Pegunigalsidase alfa (PRX-102) Clinical Study Report

[also known as a PEGylated crosslinked human alpha galactosidase-A]

PROTOCOLS PB-102-F01 AND PB-102-F02

Protocol PB-102-F01 Title: A Phase 1/2, Open Label, Dose Ranging Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Exploratory Efficacy Parameters of PRX-102 Administered by Intravenous Infusion Every 2 Weeks for 12 Weeks to Adult Fabry Patients

Protocol PB-102-F02 Title: An Extension of Phase 1/2, Open Label, Dose Ranging Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Exploratory Efficacy Parameters of PRX-102 Administered by Intravenous Infusion Every 2 Weeks for 38 Weeks (9 Months) to Adult Fabry Patients

Indication studied:	pegunigalsidase alfa (PRX-102) is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (alpha galactosidase deficiency)
Developmental phase of study:	Phase 1/2
First patient enrolled:	5Nov2012
Last patient completed:	6Mar2016
Release date of Final CSR:	9May2017
Company/Sponsor signatory:	Protalix Ltd. Telephone: 972-4-988-9488 Fax: 972-4-988-9489

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

2. SYNOPSIS

Name of Sponsor/Company: Protalix Ltd. 2 Snunit Street Science Park POB 455, Carmiel 20100, Israel Ph: 972-4-988-9488, Fax: 972-4-988-9489	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: pegunigalsidase alfa (PRX-102)		
Name of Active Ingredient: alpha galactosidase-A (alfa-GAL-A)		

Title of Study: Protocol PB-102-F01 Title: A Phase 1/2, Open Label, Dose Ranging Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Exploratory Efficacy Parameters of PRX-102 Administered by Intravenous Infusion Every 2 Weeks for 12 Weeks to Adult Fabry Patients

Protocol PB-102-F02 Title: An Extension of Phase 1/2, Open Label, Dose Ranging Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Exploratory Efficacy Parameters of PRX-102 Administered by Intravenous Infusion Every 2 Weeks for 38 Weeks (9 Months) to Adult Fabry Patients

Investigators:

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*Site 16 had no eligible patients for enrollment.

Study Center(s): 13 study centers from 6 countries	
Publication (Reference): Not applicable	
Studied Period (Years): Date of first enrolment: 5Nov2012 Date of last completed: 6Mar2016	**Phase of Development:** Phase 1/2

Objectives: The objectives of study PB-102-F01 were to evaluate the safety, tolerability, pharmacokinetics, immunogenicity and exploratory efficacy parameters of pegunigalsidase alfa (PRX-102) in adult Fabry patients over 3 month (12 weeks) of treatment.

The objectives of study PB-102-F02 were to further evaluate the safety, tolerability, pharmacokinetics, immunogenicity and exploratory efficacy parameters of pegunigalsidase alfa (PRX-102) in adult Fabry patients who successfully completed 12 weeks of treatment with pegunigalsidase alfa (PRX-102) in study PB-102-F01, and continued to receive treatment for an additional 9 months, at the dose assigned to each patient in study PB-102-F01.

Methodology: PB-102-F01 was an open-label, dose ranging study to evaluate the safety, tolerability, pharmacokinetics, immunogenicity and exploratory efficacy parameters of pegunigalsidase alfa (PRX-102) in adult (>18 years of age) Fabry patients. Patients were enrolled into one of three pegunigalsidase alfa (PRX-102) treatment groups (0.2, 1.0 or 2.0 mg/kg; up to 6-8 patients per group) and received intravenous infusions every 2 weeks for 12 weeks (total of 7 infusions). Patients were to receive infusions sequentially and stepwise in order to evaluate tolerability. Initially, at Study PB-102-F01, all infusions were to be given during hospitalization. If the first 4 infusions were well tolerated the treatment continued to be at an outpatient setup at a selected medical center with adequate emergency treatment facilities throughout the rest of PB-102-F01 and PB-102-F02 studies.

Up to 24 adult (males and females) Fabry patients (≥18 yrs) were planned to be enrolled into this study PB-102-F01 with a minimum of 4 males and 2 females per dose cohort. Upon completion of the 12-week treatment period (3 months), patients had the option to enroll in an open-label extension study PB-102-F02 for an additional 9 month treatment period.

Patients who enrolled into the extension study PB-102-F02 were to continue to receive the same dose of pegunigalsidase alfa (PRX-102) they received in study PB-102-F01, as an intravenous infusion every 2 weeks for 38 weeks (9 months).

An analysis to evaluate the exploratory efficacy parameters was performed following a total of 12 months of treatment (completion of both PB-102-F0 and PB-102-F02 studies). These parameters included the change in baseline Gb3 concentrations in renal tissue, LVM, MSSI and cardiac function tests (echocardiography and stress test).

Patients who completed 12 months treatment of pegunigalsidase alfa (PRX-102) were eligible to enter PB-102-F03 for an additional 24 month treatment period which was further amended to a 60 month study duration.

Number of Patients (Planned and Analyzed): Up to 24 adult patients were planned to be enrolled into study PB-102-F01. Nineteen (19) patients were eligible for enrollment. One patient voluntarily withdrew (withdrew consent) from the study prior to receiving any study treatment. Six (6) patients were enrolled in the 0.2 mg/kg treatment group, 9 in the 1.0 mg/kg and 4 in the 2.0 mg/kg treatment groups. Two (2) patients in the 1.0 mg/kg treatment group discontinued from the study, one experienced a hypersensitivity reaction and one was non-compliant. The safety population included 18 patients and the efficacy population included 16 patients. Efficacy was analyzed in patients with classic Fabry disease that included 9 males and one female patients (n=10), the male population (n=9) and female population (n=7).

Diagnosis and Main Criteria for Inclusion: For inclusion into the study, patients are required to fulfill all of the following criteria:

1. Symptomatic adult Fabry patients (≥18 yrs, males and females)
2. Males: plasma and/or leucocyte alpha galactosidase activity (by activity assay) less than lower limit of normal (LLN) in plasma (3.2 nmol/hr/mL) and/or leucocytes (32 nmol/hr/mg/protein)
3. Females: historical genetic test results consistent with Fabry mutations
4. Globotriaosylceramide (Gb3) concentration in urine > 1.5 times upper limit of normal (ULN)
5. Patients who have never received ERT in the past, or patients who have not received ERT in the past 6 months and have a negative anti pegunigalsidase alfa (PRX-102) antibody test
6. eGFR ≥ 60 mL/min/1.73m^2
7. Signed informed consent
8. Female patients and male patients whose partners are of child-bearing potential agree to use a medically acceptable method of contraception, not including the rhythm method

Test Product, Dose and Mode of Administration: Three doses of pegunigalsidase alfa (PRX-102) (0.2, 1.0, 2.0 mg/kg) were administered sequentially. The individual dose for each patient was prepared according to patient's weight and assigned dose and prepared by a pharmacist or nurse at each site. The required amount of enzyme for 0.2 or 1.0 mg/kg infusion was adjusted with normal saline (0.9% NaCl) to a final volume of 150 mL/infusion and for 2.0 mg/kg infusion was adjusted to 350 mL/infusion. The infusion rate could be adjusted according to individual subject's signs and symptoms.

Duration of Treatment: Pegunigalsidase alfa (PRX-102) was administered for 12 weeks in study PB-102-F01 (7 infusions) and 38 weeks in study PB-102-F02 (20 infusions).

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable

Criteria for evaluation:

Efficacy Endpoints: (Exploratory)

- Kidney function assessment:
  - Estimated GFR (eGFR) evaluation.
  - eGFR levels and the annualized slope of eGFR.
  - Spot urine test results: creatinine random urine, total protein random urine, and protein/creatinine ratio.
- Gb3 concentration in Kidney biopsies: using quantitative Barisoni Lipid Inclusion Scoring System (BLISS).
- Plasma Gb3 concentration (mg/mL) and plasma Lyso-Gb3 concentration (ng/mL).
- Cardiac Function by echocardiography and stress test.
- Cardiac MRI
- Short Form Brief Pain Inventory (BPI): Pain severity and pain interference
- Brain MRI: Qualitative assessments regarding evidence of stroke
- Gastrointestinal Symptoms Questionnaire.
- Mainz Severity Score Index (MSSI): Qualitative assessments regarding the sign/symptom in general, neurological, cardiovascular, renal dysfunction.

Safety:

- Adverse events
- Physical examination (changes in vital signs and body weight)
- Concomitant medications
- Laboratory test results
  - Hematology

- Biochemistry
- Urinalysis
- Anti-pegunigalsidase alfa (PRX-102) Antibodies
- Electrocardiogram
- Echocardiogram

- Hypersensitivity reactions

Statistical Methods:

Descriptive statistics for continuous variables, sample size (n), mean and its standard error, standard deviation, median and range are presented; for categorical variables, number and percentage of patients are presented. All of the safety and efficacy summary tables were performed by gender within dose group, dose group and overall. For efficacy, a subgroup analysis of patients with classic Fabry, males and females were conducted as well.

All volunteered, elicited and observed adverse events (AEs) are documented. AEs were coded using the MedDRA dictionary and were displayed by frequency, severity, and relationship for each treatment group.

Summary – Conclusions

Efficacy Results: All 16 patients who completed study PB-102-F01 enrolled into the extension study PB-102-F02. The efficacy analysis included 16 patients (male, 9; female, 7): 6 patients (male, 4; female, 2) each in the 0.2 mg/kg and 1.0 mg/kg treatment groups and 4 (male, 1; female, 3) in the 2.0 mg/kg treatment group. All 16 patients also completed the extension study PB-102-F02. Ten (10) of the 16 patients, 9 males and 1 female (01-F101) met the definition of phenotypic classic Fabry disease.

Pegunigalsidase alfa (PRX-102) PK profiles show that, the enzyme was available throughout the 2-week infusion intervals with a plasma half-life of approximately 80 hours. The PK parameters indicate linear dose-proportionality. T_{max} generally occurred at the end of the infusion or shortly thereafter. The mean values for $t_{1/2}$ were similar at each of the sampling times, indicating no trend for change with duration of treatment. For patients who received 0.2 mg/kg pegunigalsidase alfa (PRX-102) increased inter-subject variability was noted at Months 3 and 6, probably due to development of treatment-induced antidrug antibodies (ADA) in two patients, the variability and mean values for $AUC_{0-\infty}$ observed at Months 3 and 6 returned to levels observed at Day 1 or slightly higher at Month 12, indicating that the ADA impact on the PK parameters was transient. For patients who received 1.0 and 2.0 mg/kg pegunigalsidase alfa (PRX-102), there were increases in mean $t_{1/2}$, $AUC_{0-\infty}$ values with increasing duration of treatment and corresponding decreases in Cl and V_z. Only one patient who received 1.0 mg/kg of pegunigalsidase alfa (PRX-102) had a positive ADA result with low titers and none of the subjects who received 2.0 mg/kg were positive for ADA; thus, there was no effect of ADA on the PK parameters for 1.0 and 2.0 mg/kg treatment groups.

Kidney biopsies of peritubular capillary were analyzed for Gb3 inclusions with randomized blinded scoring using the quantitative BLISS. At Month 6, pegunigalsidase alfa (PRX-102) demonstrated a substantial mean reduction in BLISS score from baseline. Of the 14 patients with available kidney Gb3 biopsies, 12 showed a reduction in BLISS score from baseline at Month 6. Pegunigalsidase alfa (PRX-102) treatment showed a 67.8% mean reduction in BLISS scored for Gb3 in the overall population (n=13), and 84.1% mean reduction in patients with classic Fabry disease (n=8).

Estimated GFR (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. At Month 12, the eGFR results indicate stability in kidney function. At baseline, mean eGFR was 111 mL/min/1·73m^2 and was stable throughout the 1 year treatment with a mean change of -0.8 (± 1.9) mL/min/1·73m^2 for the entire population (n=16) and a mean change of -0.0 (± 2.8) mL/min/1·73m^2 for the classic Fabry disease patients (n=10). A mean

annualized eGFR slope of 0.01(±1.37) mL/min/1.73 m^2/year was observed in 9 out 10 patients with classic Fabry disease (excluding one patient who was exposed intermittently to doxycycline with an important influence in the kidney function).

An overall mean reduction of -22.2% from baseline in plasma Gb3 concentration was observed in 16 patients who received 12 months of treatment of pegunigalsidase alfa and -33.3% from baseline in plasma Gb3 concentration in classic Fabry disease patients (n=9). An overall mean reduction of -48.9% from baseline in plasma Lyso-Gb3 concentration was observed in 16 patients who received 12 months of treatment of pegunigalsidase alfa and -57.6% from baseline in plasma Lyso-Gb3 concentration in classic Fabry disease patients (n=10).

Cardiac MRI results showed that the majority of patients maintained normal cardiac parameters (LVM, LVMI, and EF) throughout the study. No cardiac fibrosis was observed at baseline nor after 12 months of treatment of pegunigalsidase alfa. Cardiac function assessed by echocardiography also concludes the majority of the assessed parameters exhibited stable cardiac function after 12 months of treatment.

There was no evidence of stroke detected in patients' MRIs of the brain at baseline and throughout the study.

After 12 months of treatment; a mean reduction in the total score of MSSI to assess the severity of Fabry disease in general, neurological, cardiovascular, and renal systems showed stable or favorable trends. Similar observations were made in the severity and frequency of abdominal pain and diarrhea in the Gastrointestinal Symptoms Assessment (GSA). The reduction in pain severity score and pain interference score with the Brief Pain Inventory (BPI) scale indicated improvement in general activity, mood, walking, working, sleeping, and enjoyment of life and other people. Similar efficacy results were observed in patients with Fabry disease or classic Fabry disease.

Safety Results: Overall, PRX 102 was found safe and well tolerated with the majority of adverse events mild and moderate.

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 highest titers of 4633 and 2198, one of the patients also had an IgG at the baseline visit (titer <60), both patients were also positive for neutralizing antibody. One (1) patient from the 1.0 mg/kg treatment group had highest titers of 237. Overall, low incidence of treatment induced ADA with reversible and transient effect on PK was observed. ADA response was transient and tolerization was observed.

Similar safety results were observed in the efficacy population

Conclusion: Pegunigalsidase alfa (PRX-102) is a PEGylated recombinant plant cell expressed, chemically modified human alpha-Galactosidase-A enzyme.

These two Phase I/II studies included 18 adult naïve patients (11 males and 7 females) with Fabry disease; three doses of 0.2 mg/kg, 1.0 mg/kg and 2.0 mg/kg were administered intravenously every two weeks. Sixteen (16) patients completed 12 months of treatment that included 6-8 patients in each dose group who were further enrolled into Study PB-102-F03. Two patients from the 1.0 mg/kg group discontinued from the study: one due to investigator decision of noncompliance and one due to a hypersensitivity event.

Study results demonstrated that all patients exhibited stable renal and cardiac function with favorable trends after receiving 12 months of pegunigalsidase alfa. An overall mean reduction of Gb3 inclusions in kidney peritubular capillaries using BLISS scoring was observed after 6 months of treatment with pegunigalsidase alfa and reduction from baseline in plasma Gb3 and Lyso-Gb3.

After 12 months of treatment of pegunigalsidase alfa, the mean total score of the MSSI, assessing the severity of Fabry disease in general, neurological, cardiovascular and renal systems, was reduced. A stable or favorable trend was observed in the severity and frequency of abdominal pain and frequency of

diarrhea as tabulated by the GSA scale. Further, pain severity and interference scores as assessed by the BPI scale indicated improvement in general activity, mood, walking, working, sleeping, and enjoyment of life and other people.

The PK results for all three dose levels demonstrated that the enzyme was found to be available throughout the 2-week intervals with a plasma half-life of approximately 80 hours. The mean values for $AUC_{0-\infty}$ increased with increasing dose on Day 1 and at Months 3, 6, and 12.

One year of treatment showed that pegunigalsidase alfa is well tolerated with a favorable safety profile; the majority of adverse events were mild or moderate in severity and a low rate (18.8%) of treatment-induced antibody formation. No correlation between ADA positivity with safety and/or efficacy was found.