



Clinical trial results:

Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Pegunigalsidase Alfa (PRX-102) in Patients With Fabry Disease

Summary

EudraCT number	2018-001148-67
Trial protocol	GB NO CZ ES SI NL HU IT FI FR
Global end of trial date	21 January 2025

Results information

Result version number	v1 (current)
This version publication date	04 January 2026
First version publication date	04 January 2026

Trial information

Trial identification

Sponsor protocol code	CLI-06657AA1-04
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03566017
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., +39 05212791, clinicaltrials_info@chiesi.com
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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	13 October 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 January 2025
Global end of trial reached?	Yes
Global end of trial date	21 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the ongoing safety, tolerability and efficacy parameters of 1 mg/kg pegunigalsidase alfa every 2 weeks in adult patients with Fabry disease who have completed studies PB-102-F20 or PB-102-F30 or completed at least 48 months in study PB-102-F03.

Protection of trial subjects:

Safety was monitored throughout. For subjects who received pegunigalsidase alfa in studies PB-102-F03/F30, the first infusion in study CLI-06657AA1-04 was of the same duration (but not <60 minutes [min]), with the same premedication (if used) and post-dose observation of 60 min. Subjects had received pegunigalsidase alfa or agalsidase beta in study PB-102-F20. The blind was still maintained for study PB-102-F20 when subjects enrolled in study CLI-06657AA1-04. As some subjects would receive pegunigalsidase alfa for the first time, the duration of the first infusion was 3 hours, with premedication (if used) and with post-dose observation of 2 hours. Subsequent infusions and premedications were managed as per protocol-specified guidance for all enrolled subjects. Tolerability was assessed during infusions and subjects were monitored for hypersensitivity, anaphylaxis and anaphylactoid reactions during and after infusions. Adverse events and concomitant medications were collected throughout. Vital signs were assessed pre-infusion, every 30 min in the first hour, every 60 min during observation and at the end of observation. Safety, pain and quality of life (QoL) assessments were performed 6-monthly (more often in the first year for subjects who enrolled from study PB-102-F20) : physical examination, recording of body weight, electrocardiograms (ECGs), laboratory tests (haematology, biochemistry, urinalysis, anti-drug antibodies [ADA], serum creatinine and cystatin C), short form Brief Pain Inventory (BPI) and EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire. Cardiac function and exercise tolerance were assessed 12-monthly by magnetic resonance imaging (MRI)/echocardiogram and stress test, respectively. Brain MRI was performed 24-monthly. Regular phone calls were made to subjects receiving home infusions. Pregnancy tests were performed in females of childbearing potential. Measures to protect subjects during the coronavirus pandemic were included in study plans.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 September 2018
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	Australia: 1
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 55
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Spain: 5

Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	97
EEA total number of subjects	30

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)	97
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who had completed studies PB-102-F20 or PB-102-F30 or at least 48 months in study PB-102-F03 were enrolled. The first subject first visit was on 16 September 2018. There were 30 study centres in 13 countries.

Pre-assignment

Screening details:

The trial was an extension of studies PB-102-F03/F20/F30. The Screening Visit was the last visit of the previous trial and all information at these visits was included as the screening information for study CLI-06657AA1-04. Subjects from study PB-102-F03 had additional screening assessments of serum creatinine and cystatin C and QoL.

Period 1

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

Arms

Arm title	Overall population
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Arm description:

All subjects received pegunigalsidase alfa 1 mg/kg by intravenous infusion every 2 weeks.

Arm type	Experimental
Investigational medicinal product name	Pegunigalsidase alfa
Investigational medicinal product code	Pegunigalsidase alfa
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Pegunigalsidase alfa was administered at a dose of 1 mg/kg every 2 weeks (± 3 days) by intravenous infusion. For each subject, the dose was prepared according to their screening weight and adjusted according to their weight every 6 months if the weight had changed by 25% from the previous adjustment. The total volume of infusion was adjusted with normal saline to a final volume of 150, 250 or 500 mL per infusion for subjects weighing 70, 70-100 or >100 kg, respectively and recalculated only if dose was adjusted. Infusion rate was adjusted according to individual symptoms/signs as per protocol-specified guidance.

Number of subjects in period 1	Overall population
Started	97
Completed	81
Not completed	16
Adverse event, serious fatal	4
Consent withdrawn by subject	7
Physician decision	1
Adverse event, non-fatal	1
On advice of physician	1

Lost to follow-up	2
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Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	97	97	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	97	97	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	45.0		
standard deviation	± 10.80	-	
Gender categorical			
Units: Subjects			
Female	37	37	
Male	60	60	
Fabry disease classification			
Units: Subjects			
Classic Fabry disease	53	53	
Non-classic Fabry disease	44	44	
Immunoglobulin G (IgG) ADA status			
The ADA status was assessed based on sequential evaluation. The subject was considered ADA-positive if IgG screening was presumptive positive and subsequent IgG immunodepletion was positive. The subject was considered ADA-negative if the IgG screening was negative, or if the IgG screening was presumptive positive and subsequent IgG immunodepletion was negative.			
Units: Subjects			
ADA-positive	25	25	
ADA-negative	72	72	
Severe proteinuria			
Urine protein to creatinine ratio (UPCR) >0.5 g/g was considered severe proteinuria. This included the UPCR categories >0.5 - <1 g/g and ≥1 g/g.			
Units: Subjects			
UPCR <0.15 g/g	54	54	
UPCR ≥0.15 - ≤0.5 g/g	21	21	
UPCR >0.5 - <1 g/g	11	11	
UPCR ≥1 g/g	11	11	
Previous treatment with enzyme			

replacement therapy			
Units: Subjects			
Agalsidase alfa	18	18	
Agalsidase beta	69	69	
None	10	10	
Estimated glomerular filtration rate (eGFR)			
Units: mL/min/1.73 m2			
arithmetic mean	78.2		
standard deviation	± 23.27	-	
Plasma globotriaosylsphingosine (Lyso-Gb3) concentration			
Plasma Lyso-Gb3 was assessed in different laboratories in studies PB-102-F01/F02/F03 and studies PB-102-F20, PB-102-F30 and CLI-06657AA1-04. Change from baseline was assessed in the pooled sample of subjects enrolled from studies PB-102-F20 and PB-102-F30. The Intent-to-treat (ITT) Population excluding subjects enrolled from study PB-102-F03 included 87 subjects. Baseline data for plasma Lyso-Gb3 concentrations were available for 86 subjects.			
Units: nM			
arithmetic mean	27.8		
standard deviation	± 30.59	-	

End points

End points reporting groups

Reporting group title	Overall population
Reporting group description: All subjects received pegunigalsidase alfa 1 mg/kg by intravenous infusion every 2 weeks.	
Subject analysis set title	Intent-to-treat (ITT) Population excluding Cohort F03
Subject analysis set type	Intention-to-treat
Subject analysis set description: Some efficacy variables were assessed in the ITT Population excluding subjects enrolled from study PB-102-F03 (Cohort F03). The ITT Population excluding Cohort F03 included 87 subjects. Plasma Lyso-Gb3 was assessed in different laboratories in studies PB-102-F01/F02/F03 and in studies PB-102-F20, PB-102-F30 and CLI-06657AA1-04. Plasma globotriaosylceramide (Gb3) was assessed in a different unit in in studies PB-102-F01/F02/F03 and in studies PB-102-F20, PB-102-F30 and CLI-06657AA1-04 and conversion between the units was not possible. The EQ-5D-5L questionnaire was not administered during study PB-102-F03. Change from baseline for these variables was assessed in the pooled sample of subjects enrolled from studies PB-102-F20 and PB-102-F30.	
Subject analysis set title	Safety Population excluding Cohort F03
Subject analysis set type	Safety analysis
Subject analysis set description: Infusion premedications were not collected in studies PB-102-F01/F02/F03; analysis of infusion premedications was performed separately in the Safety Population excluding Cohort F03.	
Subject analysis set title	ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT population included all subjects who provided informed consent for study CLI-06657AA1-04 and received any dose, including a partial dose of pegunigalsidase alfa in study CLI-06657AA1-04.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety Population included all subjects who provided informed consent for study CLI-06657AA1-04 and received any dose, including a partial dose of pegunigalsidase alfa in study CLI-06657AA1-04.	

Primary: Number of subjects with treatment-related adverse events (AEs)

End point title	Number of subjects with treatment-related adverse events (AEs) ^[1]
End point description: No primary or secondary endpoints were specified. Evaluation of safety was a main objective. A treatment-emergent AE (TEAE) was defined as any AE occurring after the start of study treatment and within the time of residual drug effect (20 days after the last administration of study treatment) or a pre-treatment AE or pre-existing medical condition that worsened in severity after the start of study treatment and within the time of residual drug effect. Each TEAE was classified for severity based on the Common Terminology Criteria for Adverse Events version (v) 4.03 and classified for causality in the categories unrelated, unlikely, possible, probable and definitely. TEAEs with causality assessed as possible, probable or definitely were categorised as related to study treatment (treatment-related AEs). TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v19.0. Related TEAEs reported in $\geq 2\%$ of subjects by Preferred Term (PT) are reported by subject.	
End point type	Primary
End point timeframe: From first infusion until 90 days following the final visit dose for each subject. Mean (standard deviation) individual exposure to study treatment was 5.5 (1.96) years.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No primary endpoint was defined for the trial. Evaluation of safety was a main objective. Therefore, the number of subjects with treatment-related TEAEs has been reported as a primary endpoint.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	97 ^[2]			
Units: Subjects				
At least one related TEAE	46			
Infusion related reaction	8			
Nausea	6			
Pruritus	5			
Headache	4			
Abdominal pain	3			
Chills	3			
Dizziness	3			
Fatigue	3			
Vomiting	3			
Body temperature increased	2			
Chest discomfort	2			
Diarrhoea	2			
Hypersensitivity	2			
Infusion site extravasation	2			
Oedema peripheral	2			
Paraesthesia	2			
Peripheral swelling	2			
Sneezing	2			
Supraventricular extrasystoles	2			
Weight increased	2			

Notes:

[2] - All subjects were included in the Safety Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in eGFR

End point title	Change from baseline in eGFR
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End point description:

The eGFR was calculated based on serum creatinine values, according to the Chronic Kidney Disease - Epidemiology Collaboration (CKD-EPI) formula (2009).

End point type	Secondary
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End point timeframe:

Change from baseline (last assessment prior to first infusion) to last observation (last non-missing assessment for a subject). Mean (standard deviation) duration of treatment at the last observation: 5.4 (2.03) years.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	97 ^[3]			
Units: mL/min/1.73 m ²				
arithmetic mean (standard deviation)	-10.5 (± 12.91)			

Notes:

[3] - All subjects were included in the Intention-to-treat (ITT Population)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised eGFR slope

End point title	Annualised eGFR slope
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End point description:

The annualised eGFR slope was added in the statistical analysis plan. Individual eGFR slopes were derived for each subject using a linear regression model and summarised descriptively.

End point type	Secondary
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End point timeframe:

From first infusion until the end of the study; mean (standard deviation) individual duration of exposure was 5.5 (1.96) years.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	97 ^[4]			
Units: mL/min/1.73 m ² /year				
arithmetic mean (standard deviation)	-2.2 (± 3.52)			

Notes:

[4] - All subjects were included in the ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Shift from baseline UPCR category <0.15 g/g at last scheduled visit

End point title	Shift from baseline UPCR category <0.15 g/g at last scheduled visit
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End point description:

At baseline, subjects were categorised by UPCR. Shifts from baseline UPCR category to UPCR category at the last scheduled visit are presented.

End point type	Secondary
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End point timeframe:

Shift from baseline (last assessment before first infusion) UPCR category to the last scheduled visit.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	54 ^[5]			
Units: Subjects				
UPCR <0.15 g/g at the last scheduled visit	45			
UPCR ≥0.15 - ≤0.5 g/g at the last scheduled visit	9			
UPCR >0.5 - <1 g/g at the last scheduled visit	0			
UPCR ≥1 g/g at the last scheduled visit	0			

Notes:

[5] - Fifty four subjects had UPCR <0.15 g/g at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Shift from baseline UPCR category ≥0.15 - ≤0.5 g/g at the last scheduled visit

End point title	Shift from baseline UPCR category ≥0.15 - ≤0.5 g/g at the last scheduled visit
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End point description:

At baseline, subjects were categorised by UPCR. Shifts from baseline UPCR category to UPCR category at the last scheduled visit are presented.

End point type	Secondary
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End point timeframe:

Shift from baseline (last assessment before first infusion) UPCR category to the last scheduled visit.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	21 ^[6]			
Units: Subjects				
UPCR <0.15 g/g at the last scheduled visit	8			
UPCR ≥0.15 - ≤0.5 g/g at the last scheduled visit	8			
UPCR >0.5 - <1 g/g at the last scheduled visit	2			
UPCR ≥1 g/g at the last scheduled visit	3			

Notes:

[6] - Twenty-one subjects had UPCR ≥0.15 - ≤0.5 g/g at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Shift from baseline UPCR category >0.5 - <1 g/g at last scheduled visit

End point title	Shift from baseline UPCR category >0.5 - <1 g/g at last scheduled visit
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End point description:

At baseline, subjects were categorised by UPCR. Shifts from baseline UPCR category to UPCR category at the last scheduled visit are presented.

End point type	Secondary
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End point timeframe:

Shift from baseline (last assessment before first infusion) UPCR category to the last scheduled visit.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	11 ^[7]			
Units: Subjects				
UPCR <0.15 g/g at the last scheduled visit	4			
UPCR ≥0.15 - ≤0.5 g/g at the last scheduled visit	2			
UPCR >0.5 - <1 g/g at the last scheduled visit	2			
UPCR ≥1 g/g at the last scheduled visit	3			

Notes:

[7] - Eleven subjects had UPCR category >0.5 - <1 g/g at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Shift from baseline UPCR category ≥1 g/g at the last scheduled visit

End point title	Shift from baseline UPCR category ≥1 g/g at the last scheduled visit
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End point description:

At baseline, subjects were categorised by UPCR. Shifts from baseline UPCR category to UPCR category at the last scheduled visit are presented.

End point type	Secondary
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End point timeframe:

Shift from baseline (last assessment before first infusion) UPCR category to the last scheduled visit.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	11 ^[8]			
Units: Subjects				
UPCR <0.15 g/g at the last scheduled visit	3			
UPCR ≥0.15 - ≤0.5 g/g at the last scheduled visit	0			
UPCR >0.5 - <1 g/g at the last scheduled visit	2			
UPCR ≥1 g/g at the last scheduled visit	6			

Notes:

[8] - Eleven subjects had UPCR ≥ 1 g/g at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in biomarkers for Fabry disease

End point title	Change from baseline in biomarkers for Fabry disease
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End point description:

Plasma Lyso-Gb3 was assessed in different laboratories in studies PB-102-F01/F02/F03 and studies PB-102-F20/F30 and CLI-06657AA1-04. Plasma Gb3 was assessed in a different unit in studies PB-102-F01/F02/F03 and study CLI-06657AA1-04 and conversion between the units was not possible. Therefore, analyses of changes from baseline were performed in the pooled sample of participants enrolled from studies PB-102-F20 and PB-102-F30 (87 participants).

End point type	Secondary
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End point timeframe:

Change from baseline (last assessment prior to first infusion) to last observation (last non-missing assessment for each subject). Mean (standard deviation) duration of treatment at last observation for Lyso-Gb3/Gb3: 5.0 (1.65)/5.0 (1.68) years.

End point values	Intent-to-treat (ITT) Population excluding Cohort F03			
Subject group type	Subject analysis set			
Number of subjects analysed	87			
Units: nM				
arithmetic mean (standard deviation)				
Plasma Lyso-Gb3 concentration	-1.7 ($\pm$ 18.87)			
Plasma globotriaosylceramide (Gb3) concentration	-776.9 ($\pm$ 1568.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline for short form BPI pain severity items

End point title	Change from baseline for short form BPI pain severity items
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End point description:

The short form BPI consists of four pain severity items (pain at its worst, pain at its least, pain on the average and pain right now) and seven pain interference items (general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life) assessed over a 24-hour recall period. Each item is rated on a scale from 0 (no pain/interference) to 10 (worst pain imaginable/complete interference). Subjects report percentage of pain relief by analgesics over the past 24 hours as well.

End point type	Secondary
End point timeframe:	
Change from baseline (last assessment prior to first infusion) to last observation (last non-missing assessment for each subject) for the pain severity items. Mean (standard deviation) duration of treatment at the last observation: 5.4 (2.02) years.	

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	97 ^[9]			
Units: scores				
arithmetic mean (standard deviation)				
Pain at its worst in the last 24 hours	-0.3 (± 2.33)			
Pain at its least in the last 24 hours	0.2 (± 1.77)			
Pain right now	0.1 (± 1.84)			
Pain on the average	-0.1 (± 1.68)			

Notes:

[9] - All subjects were included in the ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline for the Mainz Severity Score Index (MSSI) overall score

End point title	Change from baseline for the Mainz Severity Score Index (MSSI) overall score
End point description:	
The MSSI represents patients with Fabry disease and comprises four domains covering general, neurological, cardiovascular and renal signs and symptoms. Overall scores (i.e. the sum of domain scores) of <20, ≥20 - ≤40 and >40 indicate mild, moderate and severe disease, respectively. An increase in the score indicates increased severity of disease.	
End point type	Secondary
End point timeframe:	
Change from baseline (last assessment prior to first infusion) to last observation (last non-missing assessment for the subject) in overall score. Mean (standard deviation) duration of treatment at the last observation: 5.3 (2.04) years.	

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	97 ^[10]			
Units: Score				
arithmetic mean (standard deviation)	0.6 (± 7.94)			

Notes:

[10] - All subjects were included in the ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Shift from baseline for subjects using no pain medication at baseline

End point title	Shift from baseline for subjects using no pain medication at baseline
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End point description:

At baseline, subjects were categorised by the number of pain medications used (0, 1 and 2+ pain medications). Shifts from baseline to 72 months in the number of subjects using pain medications (categorised by number of pain medications used) are presented. Forty subjects used no pain medication at baseline. Of these, data were available for 21 subjects at 72 months.

End point type	Secondary
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End point timeframe:

Shift from baseline (last assessment prior to first infusion) to 72 months in number of subjects using no pain medication at baseline.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	40 ^[11]			
Units: Subjects				
Subjects using no pain medication at 72 months	9			
Subjects using 1 pain medication at 72 months	11			
Subjects using 2+ pain medications at 72 months	1			

Notes:

[11] - Forty subjects used no pain medications at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Shift from baseline for subjects using 1 pain medication at baseline

End point title	Shift from baseline for subjects using 1 pain medication at baseline
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End point description:

At baseline, subjects were categorised by the number of pain medications used (0, 1 and 2+ pain medications). Shifts from baseline to 72 months in the number of subjects using pain medications (categorised by number of pain medications used) are presented. Thirty-one subjects used 1 pain medication at baseline. Of these, 17 subjects had data available at 72 months.

End point type	Secondary
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End point timeframe:

Shift from baseline (last assessment prior to first infusion) to 72 months in number of subjects using 1 pain medication at baseline.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	31 ^[12]			
Units: Subjects				
Subjects using no pain medication at 72 months	0			
Subjects using 1 pain medication at 72 months	7			
Subjects using 2+ pain medications at 72 months	10			

Notes:

[12] - Thirty-one subjects used 1 pain medication at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Shift from baseline for subjects using 2+ pain medications at baseline

End point title	Shift from baseline for subjects using 2+ pain medications at baseline
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End point description:

At baseline, subjects were categorised by the number of pain medications used (0, 1 and 2+ pain medications). Shifts from baseline to 72 months in the number of subjects using pain medications (categorised by number of pain medications used) are presented. Twenty-six subjects used 2+ pain medications at baseline. Of these, 9 subjects had data available at 72 months.

End point type	Secondary
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End point timeframe:

Shift from baseline (last assessment prior to first infusion) to 72 months in number of subjects using 2+ pain medications at baseline.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	26 ^[13]			
Units: Subjects				
Subjects using no pain medication at 72 months	0			
Subjects using 1 pain medication at 72 months	1			
Subjects using 2+ pain medications at 72 months	8			

Notes:

[13] - Twenty-six subjects used 2+ pain medications at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline for QoL assessment

End point title	Change from baseline for QoL assessment
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End point description:

Quality of life was assessed by administering the EQ-5D-5L questionnaire. This consists of the EuroQoL 5 Dimensions (EQ-5D) descriptive system and the EuroQoL visual analogue scale (EQ VAS). For the EQ VAS, subjects rated their current health on a vertical VAS which has endpoints labelled 'the best health you can imagine' (score of 100) and 'the worst health you can imagine' (score of 0). An increase in score indicates worsening.

End point type	Secondary
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End point timeframe:

Change from baseline (last assessment prior to first infusion) to last observation (last non-missing assessment for the subject) for the EQ VAS. Mean (standard deviation) duration of treatment at the last observation was 5.0 (1.65) years.

End point values	Intent-to-treat (ITT) Population excluding Cohort F03			
Subject group type	Subject analysis set			
Number of subjects analysed	87			
Units: Score				
arithmetic mean (standard deviation)	0.9 (± 17.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline for left ventricular mass index (LVMI) assessed by cardiac magnetic resonance imaging (MRI)

End point title	Change from baseline for left ventricular mass index (LVMI) assessed by cardiac magnetic resonance imaging (MRI)
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End point description:

The LVMI with and without hypertrophy was assessed by cardiac MRI.

End point type	Secondary
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End point timeframe:

Change from baseline (last assessment prior to first infusion) to last observation (last non-missing assessment for the subject). Mean duration of treatment at last observation for LVMI with/without hypertrophy: 4.5/5.1 years.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	97 ^[14]			
Units: g/m ²				
arithmetic mean (standard deviation)				
LVMI without hypertrophy	9.0 (± 11.73)			
LVMI with hypertrophy	7.5 (± 19.97)			

Notes:

[14] - All subjects were included in the ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who had ADA at any post-baseline visit

End point title	Number of subjects who had ADA at any post-baseline visit
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End point description:

The ADA status was assessed as per the schedule of assessments based on sequential evaluation. The subject was considered ADA-positive if IgG screening was presumptive positive and subsequent IgG immunodepletion was positive.

End point type	Secondary
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End point timeframe:

From first infusion until the end of the study: mean (standard deviation) individual duration of treatment was 5.5 (1.96) years.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	97 ^[15]			
Units: Subjects	47			

Notes:

[15] - All subjects were included in the Safety Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent ADA who had titre-boostered or treatment-induced ADA

End point title	Number of subjects with treatment-emergent ADA who had titre-boostered or treatment-induced ADA
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End point description:

The ADA status at a visit was decided based on a sequential evaluation as per the schedule of assessments. If the IgG screening was negative, the subject was ADA-negative at that visit. If the IgG screening was presumptive positive, an IgG immunodepletion test was performed and the subject was considered ADA-positive or -negative at the visit based on whether the test was positive or negative. Baseline was the last assessment before the first infusion of pegunigalsidase alfa. Subjects were considered to be treatment-emergent ADA-positive if they had titre-boostered or treatment-induced ADA. The ADA were titre-boostered if subjects were ADA-positive at baseline and ADA titre had increased by at least 4-fold from baseline during treatment. The ADA were treatment-induced if subjects were ADA-negative at baseline and ADA-positive in at least one timepoint post-first infusion.

End point type	Secondary
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End point timeframe:

From first infusion until the end of the study: mean (standard deviation) individual duration of treatment was 5.5 (1.96) years.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	31 ^[16]			
Units: Subjects				
Subjects with titre-boosted ADA	7			
Subjects with treatment-induced ADA	24			

Notes:

[16] - Thirty-one subjects had treatment-emergent ADA.

Statistical analyses

No statistical analyses for this end point

Secondary: Shift from baseline for subjects using 0 infusion premedication at baseline

End point title	Shift from baseline for subjects using 0 infusion premedication at baseline
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End point description:

Infusion premedications were not collected in studies PB-102-F01/F02/F03. Infusion premedications were analysed as a safety endpoint in the Safety Population excluding Cohort F03. Subjects were categorised according to number of infusion premedications used (0, 1, 2 and 3+) at baseline and subsequent time points. Shifts from baseline to Months 12, 24, 48 and 72 are presented for subjects with no infusion premedication use at baseline.

End point type	Secondary
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End point timeframe:

Shift from baseline to Months 12, 24, 48 and 72.

End point values	Safety Population excluding Cohort F03			
Subject group type	Subject analysis set			
Number of subjects analysed	65 ^[17]			
Units: Subjects				
No use of infusion premedication at Month 12	61			
Use of 1 infusion premedication at Month 12	1			
Use of 2 infusion premedications at Month 12	2			
Use of 3+ infusion premedications at Month 12	1			
No use of infusion premedication at Month 24	55			
Use of 1 infusion premedication at Month 24	4			
Use of 2 infusion premedications at Month 24	1			

Use of 3+ infusion premedications at Month 24	1			
No use of infusion premedication at Month 48	45			
Use of 1 infusion premedication at Month 48	3			
Use of 2 infusion premedications at Month 48	0			
Use of 3+ infusion premedications at Month 48	1			
No use of infusion premedication at Month 72	25			
Use of 1 infusion premedication at Month 72	1			
Use of 2 infusion premedications at Month 72	0			
Use of 3+ infusion premedications at Month 72	1			

Notes:

[17] - A total of 65 subjects used 0 infusion premedication at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Shift from baseline for subjects using 1 infusion premedication at baseline

End point title	Shift from baseline for subjects using 1 infusion premedication at baseline
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End point description:

Infusion premedications were not collected in studies PB-102-F01/F02/F03. Infusion premedications were analysed as a safety endpoint in the Safety Population excluding Cohort F03. Subjects were categorised according to number of infusion premedications used (0, 1, 2 and 3+) at baseline and subsequent time points. Shifts from baseline to Months 12, 24, 48 and 72 are presented for subjects using 1 infusion premedication at baseline (first infusion).

End point type	Secondary
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End point timeframe:

Shift from baseline to Months 12, 24, 48 and 72.

End point values	Safety Population excluding Cohort F03			
Subject group type	Subject analysis set			
Number of subjects analysed	9 ^[18]			
Units: Subjects				
No use of infusion premedication at Month 12	6			
Use of 1 infusion premedication at Month 12	3			
Use of 2 infusion premedications at Month 12	0			
Use of 3+ infusion premedications at Month 12	0			

No use of infusion premedication at Month 24	6			
Use of 1 infusion premedication at Month 24	3			
Use of 2 infusion premedications at Month 24	0			
Use of 3+ infusion premedications at Month 24	0			
No use of infusion premedications at Month 48	5			
Use of 1 infusion premedication at Month 48	1			
Use of 2 infusion premedications at Month 48	1			
Use of 3+ infusion premedications at Month 48	0			
No use of infusion premedication at Month 72	2			
Use of 1 infusion premedication at Month 72	0			
Use of 2 infusion premedications at Month 72	0			
Use of 3+ infusion premedications at Month 72	1			

Notes:

[18] - A total of 9 subjects used 1 infusion premedication at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Shift from baseline for subjects using 2 infusion premedications at baseline

End point title	Shift from baseline for subjects using 2 infusion premedications at baseline
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End point description:

Infusion premedications were not collected in studies PB-102-F01/F02/F03. Infusion premedications were analysed as a safety endpoint in the Safety Population excluding Cohort F03. Subjects were categorised according to number of infusion premedications used (0, 1, 2 and 3+) at baseline and subsequent time points. Shifts from baseline to Months 12, 24, 48 and 72 are presented for subjects using 2 infusion premedications at baseline (first infusion).

End point type	Secondary
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End point timeframe:

Shift from baseline to Months 12, 24, 48 and 72.

End point values	Safety Population excluding Cohort F03			
Subject group type	Subject analysis set			
Number of subjects analysed	8 ^[19]			
Units: Subjects				
No use of infusion premedication at Month 12	8			

Use of 1 infusion premedication at Month 12	0			
Use of 2 infusion premedications at Month 12	0			
Use of 3+ infusion premedications at Month 12	0			
No use of infusion premedication at Month 24	8			
Use of 1 infusion premedication at Month 24	0			
Use of 2 infusion premedications at Month 24	0			
Use of 3+ infusion premedications at Month 24	0			
No use of infusion premedication at Month 48	7			
Use of 1 infusion premedication at Month 48	1			
Use of 2 infusion premedications at Month 48	0			
Use of 3+ infusion premedications at Month 48	0			
No use of infusion premedication at Month 72	5			
Use of 1 infusion premedication at Month 72	0			
Use of 2 infusion premedications at Month 72	0			
Use of 3+ infusion premedications at Month 72	0			

Notes:

[19] - A total of 8 subjects used 2 infusion premedications at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Shift from baseline for subjects using 3+ infusion premedications at baseline

End point title	Shift from baseline for subjects using 3+ infusion premedications at baseline
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End point description:

Infusion premedications were not collected in studies PB-102-F01/F02/F03. Infusion premedications were analysed as a safety endpoint in the Safety Population excluding Cohort F03. Subjects were categorised according to number of infusion premedications used (0, 1, 2 and 3+) at baseline and subsequent time points. Shifts from baseline to Months 12, 24, 48 and 72 are presented for subjects using 3+ infusion premedications at baseline (first infusion).

End point type	Secondary
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End point timeframe:

Shifts from baseline to Months 12, 24, 48 and 72.

End point values	Safety Population excluding Cohort F03			
Subject group type	Subject analysis set			
Number of subjects analysed	5 ^[20]			
Units: Subjects				
No use of infusion premedication at Month 12	3			
Use of 1 infusion premedication at Month 12	1			
Use of 2 infusion premedications at Month 12	0			
Use of 3+ infusion premedications at Month 12	1			
No use of infusion premedication at Month 24	2			
Use of 1 infusion premedication at Month 24	0			
Use of 2 infusion premedications at Month 24	0			
Use of 3+ infusion premedications at Month 24	3			
No use of infusion premedication at Month 48	2			
Use of 1 infusion premedication at Month 48	1			
Use of 2 infusion premedications at Month 48	0			
Use of 3+ infusion premedications at Month 48	2			
No use of infusion premedication at Month 72	1			
Use of 1 infusion premedication at Month 72	1			
Use of 2 infusion premedications at Month 72	0			
Use of 3+ infusion premedications at Month 72	0			

Notes:

[20] - A total of 5 subjects used 3+ infusion premedications at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with infusion-related reactions (IRRs) during infusion or within 2 hours after its completion (IRR-2H)

End point title	Number of subjects with infusion-related reactions (IRRs) during infusion or within 2 hours after its completion (IRR-2H)
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End point description:

An IRR was defined as a reaction to the infusion of pharmacological and/or biological substances; symptoms could appear within minutes to 2 hours following the end of the infusion and could include pruritus, flushing, swelling, dyspnoea, bronchospasm and hypotension. IRRs could be evaluated up to 24 hours from occurrence. Two time frames were considered for IRR analysis: IRR-2H and IRRs occurring during the infusion or within 24 hours after its completion (IRR-24H). All IRR-2H were also classified as IRR-24H. IRR-2H reported for >1 subject overall by MedDRA PT are presented by subject. A total of 23 subjects experienced 67 IRR-2H.

End point type	Secondary
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End point timeframe:

From the first infusion of pegunigalsidase alfa until the last infusion for each subject. Mean (standard deviation) duration of exposure was 5.5 (1.96) years.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	97 ^[21]			
Units: Subjects				
Infusion related reaction	7			
Pruritus	4			
Chills	3			
Body temperature increased	2			
Dizziness	2			
Hypersensitivity	2			
Nausea	2			
Sneezing	2			

Notes:

[21] - All subjects were included in the Safety Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with IRRs during infusion or within 24 hours after its completion (IRR-24H)

End point title	Number of subjects with IRRs during infusion or within 24 hours after its completion (IRR-24H)
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End point description:

An IRR was defined as a reaction to the infusion of pharmacological and/or biological substances; symptoms could appear within minutes to 2 hours following the end of the infusion and could include pruritus, flushing, swelling, dyspnoea, bronchospasm and hypotension. IRRs could be evaluated up to 24 hours from occurrence. Two time frames were considered for IRR analysis: IRR-2H and IRR-24H. All IRR-2H were also classified as IRR-24H. IRR-24H reported for >1 subject overall by MedDRA PT are presented by subject. A total of 29 subjects experienced 83 IRR-24H.

End point type	Secondary
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End point timeframe:

From the first infusion of pegunigalsidase alfa until the last infusion for each subject. Mean (standard deviation) duration of exposure was 5.5 (1.96) years.

End point values	Overall population			
Subject group type	Reporting group			
Number of subjects analysed	97 ^[22]			
Units: Subjects				
Infusion related reaction	8			
Nausea	4			
Pruritus	4			
Chills	3			

Fatigue	3			
Abdominal pain	2			
Body temperature increased	2			
Dizziness	2			
Hypersensitivity	2			
Sneezing	2			
Vomiting	2			

Notes:

[22] - All subjects were included in the Safety Population.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the first ever infusion of pegunigalsidase alfa until 90 days following the final visit dose for each subject.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Overall population
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Reporting group description:

All subjects received pegunigalsidase alfa 1 mg/kg by intravenous infusion every 2 weeks

Serious adverse events	Overall population		
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 97 (46.39%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	4		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Extremity necrosis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis limb			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Implantable defibrillator insertion			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Medical device battery replacement subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrectomy subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative care subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden death subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Chills subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypothermia subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			

subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eosinophilic bronchitis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obstructive airways disorder			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Agitation			

subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anxiety			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Troponin I increased			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Alcohol poisoning			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clavicle fracture			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Meniscus injury			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon rupture			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaccination complication			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Left ventricular outflow tract obstruction			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			

subjects affected / exposed	2 / 97 (2.06%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	2 / 97 (2.06%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	2 / 97 (2.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cardiac failure congestive				
subjects affected / exposed	2 / 97 (2.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	2 / 97 (2.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Acute coronary syndrome				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block complete				

subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block second degree			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Left ventricular dysfunction			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus arrest			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular tachycardia			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Ischaemic stroke			

subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pneumoperitoneum			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Protein-losing gastroenteropathy			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Chronic kidney disease			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
End stage renal disease			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Soft tissue mass			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Sepsis				
subjects affected / exposed	3 / 97 (3.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Coronavirus infection				
subjects affected / exposed	2 / 97 (2.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridial infection				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infectious mononucleosis				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis aseptic				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				

subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 97 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 97 (8.25%)		
occurrences (all)	11		
Hypotension			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	26 / 97 (26.80%)		
occurrences (all)	30		
Pyrexia			
subjects affected / exposed	18 / 97 (18.56%)		
occurrences (all)	23		
Oedema peripheral			
subjects affected / exposed	12 / 97 (12.37%)		
occurrences (all)	23		

Infusion site extravasation subjects affected / exposed occurrences (all)	10 / 97 (10.31%) 18		
Chest pain subjects affected / exposed occurrences (all)	8 / 97 (8.25%) 15		
Pain subjects affected / exposed occurrences (all)	8 / 97 (8.25%) 10		
Oedema subjects affected / exposed occurrences (all)	7 / 97 (7.22%) 7		
Peripheral swelling subjects affected / exposed occurrences (all)	5 / 97 (5.15%) 6		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	6 / 97 (6.19%) 7		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	28 / 97 (28.87%) 39		
Oropharyngeal pain subjects affected / exposed occurrences (all)	17 / 97 (17.53%) 23		
Dyspnoea subjects affected / exposed occurrences (all)	13 / 97 (13.40%) 15		
Nasal congestion subjects affected / exposed occurrences (all)	6 / 97 (6.19%) 15		
Rhinorrhoea subjects affected / exposed occurrences (all)	6 / 97 (6.19%) 9		
Upper respiratory tract congestion			

subjects affected / exposed occurrences (all) Sleep apnoea syndrome subjects affected / exposed occurrences (all)	5 / 97 (5.15%) 8 5 / 97 (5.15%) 5		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all)	9 / 97 (9.28%) 12 8 / 97 (8.25%) 10 7 / 97 (7.22%) 7		
Investigations Coronavirus test positive subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all) Urine protein/creatinine ratio increased subjects affected / exposed occurrences (all)	9 / 97 (9.28%) 13 8 / 97 (8.25%) 12 7 / 97 (7.22%) 9		
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) Vaccination complication subjects affected / exposed occurrences (all) Limb injury subjects affected / exposed occurrences (all) Contusion	10 / 97 (10.31%) 29 9 / 97 (9.28%) 15 6 / 97 (6.19%) 6		

subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	12 / 97 (12.37%)		
occurrences (all)	20		
Palpitations			
subjects affected / exposed	11 / 97 (11.34%)		
occurrences (all)	14		
Bradycardia			
subjects affected / exposed	10 / 97 (10.31%)		
occurrences (all)	12		
Left ventricular hypertrophy			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	9		
Bundle branch block right			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	7		
Mitral valve incompetence			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	7		
Bundle branch block left			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	6		
Arrhythmia			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		
Tricuspid valve incompetence			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		
Nervous system disorders			
Headache			
subjects affected / exposed	29 / 97 (29.90%)		
occurrences (all)	52		
Dizziness			

subjects affected / exposed	16 / 97 (16.49%)		
occurrences (all)	27		
Paraesthesia			
subjects affected / exposed	13 / 97 (13.40%)		
occurrences (all)	17		
Migraine			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	7		
Sciatica			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	8		
Transient ischaemic attack			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	6		
Hypoaesthesia			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 97 (10.31%)		
occurrences (all)	11		
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	9 / 97 (9.28%)		
occurrences (all)	13		
Vertigo			
subjects affected / exposed	9 / 97 (9.28%)		
occurrences (all)	10		
Tinnitus			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	7		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	22 / 97 (22.68%)		
occurrences (all)	37		
Vomiting			

subjects affected / exposed	20 / 97 (20.62%)		
occurrences (all)	28		
Abdominal pain			
subjects affected / exposed	17 / 97 (17.53%)		
occurrences (all)	35		
Nausea			
subjects affected / exposed	15 / 97 (15.46%)		
occurrences (all)	22		
Abdominal discomfort			
subjects affected / exposed	10 / 97 (10.31%)		
occurrences (all)	19		
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 97 (8.25%)		
occurrences (all)	9		
Abdominal pain upper			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	11		
Toothache			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	11		
Dyspepsia			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	6		
Haemorrhoids			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	14 / 97 (14.43%)		
occurrences (all)	26		
Pruritus			
subjects affected / exposed	8 / 97 (8.25%)		
occurrences (all)	9		

Erythema subjects affected / exposed occurrences (all)	5 / 97 (5.15%) 5		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all) Haematuria subjects affected / exposed occurrences (all) Renal impairment subjects affected / exposed occurrences (all)	14 / 97 (14.43%) 17 10 / 97 (10.31%) 13 5 / 97 (5.15%) 7		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Osteoarthritis subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all)	26 / 97 (26.80%) 34 23 / 97 (23.71%) 33 22 / 97 (22.68%) 29 11 / 97 (11.34%) 11 8 / 97 (8.25%) 12 5 / 97 (5.15%) 6 5 / 97 (5.15%) 5		
Infections and infestations			

Coronavirus infection			
subjects affected / exposed	46 / 97 (47.42%)		
occurrences (all)	59		
Nasopharyngitis			
subjects affected / exposed	35 / 97 (36.08%)		
occurrences (all)	74		
Upper respiratory tract infection			
subjects affected / exposed	23 / 97 (23.71%)		
occurrences (all)	43		
Viral infection			
subjects affected / exposed	19 / 97 (19.59%)		
occurrences (all)	25		
Urinary tract infection			
subjects affected / exposed	17 / 97 (17.53%)		
occurrences (all)	18		
Sinusitis			
subjects affected / exposed	14 / 97 (14.43%)		
occurrences (all)	22		
Respiratory tract infection			
subjects affected / exposed	13 / 97 (13.40%)		
occurrences (all)	25		
Influenza			
subjects affected / exposed	13 / 97 (13.40%)		
occurrences (all)	16		
Viral upper respiratory tract infection			
subjects affected / exposed	11 / 97 (11.34%)		
occurrences (all)	22		
Bronchitis			
subjects affected / exposed	11 / 97 (11.34%)		
occurrences (all)	21		
Gastroenteritis viral			
subjects affected / exposed	8 / 97 (8.25%)		
occurrences (all)	10		
Gastroenteritis			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	11		

Cellulitis			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	7		
Ear infection			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	6		
Lower respiratory tract infection			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	6		
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2018	This amendment resulted in Protocol version 2.0 dated 17 July 2018. The duration of treatment was changed from 'no less than 24 months and up to 48 months' to 'up to 48 months'. Appendix 3 of the protocol was adapted and subjects with progressive or severe hypersensitivity were to be withdrawn from the study only if not allayed with pre-treatment. A visit for dose adjustment according to the subject's weight was removed. Flow charts and visits were adapted as intervals between sampling timepoints for some efficacy assessments and ADA assessments were increased to ease subject burden. Plasma Gb3 and Lyso-Gb3 concentrations were removed from the list of efficacy variables. The timing of vital sign evaluations was changed to every 30 min during the first hour of infusion and then every 60 min for subjects who tolerated the infusion, to reduce subject burden without compromising subject safety.
28 February 2020	This amendment resulted in Protocol version 4.0 dated 25 September 2019. Safety-related content was updated in the introduction. Visits were added for dose adjustment according to the subject's weight. Galafold TM was added as a prohibited concomitant medication. Assessment of plasma Gb3 concentrations was added as an efficacy assessment and it was specified that the clinical events mentioned in the endpoint in the synopsis referred to Fabry clinical events. The intervals between sampling timepoints for some efficacy assessments were decreased and more frequent assessments were included for subjects enrolled from study PB-102-F20. Intervals between sampling timepoints for ADA assessments were decreased and more frequent assessments were included for subjects enrolled from study PB-102-F20. Screening assessments of serum creatinine and cystatin C and of QoL were added for subjects enrolled from study PB-102-F03. Accordingly, flow charts and visits were modified. Creatine was replaced with creatine phosphokinase in biochemistry assessments and assessment of nitrite and leukocytes was included in urinalysis. The number of follow-up calls for subjects in the Home Care programme was reduced.
15 October 2021	This amendment resulted in Protocol version 5.0 dated 29 June 2021. Safety-related content was updated. The duration of treatment was changed from 'up to 48 months' to 'up to 60 months'. Further dose adjustment visits were planned. In the safety assessments, instructions were included regarding continuation of assessments of serum creatinine and cystatin C in case of end-stage renal disease. A more specific definition of acute kidney injury was included. Instructions were included regarding reporting and follow-up of pregnancies. The flow chart was updated. In the appendices, cardiac MRI parameters were specified and Appendix 9 on chronic kidney disease stages was added. In the statistical analysis section of the protocol, text was added on the statistical analysis plan, study PB-102-F03 was reflected in the sample size wording and analysis specifications were added. Instructions were added regarding postponing visits planned to study PB-102-F20 to study CLI-06657AA1-04 during the coronavirus disease (COVID-19) pandemic.

09 December 2022	This amendment resulted in Protocol version 6.0 dated 25 April 2022. Sponsor's Medical Expert (details) replaced the Medical Monitor. The protocol number was changed from PB-102-F60 to CLI-06657AA1-04. Sponsor was changed from Protalix Ltd to Chiesi and Sponsor/details were updated. Contraception needs were clarified and pregnancy management was updated as per Chiesi requirements. Inclusion criterion 6.3.1 was modified (enrolment had been completed). The need for Sponsor approval for changes in infusion time according to subject's weight pending subject tolerability and Investigator evaluation was deleted as the Sponsor was consulted but not responsible for the action/decision. It was further clarified that the study treatment could be permanently discontinued at Sponsor's discretion based on safety concerns, potential major protocol violation and/or fraud. It was specified that CTCAE Version 4.03, 2010 would be used to define grade toxicity. Sections of the synopsis were updated as applicable. The exclusion criteria specified that subjects could be excluded from the study as per the Investigator's judgement (earlier, Investigator's and Medical Monitor's judgement). Study results from the PRX-102 programme were deleted as complete information was included in the Investigator's Brochure. A risk/benefit assessment was added. Duration of treatment was updated (to 'until pegunigalsidase alfa was commercially available to the subject or at the Sponsor's discretion' and end of study and last visit were defined accordingly. Additional visits were included for dose adjustment. Only the Investigator's decision was sufficient for subjects to receive home infusions; Sponsor's Medical Expert was to be notified. Study flow chart was built up to include up to Visit 209. Urine pregnancy test was added (for females of childbearing potential). Schedule of MSSSI assessments was updated, infusion-related reactions were defined. Definition of the ITT Population was modified.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported