# Clinical trial results:
# 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 12 Weeks to Adult Fabry Patients.
# Please refer to PB-102-F02 study (EudraCT number 2013-002554-78) report for details.

## Summary

| | |
|---|---|
| EudraCT number | 2012-004786-40 |
| 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 2020 |
| First version publication date | 03 January 2020 |
| 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-F01 / PB-102-F02 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01678898 |
| 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 22343794411, 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 1901/2006 apply to this trial? | No |

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. The extension study provides important additional long term information on safety, tolerability and clinical outcome in patients treated with different doses of pegunigalsidase alfa.

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 | 9 Months |
| 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 | Paraguay: 1 |
| Country: Number of subjects enrolled | Spain: 2 |
| Country: Number of subjects enrolled | United Kingdom: 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).
Eighteen patients were eligible for enrollment, and 16 completed the study.

### Pre-assignment

Screening details:

Eighteen (18) patients were eligible for enrollment after meeting all inclusion criteria.

### 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 suspension for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Each patient received one of three pegunigalsidase alfa (PRX-102) doses (0.2 mg/kg, 1.0 mg/kg, 2.0 mg/kg), as an intravenous infusion every 2 weeks for 12 weeks.
All patients who completed study PB-102-F01 (12 weeks) were enrolled into extension study PB-102-F02 to receive 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<br>Units: Subjects | | | |
| Adolescents (12-17 years) | 1 | 1 | |
| Adults (18-64 years) | 17 | 17 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 7 | 7 | |
| Male | 11 | 11 | |
| All vs Classic Fabry Patients | | | |
| The efficacy population included 16 patients; the study population was composed of 9 males and 7 females, however, only 10 patients (9 males and 1 female) met the definition of classic Fabry disease. Efficacy was analyzed in all patients and in patients with classic Fabry disease.<br>The two patients (from the 1mg/kg group) who withdrew without completing the study also met the definition of phenotypic classic Fabry disease, and were only included in the safety population. | | | |
| Units: Subjects | | | |
| Classic Fabry Disease Patients | 12 | 12 | |
| Non-Classic Fabry Disease 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 included 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 included 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 | Phenotypic 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 phenotypic classic patients.

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

| **Reporting group values** | 1 mg/kg cohort | 2 mg/kg cohort | Phenotypic Classic Fabry Patients |
|---|---|---|---|
| Number of subjects | 6 | 4 | 10 |
| Age categorical<br>Units: Subjects | | | |
| Adolescents (12-17 years) | 1 | 0 | 1 |
| Adults (18-64 years) | 5 | 4 | 9 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 2 | 3 | 1 |
| Male | 4 | 1 | 9 |
| All vs Classic Fabry Patients | | | |
| The efficacy population included 16 patients; the study population was composed of 9 males and 7 females, however, only 10 patients (9 males and 1 female) met the definition of classic Fabry disease. Efficacy was analyzed in all patients and in patients with classic Fabry disease.<br>The two patients (from the 1mg/kg group) who withdrew without completing the study also met the definition of phenotypic classic Fabry disease, and were only included in the safety population. | | | |
| Units: Subjects | | | |
| Classic Fabry Disease Patients | 4 | 1 | 10 |
| Non-Classic Fabry Disease 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 included 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 included 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 | Phenotypic 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 phenotypic 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: This is a Phase 1/2 study with no formal statistical analysis 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[2] | | | |
| Units: events | | | | |
| Safety - Adverse Events (AE) | 54 | | | |

Notes:

[2] - No statistical analyses was done for this end point.

## 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 | Phenotypic 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 | Phenotypic 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 | Phenotypic 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 before treatment, 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 | Phenotypic 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 | Phenotypic 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 | Phenotypic 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 MRI - Ejection Fraction | -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 | Phenotypic 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 MRI – LVM | 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 | Phenotypic 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 MRI - LVMI | 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 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) | | | | |
| AUC | 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.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

PK parameters were determined on Day 1 and 3 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) | | | | |
| Terminal Half Life | 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) | | | | |
| Clearance of Drug (Cl) | 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) | | | | |
| Volume of Distribution (Vz) | 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) | | | | |
| Cmax | 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: subjects | | | | |
| Safety - Anti-Drug Antibodies | 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. all AE are reported under Clinical trial results 2013-002554-78

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 or 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. | | |
| 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: 0.05 %

| **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 | Additional description: Reported during infusion or up to 2h post infusion. | | |
| 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