March 2016
Global end of trial reached?	Yes
Global end of trial date	06 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability, pharmacokinetics and exploratory efficacy parameters of pegunigalsidase alfa (PRX-102) in adult Fabry patients who have successfully completed treatment with pegunigalsidase alfa in the core study PB-102-F01, and continued to receive treatment (at the same dose that was initially assigned to each patient) in the PB-102-F02 extension study.

Protection of trial subjects:

Since this study (F01 and F02) represents the first administration of pegunigalsidase alfa (PRX-102) to humans, the patients were infused sequentially and stepwise in order to evaluate tolerability.
The first 6 patients were given the lowest dose (0.2 mg/kg) for at least 2 infusions each and if well tolerated, the next 6 patients were given the 1 mg/kg dose for at least 2 infusions each, and if well tolerated, the last 6 patients were given the highest dose (2 mg/kg).

Specifically in the 2mg/kg treatment group, patients were provided with premedication as a preventive measure.

Custom tailoring of infusion volume and rate were implemented for patients weighing over 100Kg in the 1mg/kg and 2mg/kg treatment groups.

Background therapy:

Not Applicable

Evidence for comparator:

Not Applicable

Actual start date of recruitment	05 November 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Paraguay: 1

Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	18
EEA total number of subjects	3

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)	1
Adults (18-64 years)	17
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment efforts were conducted in North and South America, Europe and Australia for PB-102-F01 (3 months), and all patients who completed this study continued to the PB102-F02 extension study for an additional 9 months, to complete a total of 12 months of treatment.
Eighteen patients were eligible for enrollment, and 16 completed the study.

Pre-assignment

Screening details:

Eighteen (18) patients were eligible for enrollment for PB-102-F01 study after meeting all inclusion criteria.
The eligible patients who completed PB-102-F01, needed to sign an informed consent for PB-102-F02.

Pre-assignment period milestones

Number of subjects started	18
Number of subjects completed	18

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Pegunigalsidase alfa

Arm description:

Safety analysis was performed on all 18 treated patients, and efficacy analysis was performed on the 16 patients who completed the study and received all infusions. Efficacy was analyzed on all 16 patients (9 males and 7 females), and additionally on phenotypically classic Fabry disease patients (9 males and 1 female).

Arm type	Dose range finding
Investigational medicinal product name	pegunigalsidase alfa
Investigational medicinal product code	
Other name	PRX-102, Alpha-galactosidase-A
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All patients who completed study PB-102-F01 (12 weeks) were enrolled into extension study PB-102-F02 to receive one of three pegunigalsidase alfa (PRX-102) doses (0.2 mg/kg, 1.0 mg/kg, 2.0 mg/kg), which was the same dose they had received in study PB-102-F01, and continued to receive pegunigalsidase alfa (PRX-102) as an intravenous infusion every 2 weeks for an additional 38 weeks, i.e. for a total of 12 months of treatment.

Number of subjects in period 1	Pegunigalsidase alfa
Started	18
Completed	16
Not completed	2
Physician decision	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	18	18	
Age categorical Units: Subjects			
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	17	17	
Gender categorical Units: Subjects			
Female	7	7	
Male	11	11	
All vs Phenotypically Classic Fabry Patients			
The efficacy population included 16 patients; the study population was composed of 9 males and 7 females, 10 of whom (9 males and 1 female) met the definition of phenotypically classic Fabry disease. Efficacy was analyzed on all patients and on patients with phenotypically classic Fabry disease. The two patients (from the 1mg/kg group) who withdrew without completing the study also met the definition of phenotypically classic Fabry disease, and were only included in the safety population.			
Units: Subjects			
Phenotypically Classic Fabry patients	12	12	
Non Classic Fabry patients	6	6	

Subject analysis sets

Subject analysis set title	Efficacy group
Subject analysis set type	Per protocol

Subject analysis set description:

The efficacy population in the study inlcuded 16 patients: 6 patients in the 0.2 mg/kg treatment group, 6 patients in the 1.0 mg/kg after one patient withdrew due to an AE and one patient was discontinued from the study by the investigator, and 4 patients in the 2.0 mg/kg treatment group.

Subject analysis set title	Safety group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The safety population in the study inlcuded 18 patients: 6 patients in the 0.2 mg/kg treatment group, 8 patients in the 1.0 mg/kg (6 completed the study; 1 was discontinued by the investigator and 1 withdrew due to an AE), and 4 patients in the 2.0 mg/kg treatment groups.

Subject analysis set title	0.2 mg/kg cohort
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Six patients were enrolled in the 0.2mg/kg treatment group and completed the study (12 months).

Subject analysis set title	1 mg/kg cohort
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Eight patients were enrolled in the 1.0 mg/kg treatment group, however only 6 patients completed the study (12 months), after one withdrew due to an AE and one patient was discontinued from the study by the investigator.

Subject analysis set title	2 mg/kg cohort
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Four patients were enrolled in the 2.0 mg/kg treatment group and completed the study (12 months).

Subject analysis set title	Phenotypically Classic Fabry Patients
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Of the 16 patients who completed the 12 months treatment period, 10 (9 males and 1 female) fit the description of phenotypically classic patients.

Reporting group values	Efficacy group	Safety group	0.2 mg/kg cohort
Number of subjects	16	18	6
Age categorical Units: Subjects			
Adolescents (12-17 years)	1	1	0
Adults (18-64 years)	15	17	6
Gender categorical Units: Subjects			
Female	7	7	2
Male	9	11	4
All vs Phenotypically Classic Fabry Patients			
The efficacy population included 16 patients; the study population was composed of 9 males and 7 females, 10 of whom (9 males and 1 female) met the definition of phenotypically classic Fabry disease. Efficacy was analyzed on all patients and on patients with phenotypically classic Fabry disease. The two patients (from the 1mg/kg group) who withdrew without completing the study also met the definition of phenotypically classic Fabry disease, and were only included in the safety population.			
Units: Subjects			
Phenotypically Classic Fabry patients	10	12	5
Non Classic Fabry patients	6	6	1

Reporting group values	1 mg/kg cohort	2 mg/kg cohort	Phenotypically Classic Fabry Patients
Number of subjects	6	4	10
Age categorical Units: Subjects			
Adolescents (12-17 years)	1	0	1
Adults (18-64 years)	5	4	9
Gender categorical Units: Subjects			
Female	2	3	1
Male	4	1	9
All vs Phenotypically Classic Fabry Patients			
The efficacy population included 16 patients; the study population was composed of 9 males and 7 females, 10 of whom (9 males and 1 female) met the definition of phenotypically classic Fabry disease. Efficacy was analyzed on all patients and on patients with phenotypically classic Fabry disease. The two patients (from the 1mg/kg group) who withdrew without completing the study also met the definition of phenotypically classic Fabry disease, and were only included in the safety population.			
Units: Subjects			
Phenotypically Classic Fabry patients	4	1	10
Non Classic Fabry patients	2	3	0

End points

End points reporting groups

Reporting group title	Pegunigalsidase alfa

Reporting group description:

Safety analysis was performed on all 18 treated patients, and efficacy analysis was performed on the 16 patients who completed the study and received all infusions. Efficacy was analyzed on all 16 patients (9 males and 7 females), and additionally on phenotypically classic Fabry disease patients (9 males and 1 female).

Subject analysis set title	Efficacy group
Subject analysis set type	Per protocol

Subject analysis set description:

The efficacy population in the study inlcuded 16 patients: 6 patients in the 0.2 mg/kg treatment group, 6 patients in the 1.0 mg/kg after one patient withdrew due to an AE and one patient was discontinued from the study by the investigator, and 4 patients in the 2.0 mg/kg treatment group.

Subject analysis set title	Safety group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The safety population in the study inlcuded 18 patients: 6 patients in the 0.2 mg/kg treatment group, 8 patients in the 1.0 mg/kg (6 completed the study; 1 was discontinued by the investigator and 1 withdrew due to an AE), and 4 patients in the 2.0 mg/kg treatment groups.

Subject analysis set title	0.2 mg/kg cohort
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Six patients were enrolled in the 0.2mg/kg treatment group and completed the study (12 months).

Subject analysis set title	1 mg/kg cohort
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Eight patients were enrolled in the 1.0 mg/kg treatment group, however only 6 patients completed the study (12 months), after one withdrew due to an AE and one patient was discontinued from the study by the investigator.

Subject analysis set title	2 mg/kg cohort
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Four patients were enrolled in the 2.0 mg/kg treatment group and completed the study (12 months).

Subject analysis set title	Phenotypically Classic Fabry Patients
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Of the 16 patients who completed the 12 months treatment period, 10 (9 males and 1 female) fit the description of phenotypically classic patients.

Primary: Safety - Adverse Events (AE)

End point title	Safety - Adverse Events (AE)[1]

End point description:

Reportings of adverse events reported by the patient and from monitoring with clinical laboratory, physical examination and ECG.
For the complete analysis, please refer to the AEs section.

Results represent the number of adverse events that were considered possibly, probably, or definitely related to treatment, experienced by 11/18 patients in the safety group.

End point type	Primary

End point timeframe:

Patients were evaluated for AEs throughout the 12 months, from signing ICF up to 2 months after the last infusion.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Justification: This is a Phase 1/2 study with no formal statistical analyses required of pre-specified. Results of safety evaluations were summarized and described.

End point values	Safety group			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: not applicable				
number (not applicable)				
Safety	54			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Kidney Function Assessment - eGFR - mean change from baseline

End point title	Kidney Function Assessment - eGFR - mean change from baseline

End point description:

Estimated GFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
The mean annualized eGFR slope of the phenotypically classic patients (n=9, after excluding one patient from the analysis due to intermittent treatment with doxycycline throughout the year) was 0.01 (±1.37).

The results presented here represent the absolute mean change from baseline (visit 1) to 12 months.

End point type	Other pre-specified

End point timeframe:

Levels of estimated glomerular filtration rate (eGFR) calculated by the CKD-EPI equation, based on measured serum creatinine, were determined on day 1 and weeks 4, 8, 12, 26, 38 and 52, and used to determine the annualized slope of eGFR per patient.

End point values	Pegunigalsidase alfa	Phenotypically Classic Fabry Patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	16	10		
Units: mL/min/1.73 m2				
arithmetic mean (standard error)				
Kidney function assessment	-0.8 (± 1.9)	0 (± 2.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasma Gb3 levels

End point title	Plasma Gb3 levels

End point description:

Results are presented as mean percent change from baseline (visit 1) to 12 months +/- standard error.

End point type	Other pre-specified

End point timeframe:

Plasma Gb3 concentration (ug/mL) was measured at baseline and every 3 months up to 12 months.

End point values	Pegunigalsidase alfa	Efficacy group	0.2 mg/kg cohort	1 mg/kg cohort
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	16	6	6
Units: ug/ml				
arithmetic mean (standard error)				
Biomarkers	-22.2 (± 6.1)	-22.2 (± 6.1)	-16.8 (± 8.6)	-30.7 (± 11.2)

End point values	2 mg/kg cohort	Phenotypically Classic Fabry Patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	9		
Units: ug/ml				
arithmetic mean (standard error)				
Biomarkers	-16.2 (± 12.7)	-33.3 (± 7.6)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasma Lyso-Gb3 Levels

End point title	Plasma Lyso-Gb3 Levels

End point description:

Results are presented as mean percent change from baseline (visit 1) to 12 months +/- standard error.

End point type	Other pre-specified

End point timeframe:

Plasma Lyso-Gb3 concentration (ng/mL) was measured at baseline and every 3 months up to 12 months.

End point values	Pegunigalsidase alfa	Efficacy group	0.2 mg/kg cohort	1 mg/kg cohort
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	16	6	6
Units: ng/ml				
arithmetic mean (standard error)				
Biomarkers	-48.9 (± 5.7)	-48.9 (± 5.7)	-43.4 (± 12.2)	-59.9 (± 7.1)

End point values	2 mg/kg cohort	Phenotypically Classic Fabry Patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	10		
Units: ng/ml				
arithmetic mean (standard error)				
Biomarkers	-40.4 (± 7.5)	-57.6 (± 6.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Kidney Gb3 accumulation – biopsies

End point title	Kidney Gb3 accumulation – biopsies

End point description:

Kidney biopsy was performed at baseline of study PB-102-F01 and following a total of 6 months treatment with pegunigalsidase alfa (at Month 3 visit of study PB-102-F02). Approximately 300 capillaries were scored in each specimen. The Barisoni Lipid Inclusion Scoring System (BLISS) was used as the quantitative scoring methodology for scoring Gb3 inclusions in kidney peritubular capillary (PTC) biopsy samples.
The final score of each biopsy was the average number of inclusions per capillary.
The scoring system was implemented by 3 pathologists/readers, who were blinded to patient, dose, and duration of treatment.
A decrease in scoring from baseline to 6 Month is considered an indication for clinical improvement.
Results are presented as percent change from baseline (visit 1) to month 6.

End point type	Other pre-specified

End point timeframe:

Two kidney biopsies were performed: the first was at visit 1 in PB-102-F01 study and the second was after a total of 6 months of treatment (i.e., at 3 months into study PB-102-F02).

End point values	Efficacy group	Phenotypically Classic Fabry Patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	8		
Units: percent				
arithmetic mean (standard error)				
Tissue disease involvement	-67.8 (± 8.9)	-84.1 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cardiac Fibrosis per MRI

End point title	Cardiac Fibrosis per MRI

End point description:

Cardiac MRI was performed to estimate left ventricular mass (LVM), left ventricular mass index (LVMi), ejection fraction (EF) and percentage and mass of the myocardial fibrotic area.
Results represent the number of segments with fibrosis after 1 year of treatment.

End point type	Other pre-specified

End point timeframe:

Cardiac MRI was performed in order to assess myocardial fibrosis at baseline, 6 months and 12 months visit.

End point values	Efficacy group	Phenotypically Classic Fabry Patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	10		
Units: number				
number (not applicable)				
Cardiac Assessment	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cardiac MRI - Ejection Fraction

End point title	Cardiac MRI - Ejection Fraction

End point description:

Results are presented as mean percent change from baseline (visit 1) to 12 months.

End point type	Other pre-specified

End point timeframe:

Cardiac MRI was performed 3 times: at baseline (visit 1), 6 months and 12 months.

End point values	Efficacy group	Phenotypically Classic Fabry Patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	10		
Units: percent				
arithmetic mean (standard error)				
Cardiac Assessment	-3.1 (± 3.6)	-7.3 (± 3.2)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cardiac MRI – LVM

End point title	Cardiac MRI – LVM

End point description:

Results are presented as mean percent change from baseline (visit 1) to 12 months.

End point type	Other pre-specified

End point timeframe:

Cardiac MRI was performed 3 times: at baseline (visit 1), 6 months and 12 months.

End point values	Efficacy group	Phenotypically Classic Fabry Patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	10		
Units: percent				
arithmetic mean (standard error)				
Cardiac Assessment	0 (± 2.5)	-2.6 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cardiac MRI - LVMI

End point title	Cardiac MRI - LVMI

End point description:

Results are presented as mean percent change from baseline (visit 1) to 12 months.

End point type	Other pre-specified

End point timeframe:

Cardiac MRI was performed 3 times: at baseline (visit 1), 6 months and 12 months.

End point values	Efficacy group	Phenotypically Classic Fabry Patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	10		
Units: percent				
arithmetic mean (standard error)				
Cardiac Assessment	0.4 (± 2.6)	-3.1 (± 3.1)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetics – AUC

End point title	Pharmacokinetics – AUC

End point description:

PK parameters were derived from the plasma concentration versus time profiles.
Pegunigalsidase alfa PK parameters and profile indicate dose dependency: the PK results for all three dose levels demonstrated that mean values for AUC0-∞ (the area under the plasma concentration curve from 0 hours to infinity) increased with increasing dose on Day 1 and at Months 3, 6, and 12.
The enzyme was found to be available throughout the 2-week infusion intervals with a plasma half-life of approximately 80 hours.

Results reported represent the values following a single dosing of the study drug.

End point type	Other pre-specified

End point timeframe:

PK parameters were determined on Day 1 and 3, 6, and 12 months at these time points: pre-infusion (baseline); 1 h after the beginning of the infusion; at the end of the infusion; 1, 4, 8, 24, 48±3, 72±3, 96±3 h and 2 weeks ± 3 days post-infusion.

End point values	0.2 mg/kg cohort	1 mg/kg cohort	2 mg/kg cohort	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	6	4	
Units: ng*hr/ml				
arithmetic mean (standard error)				
Pharmacokinetics	70070 (± 26044)	390896 (± 136476)	619393 (± 158562)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetics - Terminal Half Life

End point title	Pharmacokinetics - Terminal Half Life

End point description:

PK parameters were derived from the plasma concentration versus time profiles.
t1/2 = half life.
The PK results for all three dose levels demonstrated that the enzyme was found to be available throughout the 2-week intervals with a plasma half-life of approximately 80 hours.

Results reported represent the values following a single dosing of the study drug.

End point type	Other pre-specified

End point timeframe:

PK parameters were determined on Day 1 and 3, 6, and 12 months at these time points: pre-infusion (baseline); 1 h after the beginning of the infusion; at the end of the infusion; 1, 4, 8, 24, 48±3, 72±3, 96±3 h and 2 weeks ± 3 days post-infusion.

End point values	0.2 mg/kg cohort	1 mg/kg cohort	2 mg/kg cohort	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	6	4	
Units: hour				
arithmetic mean (standard error)				
Pharmacokinetics	60.3 (± 19.6)	78.9 (± 10.3)	70.7 (± 18)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetics - Clearance of Drug (Cl)

End point title	Pharmacokinetics - Clearance of Drug (Cl)

End point description:

PK parameters were derived from the plasma concentration versus time profiles.
Clearance of drug from plasma represents the volume of plasma cleared of the drug per unit time per Kg.

Results reported represent the values following a single dosing of the study drug.

End point type	Other pre-specified

End point timeframe:

PK parameters were determined on Day 1 and 3, 6, and 12 months at these time points: pre-infusion (baseline); 1 h after the beginning of the infusion; at the end of the infusion; 1, 4, 8, 24, 48±3, 72±3, 96±3 h and 2 weeks ± 3 days post-infusion.

End point values	0.2 mg/kg cohort	1 mg/kg cohort	2 mg/kg cohort	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	6	4	
Units: ml/hr/kg				
arithmetic mean (standard error)				
Pharmacokinetics	2.96 (± 0.81)	2.85 (± 0.66)	3.41 (± 0.68)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetics - Volume of Distribution (Vz)

End point title	Pharmacokinetics - Volume of Distribution (Vz)

End point description:

PK parameters were derived from the plasma concentration versus time profiles.
Vz is the volume of distribution during the elimination phase.

Results reported represent the values following a single dosing of the study drug.

End point type	Other pre-specified

End point timeframe:

PK parameters were determined on Day 1 and 3, 6, and 12 months at these time points: pre-infusion (baseline); 1 h after the beginning of the infusion; at the end of the infusion; 1, 4, 8, 24, 48±3, 72±3, 96±3 h and 2 weeks ± 3 days post-infusion.

End point values	0.2 mg/kg cohort	1 mg/kg cohort	2 mg/kg cohort	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	6	4	
Units: ml/kg				
arithmetic mean (standard error)				
Pharmacokinetics	246 (± 68)	321 (± 71)	345 (± 105)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetics – Cmax

End point title	Pharmacokinetics – Cmax

End point description:

Pharmacokinetic (PK) parameters were derived from the plasma concentration versus time profiles.
Cmax is the maximal plasma concentration of a drug after administration.

Results reported represent the values following a single dosing of the study drug.

End point type	Other pre-specified

End point timeframe:

PK parameters were determined on Day 1 and 3, 6, and 12 months at these time points: pre-infusion (baseline); 1 h after the beginning of the infusion; at the end of the infusion; 1, 4, 8, 24, 48±3, 72±3, 96±3 h and 2 weeks ± 3 days post-infusion.

End point values	0.2 mg/kg cohort	1 mg/kg cohort	2 mg/kg cohort	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	6	4	
Units: ng/ml				
arithmetic mean (standard error)				
Pharmacokinetics	1858 (± 531)	11123 (± 2409)	16625 (± 4299)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Safety - Anti-Drug Antibodies

End point title	Safety - Anti-Drug Antibodies

End point description:

Low incidence of treatment induced ADA (3 of 16) with reversible and transient effect on PK was observed.
Three (3) patients developed treatment-induced IgG antibodies to pegunigalsidase alfa (PRX-102).
Two (2) patients from the 0.2 mg/kg treatment group had titers as high as 4633 and 2198, respectively, and both were positive for neutralizing antibodies.
One (1) patient from the 1.0 mg/kg treatment group had a titer as high as 237. This patient was negative for neutralizing antibodies.
ADA response was transient and tolerization was observed.

Results reported represent the number of patients who were ADA positive per group.

End point type	Other pre-specified

End point timeframe:

Anti-pegunigalsidase alfa (PRX-102) antibodies, including neutralizing antibodies in patients having a positive IgG antibody response, were assessed at Visit 1, 2 (Month 1), and then every 2 months during the study, and 2 months after the last infusion.

End point values	Efficacy group	0.2 mg/kg cohort	1 mg/kg cohort	2 mg/kg cohort
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	6	6	4
Units: not applicable				
number (not applicable)				
Safety	3	2	1	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from the start of treatment throughout the 12 months of the study, including a follow up at the end of the study.

Adverse event reporting additional description:

Any laboratory abnormality assessed as clinically significant by the investigator was recorded as an adverse event.
A specific analysis was performed for events that occured during and up to 2h post infusion.
Total AEs - 223; 169 not treatment related, 54 treatment related.
Reported are the infusion related AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	All patients

Reporting group description:

All patients who received at least a single partial treatment are included in this reporting group analysis.

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 18 (11.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Renal Hematoma	Additional description: One patient in the 1mg/kg group experienced a renal hematoma due to the kidney biopsy at baseline. The patient was treated and the renal hematoma was resolved. This event was considered unrelated to treatment.		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm	Additional description: A 52 y.o. male experienced a bronchospasm related to the study drug 40 minutes following the first infusion initiation, was treated, recovered, and discontinued Per Protocol. Anti PRX-102 IgG was negative and anti PRX-102 IgE was positive at baseline		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 18 (88.89%)		
Vascular disorders			
Hypotension	Additional description: Reported during infusion or up to 2h post infusion.		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	6		
Dizziness	Additional description: Reported during infusion or up to 2h post infusion.		
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
General disorders and administration site conditions			
Chest discomfort	Additional description: Reported during infusion or up to 2h post infusion.		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Infusion reaction	Additional description: Reported during infusion or up to 2h post infusion.		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea	Additional description: Reported during infusion or up to 2h post infusion.		
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Abdominal pain	Additional description: Reported during infusion or up to 2h post infusion.		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Sneezing	Additional description: Reported during infusion or up to 2h post infusion.		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Dyspnoea	Additional description: Reported during infusion or up to 2h post infusion.		

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Chest pain	Additional description: Reported during infusion or up to 2h post infusion.		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash maculo-papular	Additional description: Reported during infusion or up to 2h post infusion.		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Itching	Additional description: Reported during infusion or up to 2h post infusion.		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Sweating	Additional description: Reported during infusion or up to 2h post infusion.		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

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