CLINICAL STUDY PROTOCOL

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

Protocol Number: PB-102-F20

Investigational Product:	Pegunigalsidase alfa (PRX-102) a recombinant human alpha galactosidase-A
Indication:	PRX-102 is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (alpha galactosidase deficiency)
Phase:	3
Protocol Version:	Version 1, January 26, 2016 Version 2, April 5, 2016 Version 3, May 26, 2016 Version 4, September 29, 2016 Version 5, July 14, 2017
Name and Affiliation of Principal Investigator:	A list of the Principal Investigators is maintained in the trial master file
Name and Address of Sponsor:	Protalix Ltd. 2 Snunit Street Science Park Carmiel 20100, Israel
GCP Statement:	This study will be performed in compliance with GCP, including the archiving of essential documents.

1 SYNOPSIS

TITLE: A Randomized, Double blind, Active Control Study of the Safety and Efficacy of PRX-102 compared to Agalsidase Beta on Renal Function in Patients with Fabry Disease Previously Treated With Agalsidase Beta
INVESTIGATIONAL PRODUCT: Pegunigalsidase alfa (PRX-102), recombinant human alpha galactosidase-A
INDICATION: PRX-102 is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (alpha galactosidase deficiency)
PHASE OF DEVELOPMENT: 3
INVESTIGATIONAL SITES/LOCATIONS: Multicenter
OBJECTIVES: To evaluate the safety and efficacy of PRX-102 compared to agalsidase beta in Fabry disease patients with impaired renal function
STUDY DESIGN: This is a randomized, double blind, active control study of PRX-102 in Fabry disease patients with impaired renal function. Patients treated for approximately 1 year with agalsidase beta and on a stable dose for at least 6 months will be screened and then randomized to continue treatment with 1 mg/kg agalsidase beta or to treatment with 1 mg/kg of PRX-102. The identity of the enzyme will be blinded to the patient and the investigator. Patients will receive intravenous infusions every two weeks. No more than 50% of the patients enrolled will be female Patients will be randomized in a 2:1 ratio of PRX-102 to agalsidase beta. Randomization will be stratified by urine protein to creatinine ratio (UPCR) of < or ≥ 1 g/g (1 mg/mg or 1000 mg/g) by spot urine sample. At the time of randomization, premedication, if used for the agalsidase beta infusions before study entry will be continued and gradually tapered at the investigator's discretion during the first 3 months of the study. The first infusions of blinded agalsidase beta or PRX-102 will be administered under controlled conditions at the investigation site. The patient can receive their infusions as part of a home setup once the investigator and Sponsor Medical Director agree that it is safe to do so. An interim analysis will be conducted at 12 months and the final analysis at 24 months of treatment.
NUMBER OF SUBJECTS (PLANNED): 78 (PRX-102 n=52 and agalsidase beta

n=26) with an assumption of a 15% dropout

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Key inclusion criteria:

Eligible subjects must fulfill the following inclusion criteria:

1. Symptomatic adult Fabry disease patients, age 18-60 years
2. Males: Plasma and/or leucocyte alpha galactosidase activity (by activity assay) less than 30% mean normal levels and one or more of the characteristic features of Fabry disease
    i. neuropathic pain
    ii. cornea verticillata
    iii. clustered angiokeratoma
3. Females:
    a. historical genetic test results consistent with Fabry pathogenic mutation and one or more of the described characteristic features of Fabry disease:
        i. neuropathic pain,
        ii. cornea verticillata,
        iii. clustered angiokeratoma
    b. or in the case of novel mutations a first degree male family member with Fabry disease with the same mutation, and one or more of the characteristic features of Fabry disease
        i. neuropathic pain,
        ii. cornea verticillata,
        iii. clustered angiokeratoma
4. Screening eGFR by CKD-EPI equation 40 to 120 mL/min/1.73 m^2
5. Linear negative slope of eGFR of $\geq$ 2 mL/min/1.73 m^2 based on at least 3 serum creatinine values over approximately 1 year (range of 9 to 18 months, including the value obtained at the screening visit)
6. Treatment with a dose of 1 mg/kg agalsidase beta per infusion every 2 weeks for at least one year and at least 80% of 13 (10.4) mg/kg total dose over the last 6 months
7. Female patients and male patients whose co-partners are of child-bearing potential agree to use a medically accepted method of contraception, not including the rhythm method.

Key exclusion criteria:

The presence of any of the following excludes a subject from study enrollment:

1. History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase beta
2. Known non-pathogenic Fabry mutations
3. History of renal dialysis or transplantation
4. History of acute kidney injury in the 12 months prior to screening, including

specific kidney diseases (e.g., acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (e.g, ischemia, toxic injury); as well as extrarenal pathology (e.g., prerenal azotemia, and acute postrenal obstructive nephropathy)

5. Patient with a screening eGFR value between 91-120 mL/min/1.73 m^2, having an historical eGFR value higher than 120 mL/min/1.73 m^2 (during 9 to 18 months before screening)
6. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated or dose changed in the 4 weeks prior to screening
7. Urine protein to creatinine ratio (UPCR) > 0.5 g/g (0.5 mg/mg or 500 mg/g) and not treated with an ACE inhibitor or ARB
8. Cardiovascular event (myocardial infarction, unstable angina) in the 6 month period before randomization
9. Congestive heart failure NYHA Class IV
10. Cerebrovascular event (stroke, transient ischemic attack) in the 6 month period before randomization
11. Known history of hypersensitivity to Gadolinium contrast agent that is not managed by the use of premedication
12. Female subjects who are pregnant, planning to become pregnant during the study, or are breastfeeding
13. Presence of any medical, emotional, behavioral or psychological condition that, in the judgment of the Investigator and/or Medical Director, would interfere with the patient's compliance with the requirements of the study

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION: Pegunigalsidase alfa (PRX-102) 1 mg/kg or agalsidase beta 1 mg/kg, intravenously over 3 hours, every 2 weeks.

After the first 3 months of treatment infusion time may be reduced gradually to 1.5 hours pending patient tolerability, PI evaluation, and Medical Monitor/Director approval.

DURATION OF TREATMENT: 24 months (53 infusions), with the option to be enrolled in an open-label extension study upon completion of the study. Agalsidase beta patients are eligible for treatment in the extension study with pegunigalsidase alfa (PRX-102) 1 mg/kg.

DISCONTINUATION FROM TREATMENT:

Reasons for permanent discontinuation include the following:

- The subject experiences two or more Grade 3 toxicities or one or more Grade 4 toxicity considered by the investigator associated with PRX-102 or agalsidase beta treatment (CTCAE v. 4.03, 2010)
- The subject experiences progressive hypersensitivity or severe hypersensitivity that is

not allayed with pre-treatment
- The subject requests to discontinue treatment
- The Investigator feels that it is not in the best interest of the subject to continue treatment and/or if the investigator believes that the subject can no longer be compliant with the requirements of the study

EFFICACY ENDPOINTS:

The primary efficacy parameter is the comparison of the mean annualized change (slope) in estimated glomerular filtration rate ($eGFR_{CKD-EPI}$) between treatment groups.

Secondary efficacy endpoints:

- Left Ventricular Mass Index (g/m^2) by MRI
- Plasma Lyso-Gb3
- Plasma Gb3
- Urine Lyso-Gb3
- Protein/Creatinine ratio spot urine test
- Frequency of pain medication use
- Exercise tolerance (Stress Test)
- Short Form Brief Pain Inventory (BPI)
- Mainz Severity Score Index (MSSI)
- Quality of life EQ-5D-5L

Pharmacokinetics (PK):

For 30 subjects in the study, blood samples will be taken for PK analysis on Day 1 and at 6, 12 and 24 months of treatment. The following PK parameters will be derived from the plasma concentration versus time profiles to determine the pharmacokinetics of the study drug: C_{max}, T_{max}, AUC_{0-t}, $t_{1/2}$, and $AUC_{0-\infty}$. Blood samples will be drawn at the following time points: pre-infusion (baseline); 0.5 and 1 hour after the beginning of the infusion; at the end of the infusion, at 0.5±0.05, 1±0.25, 2±0.25, 4±0.25, 8±0.25, 24 ±0.5, 48±3, and 96±3) hours post-infusion and at 14±3 days post-infusion.

SAFETY ENDPOINTS:

Changes from baseline in:

- Clinical laboratory tests
- Physical examination
- Assessment of the injection site
- ECG
- Treatment-emergent adverse events
- Ability to taper off infusion pre-medication throughout the first 3 months of the study
- Requirement for use of pre-medication overall to manage infusion reactions

- Treatment-emergent anti-PRX-102 antibodies
- Treatment-emergent anti-agalsidase beta antibodies

STATISTICAL ANALYSIS:

Sample Size Rational

This orphan indication allows for a small number of patients, given the rarity of the disease and the difficulties in allocating patients for clinical trials. With a total of at least 66 patients at 24 months, randomized 2:1 to PRX-102:agalsidase beta, there is 80% power to detect a change of 1.1 mL/min/1.73 m^2/year using a two-sample t-test (alpha=0.049, 2-sided test) to evaluate the primary outcome of an annualized eGFR slope after 24 months. This calculation is based on the assumption that the standard deviation for the annualized eGFR slope is 1.5 mL/min/1.73 m^2/year in each treatment group. For this analysis the null hypothesis is that the difference in annualized eGFR slope between the treatment groups is 0 versus an alternative hypothesis that the difference in annualized slopes between treatment groups is not 0. A 30% improvement in the slope of eGFR would be considered a clinically relevant improvement. Based on previous research, the annualized eGFR slope in patients treated with agalsidase beta is -3.0 mL/min/1.73 m^2/year, and under the null hypothesis that is the slope assumed for both groups. Thus, a 1.1 mL/min/1.73 m^2/year reduction in the rate of decline in renal function (improvement) is anticipated to be equal to an annualized eGFR slope with PRX-102 of -1.9 mL/min/1.73 m^2/year. This sample size calculation was made using a group sequential testing procedure that used the O'Brien Fleming spending function to determine test boundaries. There is one interim analysis (see below) scheduled at the halfway (1 year) time point and will have a nominal superiority alpha level of 0.003 whereas the final analysis at 2 years will have a nominal alpha of 0.049. Since it is anticipated that some patients may not be available for any follow-up (*i.e.*, not have 24 months of follow up), 78 patients will be enrolled, with 52 randomized to PRX-102 and 26 randomized to agalsidase beta. With a potential 15% total dropout rate this would result in 44 PRX-102 and 22 agalsidase beta patients at 24 months. These power/sample size calculations were performed using PASS-13 Group Sequential Tests for Two Means procedure (Hintze, J. (2014). PASS 13. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

In addition to the primary efficacy comparison described above, a series of secondary efficacy analyses will be performed to compare groups on the secondary outcomes of interest. These analyses will be described in the statistical analysis plan (SAP).

Interim Analysis

An interim analysis for non-inferiority will be performed for purposes of submitting a marketing application to the European Medicines Agency. Consistent with the power/sample size calculation provided for the Primary 24-month Superiority

calculation described above, the following 12-month interim analysis to test for Non-inferiority will be performed. Specifically, with a total of at least 66 patients included, there is 80% power to detect whether the difference in mean annualized change in eGFR in PRX-102 is non-inferior to the rate in agalsidase beta using a 1-sided (0.025) two sample t-test. For this test the non-inferior margin is 3.0 mL/min/1.73 m^2/year and the true difference between groups is assumed to be 1.1 mL/min/1.73 m^2/year with standard deviations of the slopes being 1.5 in both groups. With the proposed sample size, non-inferiority margin and expected differences in slope, the standard deviation could be as large as 3.4 and still maintain adequate power (greater than 80%) for non-inferiority.

DOCUMENT APPROVAL

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

SPONSOR REPRESENTATIVE

July 14, 2017

_____ _____

Signature Date

PRINCIPAL INVESTIGATOR

_____ _____

Signature Date

Print Name: _____

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2 LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
AE	Adverse event
Alpha-GAL-A	Alpha galactosidase-A
ARB	Angiotensin receptor blocker
AUC_0-t	Area under the concentration-time curve from baseline to a specified time (t)
AUC_0-∞	Area under the concentration-time curve from baseline to infinity
BPI	Brief pain inventory
CHO	Chinese hamster ovary
CKD	Chronic kidney disease
C_{max}	Maximum concentration observed
CRF	Case report form
CT	Computed tomography
EC	Ethics Committee
ECG	Electrocardiography
eGFR	Estimated glomerular filtration rate
ERT	Enzyme replacement therapy
Gb3	Globotriaosylceramide
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IC	Informed consent
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
LLN	Lower limit of normal
LVH	Lt. ventricular hypertrophy
LVM	Lt. ventricular mass
Lyso-Gb3	Globotriaosylsphingosine
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
PK	Pharmacokinetic(s)
PP	Per Protocol
PT	Prothrombin time
PTT	Partial Thromboplastin time
SAE	Serious adverse event
TIA	Transient ischaemic attack
$t_{1/2}$	Time at which the concentration is half of the maximum value (C_{max})
T_{max}	Time at which the concentration is the maximum value (C_{max})

3 ETHICAL CONDUCT OF THE STUDY AND REGULATORY REQUIREMENTS

3.1 Institutional Review Board (IRB)

An Institutional Review Board (IRB) or Ethics Committee (EC) will review the study protocol and any amendments. The IRB or EC will also review the informed consent forms, their updates (if any), and any written materials given to the subjects. A list of all IRBs and ECs and contact information will be included in the study report.

3.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, in compliance with the approved protocol, GCP and applicable regulatory requirements.

3.3 Subject Information and Consent

The investigator will obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the study that are relevant to the subject's decision to participate. The consent forms must be signed and dated by the subject before he/she is exposed to any protocol-specific procedure.

The investigator will explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify.

The subject will receive a copy of the subject information and the signed informed consent forms.

The subject will be informed if information becomes available that may be relevant to his/her willingness to continue participation in the study.

Each subject will be informed that a monitor or a health authority inspector, in accordance with applicable regulatory requirements, may review the portions of their source records and source data related to the study. Data protection and confidentiality will be handled in compliance with local laws.

4 INTRODUCTION

Fabry disease is a progressive lysosomal storage disease that is seriously debilitating and ultimately life-threatening. It is caused by X-linked deficiency of the enzyme alpha galactosidase-A (alpha-GAL-A), and affects both males and females. The disease is characterized by subnormal or absent activity of alpha-GAL-A. Clinical onset of the disease typically occurs during childhood or adolescence (Schaefer et al. 2009) and will progress to end-stage renal disease, cardiac complications and cerebrovascular problems in the fourth or fifth decade of life (Wilcox et al. 2008). Although Fabry disease is a X-linked disorder, females are also affected and develop manifestations of the disease due to lack of cross-correction between cells with normal alpha-GAL-A activity (mutated X chromosome is inactivated) and cells with enzyme deficiency (non-mutated X chromosome is inactivated). The clinical abnormalities in females are more variable, and of later onset compared to males (Schiffmann 2009).

Fabry disease is regarded as a rare disease and it is estimated that 1 in 40,000 males has the disease, whereas the estimated prevalence in the general population is 1 in 117,000 (Meikle et al. 1999).

Alpha-GAL-A is a lysosomal enzyme which primarily catalyses the hydrolysis of the glycolipid globotriaosylceramide (Gb3) to galactose and lactosylceramide. Fabry disease is characterized by massive storage of Gb3, predominantly in cells of the vascular system, cardiomyocytes, neuronal cells and kidney podocytes. Progressive accumulation of Gb3, and related lipids, leads to impaired tissue and organ function. The ultimate consequence of glycolipid deposition in the vasculature and other tissues is end-organ failure, particularly the kidney, but also heart and cerebrovascular system (Schiffmann 2009). In addition, involvement of the central, peripheral and autonomic nervous systems result in episodes of pain and impaired peripheral sensation. Vascular changes in the skin also result in angiokeratomas (Hoffmann et al. 2009). The mechanism by which alpha-GAL-A deficiency and glycolipid accumulation cause such a wide variety of complications is not well understood. Based on the pathology of Fabry disease, the ongoing accumulation of alpha-*D*-galactosyl moieties, particularly of Gb3, appears to be a chronic toxicity state (Schiffmann 2009). A recent study by Aerts et al. reported that globotriaosylsphingosine (lysoGb3), a Gb3 metabolite, is dramatically increased in the plasma of male Fabry patients, and plasma and tissues of Fabry mice, and may have an important role in the pathogenesis of Fabry disease (Aerts et al. 2008). Increased levels of lysoGb3 occur also in symptomatic Fabry females (Van Breemen et al. 2011).

As Fabry disease is an X-linked disorder, the prevalence of the mutation is predicted to be two times higher in women than in men. There is considerable variation in phenotype in heterozygous females. However, despite the X-linked nature of the disease, heterozygous and therefore tissue-mosaic females can be as severely affected by Fabry disease as hemizygous males, experiencing progressive, multi-organ involvement, reduced quality of life and reduced life expectancy. Case-finding studies have reported mutations that are known to be associated with Fabry disease in 0.3–2.4% of women who had unexplained stroke, hypertrophic cardiomyopathy, or renal failure requiring haemodialysis. A recent study by Hughes et al, that compared men and women with Fabry disease, using data from FOS—the Fabry Outcome Survey, showed no significant differences between men and women for most clinical features

evaluated. Overall, both sexes responded to enzyme replacement treatment in a similar way (Hughes et al. 2011).

Most men and some women with Fabry disease exhibit deterioration of renal function (Schiffmann et al., 2009; Wanner et al., 2010; Ortiz et al., 2008), and many eventually develop end-stage renal disease (ESRD) (Ortiz et al., 2010; Mignani et al., 2010). Although progression to ESRD is much less common in women, the median age at which patients reached ESRD (38 years) was the same in both genders (Ortiz et al., 2010; Mignani et al., 2010). Studies of untreated patients with Fabry disease have identified proteinuria as a major risk factor for renal disease progression (Schiffmann et al., 2009; Wanner et al., 2010).

Enzyme replacement therapy (ERT), by exogenous administration of purified recombinant enzyme, is nowadays among the most successfully employed drug treatments for lysosomal storage disorders. The first disorder for which this treatment modality has proven to be effective is type 1 Gaucher disease (Barton et al. 1991; Hollak et al. 1995). This success has paved the way for the development of ERT for other lysosomal storage disorders, including Fabry disease.

Recombinant human alpha-GAL-A has the ability to restore enzyme function in patients, and currently two ERTs using this enzyme are commercially available; agalsidase alpha (Replagal), that was approved in Europe, and agalsidase beta (Fabrazyme), that was approved both in Europe and in the United States. Both recombinant enzymes are comparable in their properties and differ only slightly in glycan composition (Blom et al. 2003). They are produced using different protein expression systems and are administered at different doses. Fabrazyme is produced in Chinese Hamster Ovary (CHO) cells and is administered by IV infusion every 2 weeks at a dose of 1 mg/kg. Replagal is produced in a human cell line (stably expressed in human foreskin fibroblast) (Schiffmann et al. 2000), and is administrated by IV infusion every 2 weeks at a dose of 0.2 mg/kg. Both products have shown their efficacy in clinical studies with regard to clearance of Gb3 from plasma, kidney cells (such as capillary endothelial cells, glomerular endothelial cells, noncapillary endothelial cells and noncapillary smooth muscle cells), and capillary endothelial cells of the cardiac and skin (Eng & Guffon et al. 2001; Germain et al. 2007; Schaefer et al. 2009). In addition, ERT with both products leads to improvement in quality of life, reduction or stabilization of cardiac mass, preservation of renal function, and slowing down the decline of glomerular function (Wilcox et al. 2004; Schiffmann et al. 2006; Germain et al. 2007; Schiffmann 2009). Although these findings are encouraging, the clinical effects of the current treatment of Fabry patients are not as robust as anticipated and show only limited clinical improvement (Schaefer et al. 2009; Lidove et al. 2010; El Dib et al. 2011).

In clinical studies, agalsidase beta provided long-term stabilization of renal function in patients with mild renal involvement (serum creatinine <2.2 mg/dL) (Germain et al., 2007) and delayed time to renal, cardiovascular and cerebrovascular events in patients with more advanced Fabry disease (Banikazemi et al., 2007). Agalsidase beta treatment did not stabilize renal function in patients with severe renal involvement (*i.e.*, proteinuria > 1 g/24 h or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m2) at the time treatment was started (Germain et al., 2007: Banikazemi et al., 2007).

One of the major factors responsible for the limited efficacy of current treatment is the presence of irreversible organ damage. Another factor that may contribute to this is the characteristics of

the current ERTs (such as short circulatory half-life and dose regimens) which seem to be insufficient in preventing the chronic toxic effect of Gb3. One way to improve enzyme bioavailability maybe to extend circulation residence and tissue half-life. A third factor, which may influence the treatment outcome, is the induction of antibodies towards the recombinant proteins (Hollak et al. 2009). Emergence of antibodies with *in vivo* neutralizing capacities is frequently encountered in treated Fabry disease patients, resulting in inhibition of enzyme activity and adversely affecting Gb3 clearance (Hollak et al. 2009). In early clinical studies, 25 to 88% (Schiffmann et al. 2006; Eng & Banikazemi et al. 2001; Eng & Guffon et al. 2001) of male patients developed these IgG antibodies within the first 6 months of treatment. Regarding treatment outcome, it was shown that antibodies against alpha-GAL-A interfere with the clearance of Gb3 from plasma, urine (Linthorst et al. 2004; Vedder et al. 2008), and from the tissue (Benichou et al. 2009). The cross-reactivity of alpha-GAL-A antibodies suggests that it is unlikely that switching from one recombinant protein to the other may prevent the immune response and related effects (Linthorst et al. 2004; Hollak et al. 2009). Currently, administration of a higher dose of the recombinant enzyme is an effective way to overcome the negative effect of the neutralizing antibodies by providing excess enzyme (Vedder et al. 2008; Hollak et al. 2009). However, this approach is not considered a long-term solution.

Protalix has developed PRX-102, a chemically modified recombinant human alpha-GAL-A expressed in plant cell culture. As a result of this modification, PRX-102 exhibits more stabilized homo dimer with active enzyme over longer period, extended circulation residence time and enhanced bioavailability of the enzyme relative to the commercial drug. Therefore, PRX-102 provides continuous presence of enzyme over the 2 week dosing interval.

Studies have shown that human alpha-GAL-A is a non-covalently bound homodimeric glycoprotein (Garman et al. 2004) and that the dimerization is important for the enzymatic activity and stability of the enzyme (Bishop et al. 1988). The chemical modification of PRX-102 utilises the reagent bis-NHS-PEG and renders PEGylated protein subunits the majority of which are crosslinked into homodimers thus, reinforce the homodimeric structure, which is crucial for the enzymatic activity of this enzyme. In addition, the PEGylation modification may have an additive value through increasing drug retention time in blood and bioavailability (Veronese et al. 2005; Veronese et al. 2008). Preliminary non-clinical data shows that this modification improves PRX-102 stability *in vitro* under lysosomal and plasma conditions, and extends circulation residence and bioavailability *in vivo*, probably due to stabilization of its quaternary structure. Therefore, the modifications in PRX-102 have the potential to improve the efficacy of ERT.

PRX-102 has been studied in Fabry disease patients in a Phase 1/2 study PB-102-F01 for 12 weeks and continued in extension studies for long-term treatment. The extension studies are ongoing. The results of the study are summarized in the Investigator's Brochure. At the time of database freeze on 31Jul2015, six (6) patients in the 0.2 mg/kg treatment group completed 12 months of treatment, six (6) in the 1.0 mg/kg treatment group completed 6 months of treatment and four (4) in the 2.0 mg/kg completed 3 months of treatment.

The interim efficacy analysis results demonstrated that all patients exhibited stable cardiac and renal function with favorable trends after receiving six months of PRX-102. Gb3 inclusions in kidney peritubular capillaries were substantially reduced after 6 months of treatment with both

0.2 and 1.0 mg/kg doses. A mean reduction was observed in the total score of the Mainz Severity Score Index (MSSI) for the severity of Fabry disease in general, neurological, cardiovascular and renal systems; a stable or favorable trend was observed in the severity and frequency of abdominal pain, and frequency of diarrhea in Gastrointestinal Symptoms Assessment (GSA); and the reduction in pain severity score and pain interference score with the Brief Pain Inventory (BPI) scale indicates an improvement in general activity, walking, working, sleeping, enjoyment of life and other people.

PRX-102 has enhanced pharmacokinetic properties including a half-life (T½) of approximately 70 hours, and AUC of approximately 400,000 ng/mL*hour for the 1.0 mg/kg dose after one day of treatment (Day 1), which are believed to be the result of the covalent cross-linking to make PRX-102 enzyme a more stable homo-dimer.

The most commonly experienced AEs were fatigue in 6 patients, and nausea and vomiting each in 5 patients. The most commonly experienced AEs that were considered possibly related to the treatment were nausea in 3 patients, chest discomfort and fatigue each in 2 patients.

Two patients each experienced an SAE. One patient experienced a Grade 3 hypersensitivity related serious adverse event of bronchospasm. The second patient experienced renal hematoma following kidney biopsy and was not considered related to the treatment.

Currently, the safety results of the one completed and two ongoing studies showed that PRX-102 is well tolerated with a favorable safety profile, the majority of adverse events being mild and moderate in severity and a low rate of treatment induced antibody formation.

In view of the data it is concluded that dosing of PRX-102 at 1.0 mg/kg every 2 weeks offers the optimal treatment regimen for attenuating disease progression.

5 STUDY OBJECTIVES

The objective of this study is to evaluate the safety and efficacy of PRX-102 compared to agalsidase beta in adult Fabry disease patients with impaired renal function.

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan – Description

The study will be a randomized, double blind, active-control study of the efficacy and safety of PRX-102 compared to agalsidase beta in adult Fabry disease patients with impaired renal function under treatment already with agalsidase beta for at least a year. Patient age will be 18 to 60 years. The estimated glomerular filtration rate (eGFR) using the CKD-EPI equation will be 40 to 120 mL/min/1.73 m^2 and evidence of renal disease progression of at least 2 mL/min/1.73 m^2/year.

Patients will receive intravenous infusions of PRX-102 1 mg/kg or agalsidase beta 1 mg/kg every two weeks. Infusion duration will initially be 3 hours, but may be decreased gradually after establishment of tolerability by agreement of the investigator and Protalix Medical Director.

Efficacy will be determined by the slope of eGFR over the course of the study. Two analyses of efficacy will be performed – at 12 and 24 months of treatment. For regulatory purposes, demonstration of non-inferiority of PRX-102 compared to agalsidase beta at 12 months for submission of MAA to the European Medicines Agency and superiority at 24 months for FDA BLA submission will be considered trial success.

At the end of the study patients may be offered to continue to an extension open label study; patients on the agalsidase beta arm will be offered to move to PRX-102 1 mg/kg every 2 weeks.

6.2 Discussion of Study Design

Agalsidase beta has shown limited success in preventing the progression of renal function deterioration. Based on the differences in PRX-102 pharmacokinetics compared to agalsidase beta, there is the potential that PRX-102 will be demonstrated to be clinically superior to agalsidase beta when administered every 2 weeks. Therefore, a head-to-head comparison of the two products in Fabry disease patients who are at risk of renal deterioration is the appropriate study design to demonstrate whether it is superior or non-inferior. Demonstration of non-inferiority will be a successful study, particularly if there is a better safety profile.

PRX-102 and agalsidase beta are different products and immunogenicity and hypersensitivity may be different between the products. Pre-medication to prevent adverse reactions during infusion is administered in some patients receiving agalsidase beta. Because the requirements for pre-medication may be different between the two products and to maintain blinding, pre-medication will be tapered off, as tolerated, over the initial 3 months of infusions under careful observation. Pre-medication to prevent infusion reactions can be maintained or re-introduced as required.

Males and females with phenotypically classic Fabry disease will be included in the study to maximize the homogeneity of the patient population.

No more than 50% of the patients enrolled will be female.

Selection of Study Population

6.2.1 Inclusion Criteria

The subjects must fulfil the following inclusion criteria:

1. Symptomatic adult Fabry disease patients, age 18-60 years
2. Males:
   plasma and/or leucocyte alpha galactosidase activity (by activity assay) less than 30% mean normal levels and one or more of the characteristic features of Fabry disease
   i. neuropathic pain
   ii. cornea verticillata
   iii. clustered angiokeratoma
3. Females:
   a. historical genetic test results consistent with Fabry pathogenic mutation One or more of the described characteristic features of Fabry disease:
      i. neuropathic pain,
      ii. cornea verticillata,
      iii. clustered angiokeratoma
   b. or in the case of novel mutations a first degree male family member with Fabry disease with the same mutation, and one or more of the characteristic features of Fabry disease
      i. neuropathic pain,
      ii. cornea verticillata,
      iii. clustered angiokeratoma
4. Screening eGFR by CKD-EPI equation 40 to 120 mL/min/1.73 m^2
5. Linear negative slope of eGFR of $\geq$ 2 mL/min/1.73 m^2/year based on at least 3 serum creatinine values over approximately one year (range of 9 to 18 months including the value obtained at the screening visit)
6. Treatment with a dose of 1 mg/kg agalsidase beta per infusion every 2 weeks for at least one year and at least 80% of 13 (10.4) mg/kg total dose over the last 6 months
7. Female patients and male patients whose co-partners are of child-bearing potential agree to use a medically accepted method of contraception, not including the rhythm method.

6.2.2 Exclusion Criteria

The presence of any of the following excludes a subject from study enrollment:

1. History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase beta
2. Known non-pathogenic Fabry mutations (polymorphism)
3. History of renal dialysis or transplantation
4. History of acute kidney injury in the 12 months prior to screening, including specific kidney diseases (e.g., acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (e.g., ischemia, toxic injury); as well as extrarenal pathology (e.g., prerenal azotemia, and acute postrenal obstructive nephropathy)

5. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated or dose changed in the 4 weeks prior to screening
6. Patient with a screening eGFR value of 91-120 mL/min/1.73 m^2, having an historical eGFR value higher than 120 mL/min/1.73 m^2 (during 9 to 18 months before screening)
7. Urine protein to creatinine ratio (UPCR) > 0.5 g/g (0.5 mg/mg or 500 mg/g) and not treated with an ACE inhibitor or ARB
8. Cardiovascular event (myocardial infarction, unstable angina) in the 6 month period before randomization
9. Congestive heart failure NYHA Class IV
10. Cerebrovascular event (stroke, transient ischemic attack) in the 6 month period before randomization
11. Known history of hypersensitivity to Gadolinium contrast agent that is not managed by the use of premedication
12. Female subjects who are pregnant, planning to become pregnant during the study, or are breastfeeding
13. Presence of any medical, emotional, behavioral or psychological condition that, in the judgment of the Investigator and/or Medical Director, would interfere with the patient's compliance with the requirements of the study

6.2.3 Re-screening of Subjects

A subject that fails screening based on Inclusion Criteria #4 and/or #5 (eGFR range and/or slope) may be re-tested for serum creatinine with cystatin C within a period of 2 months pending the approval of the Protalix Medical Director. In those occasions, the patient will maintain same screening number with no need to perform additional evaluations.

6.2.4 Removal of Subjects from Therapy or Assessment

Reasons for permanent discontinuation include the following:

- The subject experiences two or more Grade 3 toxicities or one or more Grade 4 toxicity considered by the investigator associated with PRX-102 or agalsidase beta treatment (CTCAE v. 4.03, 2010)
- The subject experiences progressive hypersensitivity or severe hypersensitivity that is not allayed with pre-treatment
- The subject requests to discontinue treatment
- The Investigator feels that it is not in the best interest of the subject to continue treatment and/or if the investigator believes that the subject can no longer be compliant with the requirements of the study

For any discontinuation, the Investigator will obtain all the required details and document the date and the main reason for the premature termination. If the reason for discontinuation is an adverse event, the specific event or the main laboratory abnormality will be recorded in the eCRF. The Investigator will make thorough efforts to document the outcome. The Investigator will attempt to continue to follow the subject for the full duration of the study or at least for 90

days following discontinuation. If circumstances prevent the subject from completing all visits, every attempt will be made to complete all procedures listed in Section 9 for Visit 53.

7 STUDY PRODUCT

7.1 Study Medication Supply

Protalix will provide PRX-102 and agalsidase beta to the sites as needed

7.2 Description and Formulation of Study Product

PRX-102 is a purified recombinant, plant cell-expressed chemically modified human alpha galactosidase, which is described in detail in the Investigator's Brochure.

Each vial contains 10.5 ml of the following contents in liquid form:

20 mg PRX-102 (2mg/ml)
0.7% NaCl
25-30 mM Sodium Citrate (pH 5.7 - 6.3).

7.3 Description and Formulation of Comparator Product

Fabrazyme is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with Sterile Water for Injection, USP to yield a concentration of 5 mg/ml; and then further diluted with 0.9% Sodium Chloride Injection, USP for intravenous infusion. Single use vials are available in 35 mg and 5 mg dosages.

7.4 Study drug dosage and preparation

Two treatment groups will be evaluated in this study:

1. PRX-102 1 mg/kg; the individual dose for each patient will be prepared according to the patient's weight.

2. Agalsidase beta will be administered at 1 mg/kg dose according to the patient's weight.

In both treatment groups the drug dosage will be adjusted to patient weight obtained at Visits 14, 27, and 40 if the weight changes by 25% from the previous adjustment

Each dose will be prepared by an un-blinded pharmacist or nurse at each site.

The required amount of either enzyme will be adjusted with normal saline (0.9% NaCl) to a final volume of:

150 mL/infusion, for patients weighting up to 70 Kg

250 mL/infusion, for patients weighting between 70 Kg-100Kg

500 ml/infusion for patients weighting above 100 Kg

The infusion volume will be recalculated, only if dosage adjustment was performed.

7.5 Study Drug Administration

Study drug and agalsidase beta will be administered by intravenous infusion over 3 hours (0.83, 1.39 or 2.78 mL/min for 150, 250 and 500 mL volumes, respectively). After 3 months of infusions, if the patient is tolerating the infusions well, the infusion time may be reduced gradually to 1.5 hours based on investigator evaluation and Protalix Medical Director approval.

At any time the infusion rate may be adjusted according to individual subject's signs and symptoms (see Appendix 2).

7.6 Packaging and Labeling

The study drug product is packed in vials containing 20 mg PRX-102 (2mg/ml), 0.7% NaCl and 25-30 mM Sodium Citrate (pH 5.7 - 6.3).

It is presented as a liquid stored in 15 ml clear injection glass vials (Müller + Müller-Joh. GmbH + Co, Germany). Grey rubber stoppers (formulation 4432/50/Grey) used for closure (West Pharmaceutical Services Duetschland GmbH & Co KG).

Agalsidase beta is packed in vials containing: Lyophilized powder for reconstitution with Sterile Water for Injection, USP to yield 5 mg/mL. Available as 35 mg or 5 mg single-use vials.

The template labels are in Appendix 1.

7.7 Conditions for Storage and Use

The products are stored at 2-8°C (36-46°F).

7.8 Dispensing, Compliance and Accountability

Protalix will provide drug accountability forms to assist the pharmacist in maintaining current and accurate inventory records covering receipt, dispensing, and the return of investigational drug supplies. When a shipment is received, the pharmacist will verify the quantities received and return the acknowledgment to the Protalix's CTM (Clinical Trial Material) coordinator. The drug will not be used without Protalix's approval in writing. The pharmacist investigational drug accountability record includes the identification of the person to whom the drug is dispensed, the quantity and the date of dispensing and any returned or unused drug, as well as full record of CTM storage temperature. This record is in addition to any drug accountability information recorded on the Case Report Form (CRF). These records will be readily available for inspection by a monitor and/or Protalix audits and are open to regulatory authority inspection at any time.

The investigator is responsible for maintaining accountability for the receipt, dispensing, and return of all study medication.

7.9 Prior and Concomitant Therapy

Medications having the potential to interfere with the evaluation of efficacy are excluded throughout the trial.

The following medications are strictly prohibited during the study:

- Replagal® (agalsidase-alpha)
- Any other investigational or approved drug for treating Fabry disease

The use of pre-medication to prevent infusion reactions associated with agalsidase beta initiated before entry to the study and recorded in the eCRF will be continued, but subjects will be titrated down over the course of the first three months of the study. The rate of down titration/removal of the pre-medication will be at the investigator's discretion and recurrence of infusion reactions. Re-institution of pre-medication to manage infusion reactions will be allowed see also Appendix 8.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) at a stable dose for 4 weeks prior to entry into the study are allowed, but once a subject is randomized in the study, initiation of ACEI or ARB therapy is permitted only after discussion and approval of the Protalix Medical Director.

7.10 **Method of Assigning Subjects to Treatment Groups**

This is double blind, active control study and all subjects will be randomly assigned to treatment with PRX-102 1 mg/kg or agalsidase beta infused every two weeks over 3 hours.

A fixed block randomization list, stratified at Baseline by urine protein to creatinine ratio (UPCR) (< or ≥ 1 g/g, 1mg/mg or 1000 mg/g), will be generated with a 2:1 randomization (PRX-102:agalsidase beta) and incorporated into the Target e*CRF system. Once patient eligibility has been confirmed by the Protalix Medical Director, the system will generate a subject randomization id number. The investigative staff and patient will be blinded to the treatment assignment. The pharmacist preparing the study drug will be given unblinded access to the e*CRF system and will record information regarding the prepared dose for each patient.

A unique screening number (formatted as xxSF20yyy [x: site number, S: screening, F: constant mark for Fabry: protocol number (20), y: sequential subject number at the site]) will be assigned to each screened subject. Once a subject is eligible for treatment, including successful completion of screening but prior to visit 1, a subject randomization id number will be generated that will include the site and subject number (formatted as xx-F20yyy [x: site number, F: constant for Fabry, protocol number (20), y: treatment number]).

7.11 **Unblinding Procedure**

Identification of the assigned treatment group will be allowed under two circumstances: (1) emergency unblinding at the request of the Investigator for a patient with a serious adverse reaction where knowledge of the treatment group will be needed to determine the most appropriate management of the patient, and (2) unblinding for determining whether an unexpected and associated serious adverse event is a reportable event. In either circumstance, the study Safety Monitor will request the treatment from an unblinded statistician at Target Health. The treatment assignment will be communicated on a need to know basis only.

8 EFFICACY AND SAFETY ASSESSMENTS

8.1 Efficacy Variable(s)

The primary efficacy parameter is the comparison of the mean annualized change (slope) in estimated glomerular filtration rate ($eGFR_{CKD-EPI}$) between treatment groups.

Secondary efficacy variables are as follows:

1. Left Ventricular Mass Index (g/m^2) by MRI
2. Plasma Lyso-Gb3
3. Plasma Gb3
4. Urine Lyso-Gb3
5. Protein/Creatinine ratio spot urine test
6. Frequency of pain medication use
7. Exercise tolerance (Stress Test)
8. Short Form Brief Pain Inventory (BPI)
9. Mainz Severity Score Index (MSSI)
10. Quality of life EQ-5D-5L

8.2 Pharmacokinetic Variables

For 30 subjects in the study, blood samples will be taken for PK analysis on Day 1 and at 6 months, 12 months and 24 months of treatment. The following PK parameters will be derived from the plasma concentration versus time profiles to determine the pharmacokinetics of the study drug: Cmax, Tmax, AUC0-t, t1/2, and AUC0-∞. Blood samples will be drawn at the following time points: pre-infusion (baseline); 0.5 and 1 hour after the beginning of the infusion; at the end of the infusion, at 0.5±0.05, 1±0.25, 2±0.25, 4±0.25, 8±0.25, 24±0.5, 48±3, and 96±3 hours post-infusion and at 14±3 days post-infusion.

8.3 Safety Variables

- Safety will be assessed by the frequency, severity, and duration of treatment-emergent AEs (adverse events), including clinically significant laboratory abnormalities, ECG changes from baseline, physical examination findings and assessment of the injection site after administration of the study drug
- Anti-Drug (i.e. PRX-102 or agalsidase beta) IgG antibodies will be assessed before dosing at: baseline, 2 and 4 weeks after the first infusion, and then every month for the first 6 months and every 3 month until the end of study through the last infusion. If a patient continues treatment in an extension study, the anti-Drug antibodies will be assessed as part of that study. For patients who end treatment with PRX-102 or agalsidase beta, anti-PRX-102 antibodies will be assessed 1 and 3 months after last infusion
- Anti-Drug IgE antibodies and tryptase will be assessed in events of hypersensitivity reaction following Sponsor request
- Ability to taper off infusion pre-medication at the start of the study
- Requirement for use of pre-medication overall to manage infusion reactions

8.3.1 Clinical Laboratory

- Hematology: total white blood cell count hemoglobin, and platelets.
- Coagulation profile: prothrombin time (PT) and partial thromboplastin time (PTT)
- Biochemistry: sodium, potassium, glucose, blood urea nitrogen, creatinine, cystatin C, calcium, phosphate (inorganic), uric acid, total protein, albumin, bilirubin (total), alkaline phosphatase, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, and creatine phosphokinase
- Vitamin D
- Urinalysis: dipstick for presence of blood, glucose, ketones, and protein

8.3.2 Adverse Events

8.3.2.1 Adverse Events (AE) and Serious Adverse Events (SAE)

An adverse event (AE) is any untoward medical occurrence in a subject participating in a clinical trial. An adverse event can be any unfavorable and unintended sign, symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication. AEs will be collected from the start of treatment until 90 days following the final visit dose. Any events occurring prior to treatment will be recorded on the medical history page with the event name and onset date and end date if not continuing. Pre-existing, known clinically significant conditions observed at screening should be recorded as medical history.

This definition also includes accidental injuries, reasons for any change in medication (drug and/or dose) other than planned titration, reasons for admission to a hospital, or reasons for surgical procedures (unless for minor elective surgery for a pre-existing condition). It also includes adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the study medication. Any laboratory abnormality assessed as clinically significant by the Investigator must be recorded as an adverse event.

A treatment emergent adverse event is any adverse event occurring after start of study medication and within the time of residual drug effect (90 days after the last administration of the study medication), or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after start of study medication and within the time of residual drug effect.

Adverse events should be recorded as diagnoses, if available. If not, separate sign(s) and symptom(s) are recorded. One diagnosis/symptom should be entered per record. Treatment-related hypersensitivity/infusion reactions are defined in Appendix 3 and can be defined as a single AE at the Investigator's discretion.

Note that death is not an event, but the cause of death is. An exception is the event of sudden death of unknown cause. Note that hospitalization is not an event; however, the reason for hospitalization is. Procedures are not events; the reasons for conducting the procedures are. In general, only the reason for conducting the procedure will be captured as an adverse event. However, if deemed necessary by the Investigator, a procedure can be captured along with the reason for conducting the procedure.

An overdose or medication error is not an adverse event unless it is temporally associated with an unfavorable or unintended sign or symptom.

Each AE is to be classified by the investigator as serious or non-serious. A serious adverse event (SAE) is any untoward medical occurrence or effect that occurs at any dose:

- Results in death
- Is life-threatening (i.e., an immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is associated with a congenital anomaly/birth defect
- Is an important medical event

An adverse event caused by an overdose or medication error is considered serious if a criterion listed in the definition above is fulfilled.

Important adverse events that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject's safety or may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious adverse events also include any other event that the investigator or sponsor judges to be serious or which is defined as serious by the regulatory agency.

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial subject using concise medical terminology. In addition, each trial subject will be questioned about adverse events. The question asked will be "Since you began taking the study medication, have you had any health problems?"

8.3.2.2 Procedures for Assessing, Recording, and Reporting Adverse Events and Serious Adverse Events

Throughout the duration of the study, the Investigator will closely monitor each subject for evidence of drug intolerance and for the development of clinical or laboratory evidence of adverse events. All adverse events (expected or unexpected) which occur during the course of the study, whether observed by the Investigator or by the subject, and whether or not thought to be drug-related, will be reported and followed until resolution or until they become stable.

The description of the adverse event will include description of event, start date, stop date, intensity, if it was serious, relationship to test drug, change in test drug dosage, if the subject died, and if treatment was required.

Events will be recorded as one of the following severity and causality categories below:

Severity	Definition
Mild (Grade 1)	Awareness of signs or symptoms, but no disruption of usual activity
Moderate (Grade 2)	Discomfort sufficient to interfere, but not prevent, daily activity
Severe (Grade 3)	Unable to carry out usual activity
Very severe (Grade 4)	Incapacitating, requires hospitalization, results in death

Category	Definition
Unrelated	Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under possible or probable.
Unlikely	Does not follow a reasonable temporal sequence from administration. May have been produced by the subject's clinical state or by environmental factors or other therapies administered.
Possible	Follows a reasonable temporal sequence from administration, but may have been also produced by the subject's clinical state, environmental factors or other therapies administered.
Probable	Clear-cut temporal association with administration with improvement on cessation of investigational medicinal product or reduction in dose. Reappears upon rechallenge. Follows a known pattern of response to the investigational medicinal product.
Definitely	There is evidence of exposure to the test product, for example, reliable history or acceptable compliance assessment; the temporal sequence of the AE onset relative to the drug is reasonable; the AE is most likely to be explained by the drug treatment than by another cause; the challenge is positive; re-challenge (if feasible) is positive; the AE shows a pattern consistent with previous knowledge of the drug treatment.

Adverse events with the causality assessed as possible or probable are categorized as related to study medication and are called adverse drug reactions.

All SAEs must be reported immediately (no more than 24 hours after becoming aware of the event) by entering the information about the event in the eCRF forms. The Sponsor's Medical Director and Safety Monitor will be notified of the event by the eCRF system. In the case that the eCRF system is not available, the Investigator must contact Medical Director (972-54-2228472) or Safety Monitor (1-212-681-2100) to notify the Sponsor of the event.

8.3.2.3 Acute Kidney Injury

Episodes of Acute Kidney Injury (AKI) will be considered adverse events. AKI will be defined by a 1.5 fold or greater increase in serum creatinine from the immediately previous laboratory value and assessment by the investigator. The Protalix Medical Director will work with the investigator to ensure that such changes in renal function are thoroughly evaluated. See Section 10.6 Missing Data for further description of how episodes of AKI will be handled in data analysis for efficacy.

9 STUDY PROCEDURES AND FLOW CHART

9.1 Study Flow Chart

Activity Visit Number	S[4]	1	2 through 52	All odd numbered visits	2, 15, 28 and 2 weeks after Visit 53	4	2, 3, 5, 9, 11	7, 20	14	27	33, 47	40	53
Sign IC	x												
Assign screening number	x												
Inclusion/exclusion criteria	x	x											
Demographics	x												
Medical & Specific FD history	x												
Physical examination	x	x						x	x	x	x	x	x
Body weight	x	x						x	x	x	x	x	x
Body height	x												
Vital signs	x	x	x										
Current medications Pain medications Pre-medication Use	x	x	x										
Alpha-galactosidase activity in plasma	x												
Alpha-galactosidase activity in leucocytes	x												
Urine protein/creatinine ratio (UPCR)	x	x						x	x	x	x	x	x
Hematology	x	x						x	x	x	x	x	x
PT and PTT	x												
Biochemistry	x	x						x	x	x	x	x	x
Serum creatinine and Cystatin C	x	x		x									
Vitamin D	x												
Serum pregnancy (beta	x												

Activity Visit Number	**S**[4]	**1**	**2 through 52**	**All odd numbered visits**	**2, 15, 28 and 2 weeks after Visit 53**	**4**	**2, 3, 5, 9, 11**	**7, 20**	**14**	**27**	**33, 47**	**40**	**53**
HCG) for females,													
Urinalysis - dipstick	x	x						x	x	x	x	x	x
HbsAg, HCV & HIV	x												
Short Form Brief Pain Inventory (BPI)	x	x							x	x		x	x
Anti-Drug Antibodies (IgG)[2]	x	x					x	x	x	x	x	x	x
Electrocardiography (ECG)	x	x						x	x	x	x	x	x
Chest X-ray[1]	x												
Quality of Life		x							x	x		x	x
Mainz Severity Score Index (MSSI)		x							x	x		x	x
Request for randomization approval		x											
Randomization		x											
Echocardiography		x								x			x
Cardiac function assessment (stress test)		x								x			x
Cardiac MRI		x								x			x
Brain MRI		X								x			x
Adverse events assessments		x	x										
Mutation analysis		x											
Plasma samples for PK[3]		x			x				x	x			x
Urine lyso Gb3 concentration		x				x		x	x	x		x	x
Plasma Gb3 concentration[2]		x				x		x	x	x		x	x
Plasma Lyso Gb3 concentration[2]		x				x		x	x	x		x	x
Study Drug IV infusion		x	x										x

[1]will be performed only for patients who have not had the test during last 3 months before screening
[2]will be performed pre-infusion
[3]only for 30 enrolled subjects. Time points : pre-infusion (baseline); 0.5 and 1 hour after the beginning of the infusion; at the end of the infusion, at 0.5±0.05, 1±0.25, 2±0.25, 4±0.25, 8±0.25, 24±0.5, 48±3, and 96±3 hours post-infusion and at 14±3 days post-infusion
[4]Re-screening may be performed with Medical Director approval for patients failing to fulfill Inclusion criteria #2 and/or #3 within 2 months of initial screening visit

9.2 Study Visits

9.2.1 Screening (Visit S, Day -30 ± 10 Days)

1. Obtain written informed consent from the subject
2. Assign screening number
3. Review inclusion/exclusion criteria
4. Demographics
5. General medical history and specific Fabry disease history
6. Physical examination, including weight and height
7. Vital signs, including blood pressure, pulse, temperature and respiration rate
8. Current medications,
   - Review pain medications
   - Review pre-medication use
   - Review general other medications including ACEI and ARBs
9. Laboratory tests
   - Hematology
   - PT and PTT
   - Biochemistry
   - Serum creatinine and cystatin C (pre-infusion)
   - Vitamin D
   - Serum pregnancy test (beta HCG) for females
   - Urinalysis
   - Spot urine for UPCR
   - Plasma and leucocyte alpha-galactosidase activity (pre agalsidase beta infusion or at least 3 days post agalsidase beta infusion)
   - Anti-PRX-102 and anti-agalsidase beta antibodies
   - Serology for HBsAg, HCV and HIV
10. Short Form Brief Pain Inventory (BPI) (Appendix 7)
11. ECG
12. Chest X-ray (if not performed in the last 3 months)

Re-screening
A subject that fails screening based on Inclusion Criteria 4 and/or 5 (eGFR range and/or slope) may be re-screened for serum creatinine and cystatin C within 2 months with the approval of the Protalix Medical Director.

9.2.2 Visit 1 (Baseline, Day 1 ± 7 Days)

1. Review inclusion/exclusion criteria
2. Request for subject approval from Medical Director of the study
3. If Medical Director approves subject treatment, subject will be randomized to blinded treatment in the e*CRF system
4. Physical examination, including weight
5. Vital signs, including blood pressure, pulse, temperature and respiration rate
6. Current medications
   - Review pain medications

- Review pre-medication use. Subjects previously receiving pre-medication for prevention of infusion reactions will continue after randomization for the first infusion. Pre-medication will be tapered at the investigator's discretion during the first three months of the study.

7. Laboratory tests
   - Hematology
   - Biochemistry (pre-infusion)
   - Serum creatinine and cystatin C (pre-infusion)
   - Urinalysis
   - Spot urine for UPCR
   - Urine lyso GB3 (pre-infusion)
   - Plasma Gb3 (pre-infusion)
   - Plasma Lyso-Gb3 (pre-infusion)
   - Anti-PRX-102 and anti-agalsidase beta antibodies (pre-infusion)
   - Mutation analysis
   - Plasma samples for PK analysis for 30 patients enrolled in the study: pre-infusion at baseline, 0.5 and 1 hour after the beginning of the infusion, at the end of the infusion, and at 0.5±0.05, 1±0.25, 2±0.25, 4±0.25, 8±0.25, 24±0.5, 48±3, and 96±3 hours post-infusion and at 14±3 days post-infusion.
8. ECG
9. Echocardiogram
10. Cardiac function assessment (stress test)
11. Cardiac MRI (Appendix 4)
12. Brain MRI
13. Quality of life: EQ-5D-5L
14. Short Form Brief Pain Inventory (BPI) (Appendix 7)
15. Mainz Severity Score Index (MSSI) (Appendix 5)
16. Adverse events
17. Study drug administration

The following procedures will be performed after the infusion:

1. Patients will be observed clinically for a minimum of 2 hour after dosing.
2. Vital signs will be evaluated every 30 minutes for the first hour and every 60 minutes if the patient tolerates the infusion up to the end of observation time The injection site will be evaluated.
3. A follow up telephone call with the patient will be held the day after the first infusion.
4. Remind the subject of the date of their next visit.

9.2.3 Visits 2 through 52(±3 days, if not listed below)

The activities listed below are included in all visits. Other activities are listed below for other specific visits.

1. Current medications
   - Review pain medications

- Pre-medication use: Patients that were premedicated before the study will be titrated off the medication of the first 3 months of the study at the discretion of the investigator. A new requirement for pre-medication will be documented for each infusion.

2. Vital signs, including blood pressure, pulse, temperature and respiration rate
3. Adverse events
4. Study drug administration

The following procedures will be performed after the infusion:

1. Patients will be observed clinically for a minimum of 2 hour after dosing.
2. Vital signs will be evaluated every 30 minutes for the first hour and then every 60 minutes if the patient tolerates the infusion up to the end of observation time
3. The injection site will be evaluated.
4. A follow up telephone call with the patient will be held the day after the first infusion.
5. Remind the subject of the date of their next visit.

Post dosing clinical observation length time can be shortened to 60 minutes under Investigator request and Protalix Medical Director approval based on the tolerability of the infusion.

9.2.4 All Odd Numbered Visits (3 through 53)

Serum creatinine and cystatin C (pre-infusion)

9.2.5 Visits 2, 15, 28, and 2 weeks after Visit 53 (± 3 Days)

Plasma samples for PK analysis for 30 enrolled subjects, last sample at 14±3 days post infusion

9.2.6 Visits 2, 3, 5, 9, 11 (± 3 Days)

Anti-PRX-102 and anti-agalsidase beta antibodies

9.2.7 Visit 4 (±3 days)

1. Laboratory tests
   - Plasma Gb3 (pre-infusion)
   - Plasma Lyso-Gb3 (pre-infusion)
   - Urine lyso GB3 (pre-infusion)

9.2.8 Visits 7, 20 (± 3 Days)

1. Physical examination with body weight
2. Laboratory tests
   - Hematology
   - Biochemistry (pre-infusion)
   - Urinalysis
   - Spot urine for UPCR
   - Plasma Gb3 (pre-infusion)
   - Plasma Lyso-Gb3 (pre-infusion)
   - Urine lyso GB3 (pre-infusion)
3. Anti-PRX-102 and anti-agalsidase beta antibodies (pre-infusion)
4. ECG

9.2.9 Visit 14 (± 3 Days)

1. Physical examination with body weight
2. ECG
3. Laboratory tests
   - Hematology
   - Biochemistry (pre-infusion)
   - Urinalysis
   - Spot urine for UPCR
   - Plasma Gb3 (pre-infusion)
   - Plasma Lyso-Gb3 (pre-infusion)
   - Urine lyso GB3 (pre-infusion)
   - Anti-PRX-102 and anti-agalsidase beta antibodies (pre-infusion)
   - Plasma samples for PK analysis for 30 enrolled subjects: pre-infusion, 0.5 and 1 hour after the beginning of the infusion, end of infusion, 0.5 (±0.05), 1 (±0.25), 2 (±0.25), 4 (±0.25), 8 (±0.25), 24 (±0.5), 48 (±3), and 96 (±3) hours post-infusion.
4. Quality of life: EQ-5D-5L
5. Short Form Brief Pain Inventory (BPI) (Appendix 7)
6. Mainz Severity Score Index (MSSI) (Appendix 5)

9.2.10 Visit 27 (Week 52 ± 3 Days, Month 12)

1. Physical examination with body weight
2. ECG
3. Laboratory tests
   - Hematology
   - Biochemistry (pre-infusion)
   - Urinalysis
   - Spot urine for UPCR
   - Plasma Gb3 (pre-infusion)
   - Plasma Lyso-Gb3 (pre-infusion)
   - Urine lyso GB3 (pre-infusion)
   - Anti-PRX-102 and anti-agalsidase beta antibodies (pre-infusion)
   - Plasma samples for PK analysis for 30 enrolled subjects: pre-infusion, 0.5 and 1 hour after the beginning of the infusion, end of infusion, 0.5 (±0.05), 1 (±0.25), 2 (±0.25), 4 (±0.25), 8 (±0.25), 24 (±0.5), 48 (±3), and 96 (±3) hours post-infusion.
4. Quality of life: EQ-5D-5L
5. Short form Brief Pain Inventory (Appendix 7)
6. Mainz Severity Score Index (MSSI) (Appendix 5)
7. Echocardiogram
8. Cardiac function assessment (stress test)
9. Cardiac MRI (Appendix 4)
10. Brain MRI

9.2.11 Visits 33 and 47 (± 3 Days)

1. Physical examination with body weight
2. Laboratory tests

- Hematology
- Biochemistry (pre-infusion)
- Urinalysis
- Spot urine for UPCR
- Anti-PRX-102 and anti-agalsidase beta antibodies (pre-infusion)
- ECG

9.2.12 Visit 40 (± 3 Days)

1. Physical examination with body weight
2. ECG
3. Laboratory tests
   - Hematology
   - Biochemistry (pre-infusion)
   - Urinalysis
   - Spot urine for UPCR
   - Plasma Gb3 (pre-infusion)
   - Plasma Lyso-Gb3 (pre-infusion)
   - Urine lyso GB3 (pre-infusion)
   - Anti-PRX-102 and anti-agalsidase beta antibodies (pre-infusion)
4. Short Form Brief Pain Inventory (BPI) (Appendix 7)
5. Mainz Severity Score Index (MSSI) (Appendix 5)
6. Quality of life: EQ-5D-5L

9.2.13 Visit 53 (Week 104 ± 3 Days, Month 24)

1. Physical examination with body weight
2. Vital signs, including blood pressure, pulse, temperature and respiration rate
3. Current medications
   - Review pain medications
   - Review pre-medication use.
4. Laboratory tests
   - Hematology
   - Biochemistry (pre-infusion)
   - Urinalysis
   - Spot urine for UPCR
   - Plasma Gb3 (pre-infusion)
   - Plasma Lyso-Gb3 (pre-infusion)
   - Urine Lyso-Gb3 (pre-infusion)
   - Anti-PRX-102 and anti-agalsidase beta antibodies (pre-infusion)
   - Plasma samples for PK analysis for 30 enrolled subjects: pre-infusion, 0.5 and 1 hour after the beginning of the infusion, end of infusion, 0.5 (±0.05), 1 (±0.25), 2 (±0.25), 4 (±0.25), 8 (±0.25), 24 (±0.5), 48 (±3), and 96 (±3) hours post-infusion.
5. ECG
6. Echocardiogram
7. Cardiac function assessment (stress test)
8. Cardiac MRI (Appendix 4)
9. Brain MRI

10. Quality of life: EQ-5D-5L
11. Short Form Brief Pain Inventory (BPI) (Appendix 7)
12. Mainz Severity Score Index (MSSI) (Appendix 5)
13. Adverse events
14. Study drug administration

Subjects who do not continue into an extension study will have follow up anti-PRX-102 and anti-agalsidase beta antibody testing performed at 1 and 3 months after Visit 53.

9.2.14 Premature Withdrawal Visit

All attempts should be made to perform all the tests for Visit 53 at the withdrawal visit for patients who may discontinue the study before completion.

10 STATISTICAL METHODS PLANNED AND SAMPLE SIZE

10.1 Determination of Sample Size

This orphan indication allows for a small number of patients, given the rarity of the disease and the difficulties in allocating patients for clinical trials. With a total of at least 66 patients at 24 months, randomized 2:1 to PRX-102:agalsidase beta, there is 80% power to detect a change of 1.1 mL/min/1.73 m^2/year using a two-sample t-test (alpha=0.049, 2-sided test) to evaluate the primary outcome of an annualized eGFR slope after 24 months. This calculation is based on the assumption that the standard deviation for the annualized eGFR slope is 1.5 ml/min/1.73 m^2/year in each treatment group. For this analysis the null hypothesis is that the difference in annualized eGFR slope between the treatment groups is 0 versus an alternative hypothesis that the difference in annualized slopes between treatment groups is not 0. A 30% improvement in the slope of eGFR would be considered a clinically relevant improvement. Based on previous research, the annualized eGFR slope in patients treated with agalsidase beta is -3.0 mL/min/1.73 m^2/year, and under the null hypothesis that is the slope assumed for both groups. Thus, a 1.1 mL/min/1.73 m^2/year reduction in the rate of decline in renal function (improvement) is anticipated to be equal to an annualized eGFR slope with PRX-102 of -1.9 mL/min/1.73 m^2/year. This sample size calculation was made using a group sequential testing procedure that used the O'Brien Fleming spending function to determine test boundaries. There is one interim analysis (see below) scheduled at the halfway (1 year) time point and will have a nominal superiority alpha level of 0.003 whereas the final analysis at 2 years will have a nominal alpha of 0.049. Since it is anticipated that some patients may not be available for any follow-up (*i.e.*, not have 24 months of follow up), 78 patients will be enrolled, with 52 randomized to PRX-102 and 26 randomized to agalsidase beta. With a potential 15% total dropout rate this would result in 44 PRX-102 and 22 agalsidase beta patients at 24 months. These power/sample size calculations were performed using PASS-13 Group Sequential Tests for Two Means procedure (Hintze, J. (2014). PASS 13. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

10.2 Subject Populations

10.2.1 Intent-to-Treat (ITT) Population

Intent-to-treat (ITT) population includes patients who received at least one complete dose of study medication.

10.2.2 Per Protocol (PP) Population

The Per Protocol population includes patients who complete the study with no major protocol violations. Primary and secondary analyses will be performed on these participants as well.

10.2.3 Safety Population

The safety population includes as all patients who received at least one dose (partial or complete) of the study medication.

10.3 Analysis

10.3.1 Primary Efficacy Analysis

eGFR is calculated from the serum creatinine according to the CKD-EPI formula:

> eGFR (ml/min/1.73 m2) = 141 × min(Scr/κ,1)α × max(Scr/κ, 1)-1.209 × 0.993Age × 1.018 [if female] * 1.159 [if black]
>
> Scr = serum creatinine; κ = 0.7 for females and 0.9 for males; α = -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

The primary efficacy analysis compares the estimated annualized slope of the glomerular filtration rate (eGFR) between the PRX-102 group and the agalsidase beta (Control) group over 2 years. A longitudinal mixed model will be used to estimate the eGFR slope in the two groups by examining time and group as fixed effects and patient as a random effect in the model. The time by group interaction will be examined to determine if there is evidence that the eGFR slope rates are different between groups. Since the primary comparison is a test of superiority at 24-months, this interaction is expected to be statistically significant. If the interaction test is significant this would indicate that the eGFR slopes are statistically significantly different and depending on the direction of the difference it would indicate that the PRX-102 group is superior (or inferior) to the Control group for this measure. Using this longitudinal mixed model, the assumption of whether the change in eGFR is linear over time will be examined. Specifically, residual plots will be estimated from the model to determine whether there is evidence of nonlinearity over time. If there is evidence of non-linearity, transformations of the primary outcome will be considered (*i.e.*, log transformation, etc.). If a transformation is needed, the model will be re-fit with the transformation and assessments of linearity will be made again. If a transformation is used and it provides evidence of linearity, slopes will be estimated on the transformed scale with corresponding 95% confidence intervals for the difference in slopes between groups.

If there is evidence that the linearity assumption of the mixed model is not met and no adequate transformation is identified, then the two groups will be compared using the mixed model with a non-linear term added to the model. This is not anticipated to occur, but if it were needed then a polynomial term (*i.e.*, time-squared) could be added to determine if that provides a better fit to the observed data. Once an adequate model is identified that fits the data, then this model will be used to derive 1-year (for interim analysis) or 2-year (for final analysis) estimates of the eGFR values in each group at those time points. The differences in these derived values would be compared using 95% confidence intervals as described above, and the non-inferiority margin described above (1.1 ml/min/1.73 m2/year) at 12 months and the superiority test at 24 months will be examined.

By using a mixed models approach, if there are some patients with missing data and the missing data is considered to be missing at random (MAR) then the modelling will handle the missing data appropriately without the need for imputation,

In addition to this primary comparison, the slope eGFR values will be used for each group to estimate the time to a predicted 30% absolute decline in eGFR value. This comparison will not provide a separate p-value since it will be derived from the longitudinal mixed model described above, but it will allow estimates of the time to this event (30% drop in eGFR) to be derived and reported.

10.3.2 Secondary Efficacy Analyses

Additional secondary endpoint analyses will be detailed in the final Statistical Analysis Plan

10.3.3 Other Analyses

Demographics. For continuous variables, n, mean, standard deviation, median, minimum, and maximum will be presented. For categorical variables, frequency counts and percentages will be presented by dose group.

Medical History, Vital Signs, and Physical Examination. For medical history, frequency count by treatment will be provided for each body system by dose group.

For physical examination, frequency count of normal or abnormal by treatment will be tabulated for each body system by dose group.

Medications. Summary and/or data listings of the prior, concomitant medication, and class of medication will be provided by dose group. Medications for pain and premedication will be specifically listed.

10.4 Safety Analysis

Safety will be assessed by evaluation of adverse events, clinical laboratory results and anti-drug antibodies.

10.4.1 Adverse Events

Adverse events will be coded to system organ class and preferred term using MedDRA version 9.1 or higher. All adverse events occurring after the initiation of the study treatment (treatment emergent adverse events) will be reported, including events present at baseline that worsened during the study.

Adverse events will be summarized by treatment group to provide visual comparison among the treatment groups with respect to incidence of adverse events (the number of subjects reporting at least one episode of a specific adverse event), incidence of adverse events by severity within body system, incidence of adverse events by attribution within body system, and incidence of adverse events causing withdrawal and incidence of serious adverse events. Regarding severity and attribution summaries, the most extreme outcome (highest severity and closest to study drug related) will be used for those subjects who experience the same adverse event on more than one occasion.

Hypersensitivity reactions will be analyzed as adverse events of special interest using descriptive statistics.

Written narratives will be provided for all serious, unexpected or other significant adverse events that are judged to be of special interest because of their clinical importance.

10.4.2 Clinical Laboratory

Clinical Laboratory examination will be performed prior to treatment and during treatment.

Descriptive statistics will be presented for the value and abnormality of each of the clinical laboratory results by visit and dose group. Shift tables describing abnormality shifts from baseline to after treatment and follow-up will be created.

10.5 Interim Analysis

An interim analysis for non-inferiority will be performed for purposes of submitting a marketing application to the European Medicines Agency. Consistent with the power/ sample size calculation provided for the Primary 24-month Superiority calculation described above, the following 12 month interim analysis to test for Non-inferiority will be performed. Specifically, with a total of 66 patients included (44 PRX-102 and 22 agalsidase beta) there is 80% to detect whether the difference in mean annualized change in estimated glomerular filtration rate ($eGFR_{CKD\text{-}EPI}$) in PRX-102 is non-inferior to the rate in agalsidase beta using a one sided (0.025) two sample t-test. For this test the non-inferiority margin is 3.0 mL/min/1.73/m2/year and the true difference in slopes is assumed to be 1.1 with standard deviations of the slopes being 1.5 in each group. With the proposed sample size, non-inferiority margin and expected differences in slope, the standard deviation could be as large as 3.4 and still maintain adequate power (greater than 80%) for non-inferiority.

10.6 Missing Data

The primary analysis will use a mixed models approach for comparing groups. This approach handles missing data appropriately if the missing data is considered to be missing at random (MAR). This would be the expectation. Therefore, all patients should be able to provide at least some data for the primary efficacy comparisons.

For secondary efficacy analyses, since measures are being measured at multiple time points, mixed models will be used and therefore missing data will be handled by the analytic method if the missing data is MAR.

No imputation will be made for missing values of safety endpoints except for some AE parameters as described above.

Episodes of Acute Kidney Injury (AKI) will be considered missing data for the purposes of the primary efficacy analysis. AKI will be defined by a 1.5 fold increase in serum creatinine from the immediately previous laboratory value and assessment by the investigator. However, prior to data base lock and unblinding, cases of AKI will be assessed by two independent nephrology experts. Their evaluation will include whether they agree that AKI occurred in a patient and whether serum creatinine values should excluded from the eGFR slope calculations for the primary endpoint. Excluded serum creatinine values will be considered missing data.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Source Data and Records

Source data are all the information in original records and certified copies of original records of clinical findings, observations, laboratory reports, data sheets provided by the sponsor or other activities in the study, which are necessary for the reconstruction and evaluation of the study. The investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source records.

All study records will be retained for a period of time as defined by the regulatory authority for the country in which the investigation is conducted. Generally, this means at least 2 years following the date on which the drug is approved by the regulatory authority for marketing for the purposes that were the subject of the investigation. In other situations (e.g., where the investigation is not in support of or as part of an application for a research or marketing permit), a period of 2 years following the date on which the entire clinical program is completed, terminated or discontinued or the investigational application under which the investigation is being conducted is terminated or withdrawn by the regulatory authorities.

In the event the Investigator retires, relocates or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records may be transferred to any other person who will accept responsibility for the records. Notice of such a transfer must be given in writing to the Sponsor. The Investigator must contact the Sponsor prior to disposal of any records related to this study.

11.2 Reporting of Results

The Case Report Form (CRF) is an integral part of the study and subsequent reports. The CRF must be used to capture all study data recorded in the subject's medical record. The CRF must be kept current to reflect subject status during the course of the study. Only a subject screening and treatment number will be used to identify the subject.

The monitor is responsible for performing on-site monitoring at regular intervals throughout the study to verify adherence to the protocol; verify adherence to local regulations on the conduct of clinical research; and ensure completeness, accuracy, and consistency of the data entered in the CRF.

Protalix Ltd. or their designee will monitor completed Case Report Forms (CRFs). A case report form will be provided for each screened subject.

All protocol-required information collected during the study must be entered by the Investigator, or designated representative, in the Target e*CRF™, an Internet-based electronic data collection system. All details of the CRF completion and correction will be explained to the investigator. The management module of Target e*CRF™ includes edit check and query systems that seamlessly integrate with the data entry system. All modifications to the data in the eCRF are tracked by an electronic audit trail (date and identity of the person making the change are instantaneously recorded). Target e*CRF™ is 21CFR Part 11 compliant.

If the Investigator authorizes other persons to make entries in the CRF, the names, positions, and signatures of these persons must be supplied to the sponsor.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. By design, an explanation must be provided for all missing data, altered data, and/or out of range data.

The completed case report form must be reviewed and signed by the Investigator named in the study protocol or by a designated sub investigator.

Final monitored and audited eCRFs will be provided by the Sponsor to the sites at the end of the study in the format of a PDF file.

11.3 **Confidentiality of Subject Data**

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the CRF or any other documents submitted to the sponsor, the subjects will not be identified by their names, but by an identification system, which consists of their number in the study. The investigator will maintain documents not meant for submission to the sponsor, e.g., the confidential subject identification code and the signed informed consent forms, in strict confidence.

12 REPORTING AND PUBLICATION

12.1 **Confidentiality of Study Data**

Any information relating to the study product or the study, including any data and results from the study, will be the exclusive property of the sponsor. The investigator and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to Protalix Ltd.

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14 Appendices

14.1 Appendix 1. Vial Label

Sample labels for the study drug are illustrated below in Figures 1 and 2. Labels will be adapted in accordance with local regulatory and language requirements.

Figure 1. Outer Package Label (example)

Protocol #: PB-102-F20
Study drug name: pegunigalsidase alfa (PRX-102)
20 mg/vial; 10mL in each vial
Qty: N vials_____
For intravenous injections only as directed
Batch number: _____ Expiry: MM-YYYY
IND No. 110,161
Directions for use:
Store at: 2-8°C (36-46°F)
Caution: New Drug-Limited by Federal (or United States) law to investigational use.

Sponsor: Protalix Ltd, 2 Snunit St., Carmiel, Israel, Tel: +972-4-9889488

Figure 2. Individual Vials Label (example)

Study drug name: pegunigalsidase alfa (PRX-102)
20 mg/vial for intravenous injection only as directed
10mL in each vial
Batch number: _____ Expiry: MM-YYYY
Protocol #: PB-102-F20
Caution: New Drug-Limited by Federal (or United States) law to investigational use.
Subject/patient number: _____
Visit number: _____
Sponsor: Protalix Ltd, 2 Snunit St., Carmiel, Israel,
Tel: +972-4-9889488

14.2 Appendix 2. Infusion Rate Algorithm

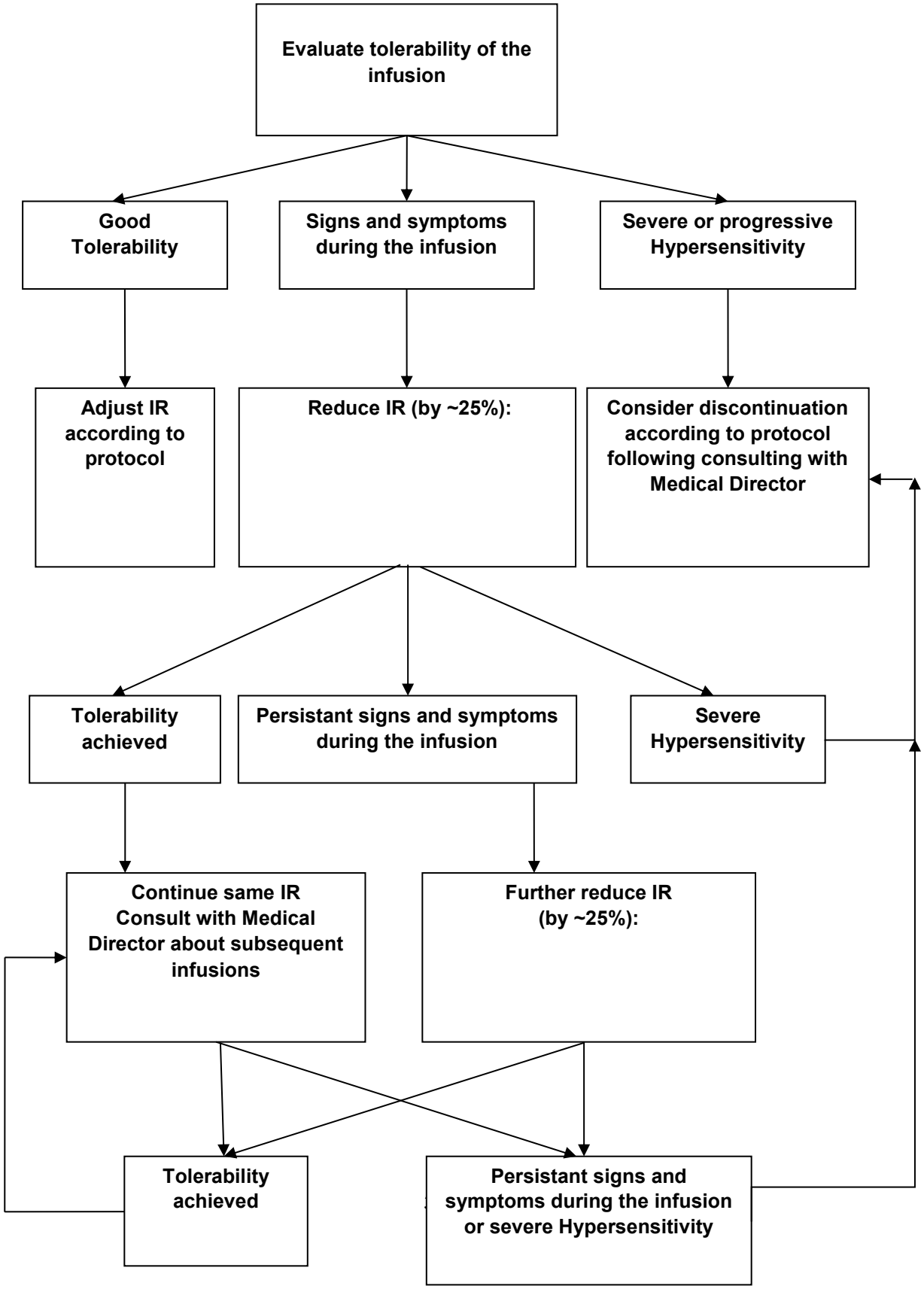
The infusion rate (IR) may be adjusted according to individual subject symptoms and signs. The infusion rate will be adjusted according to Section 7.5 Study Drug Administration under the direction of the Investigator and Protalix Medical director. Pre-medications will be tapered per Section 7.9 Prior and Concomitant Therapy under the direction of the Investigator and Protalix Medical Director. The assumptions with respect to adverse experiences to the infusion are:

1. Most of the subjects will tolerate the infusion without any special symptom or event.
2. Subjects presenting symptoms and signs of **severe** hypersensitivity will be evaluated according to the CTCAE Drug Toxicity criteria and there may be a discontinuation of treatment according to the protocol.
3. Subjects may present signs and symptoms that will respond to reducing the infusion rate and may not appear at the next infusion.
4. Tolerability and the subject specific infusion rate will be assessed and decided by the Investigator according to vital signs and clinical status of the subject.

Definitions to be applied regarding tolerability of infusions are as follows:

Good tolerability	**Partial tolerability**	**Poor tolerability**
Infusion was performed without signs and symptoms (such as burning, pruritus, flushing, discomfort, or change in vital signs).	Signs and symptoms appeared during the infusion **and resolved after slowing infusion rate** or at the end of the infusion.	Signs and symptoms meeting the definitions of CTCAE Grade 1 or 2 toxicity responding to reduction of infusion rate or responding to treatment (example, antihistamine for urticaria).

The specific algorithm for other infusion rate changes to be followed:



Changes in infusion rates according to the protocol:

The tolerability of the infusions in these patients will be determined by signs and symptoms during the infusion, and observation in the hospital, and by telephone contact the day after the infusion.

For patients with good tolerability after the first 3 months of treatment and the finalization of the attempt of premedication discontinuation (in patients who were previously on premedication) the time of infusion can be decreased by 30 minutes every third infusion, up to a minimum infusion time of 1.5 hours under the agreement between the Investigator and the Medical Director.

Infusion rate should be adjusted according to patient tolerability as described above; continuation of the rate of infusion should be agreed between the PI and the Medical Director.

14.3 Appendix 3. PRX-102 Evaluation and Treatment Algorithm

During and after infusion of PRX-102, the following algorithm will be followed to monitor and manage the occurrence of hypersensitivity, anaphylaxis, or anaphylactoid reactions.

Clinical signs

Early

- Sensation of warmth and itching
- Feelings of anxiety

Moderate

- Pruritus
- Flushing
- Urticaria
- Chest discomfort
- Mild Hypotension

Progressive

- Erythematous or massive urticarial rash
- Edema of face, neck, soft tissues

Severe

- Hypotension
- Bronchospasm (wheezing)
- Laryngeal edema (dyspnea, stridor, aphonia, drooling)
- Arrhythmias

Treatment algorithm:

With the onset of any of the above clinical signs, immediately discontinue study medication administration and initiate the following monitoring.

- Continuous electrocardiographic monitoring
- Continuous pulse oximetry
- Measure blood pressure every 5 minutes
- Perform chest auscultation every 5 minutes
- Collect blood samples for Tryptase (29-33), antibodies and C3, C4. Tryptase samples need to be withdrawn at:
    - 1st sample taken 0.25-3 hours after onset of symptoms
    - 2nd sample taken between 3-6 hours
    - 3rd sample taken 24-48 hours to verify the return to baseline.

In the case of progressive or severe hypersensitivity, treat appropriately

Treat as follows:

Urticaria or edema of the face, neck, or soft tissues

- Epinephrine 1:1000 solution, 0.5 mL subcutaneously, repeat as needed every 5-10 minutes
- Antihistamines
- Corticosteroids

Hypotension (systolic blood pressure (SBP) ≤ 90 mmHg)

- Isotonic sodium chloride solution, 1 L every 30 minutes as needed to maintain SBP > 90 mmHg
- Epinephrine 1:10,000 solution given IV at 1 μg/minute initially, then 2-10 μg/minute to maintain SBP > 90 mmHg
- Norepinephrine 4 mg in 1 L 5% dextrose in water given IV at 2-12 μg/min to maintain SBP > 90 mmHg
- Glucagon 1 mg in 1 L 5% dextrose in water give IV at 5-15 μg/minute for refractory hypotension

Bronchospasm

- Oxygen by face mask at 6-8 L/minute to maintain oxygen saturation at > 90%
- Epinephrine 1:1000 solution, 0.5 mL subcutaneously
- Albuterol 0.5 mL of 0.5% solution in 2.5 mL of sterile saline every 15 minutes up to three doses
- Inhaled beta-agonists
- Corticosteroids

Laryngeal edema

- Epinephrine 1:1000 solution, 0.5 mL subcutaneously, repeat as needed every 5 to 10 minutes
- Corticosteroids

If symptoms resolve within a single study visit and the investigator determines the symptoms were not an occurrence of progressive or severe hypersensitivity, anaphylaxis, or anaphylactoid reactions then administration of the drug may continue according to the algorithm provided above, and at the discretion of the Investigator and Medical Director.

Premedication

Premedication for subsequent PRX-102 infusions may be considered at the discretion of the investigator and Medical Director for subjects experiencing early clinical signs of hypersensitivity or rash/urticaria that responds promptly to oral antihistamine administration (see also Appendix 2 for adjustment of infusion rate). The premedication will be administered according to the following steps as needed to prevent progressive hypersensitivity:

1. Antihistamine (H1 blocker: diphenhydramine, hydroxyzine, cetirizine, loratadine, desloratidine) at a standard dose 12 hours and 2 hours before the start of the infusion.

2. H1 blocker plus H2 blocker (ranitidine, cimetidine, famotidine) at standard doses 12 hours and 2 hours before the start of the infusion.

3. H1 blocker plus H2 blocker plus prednisone up to 50 mg administered 12 hours and 2 hours before the start of the infusion.

14.4 Appendix 4. Cardiac MRI

14.4.1 Patients and sites

Seventy eight patients will be enrolled in this trial in several sites worldwide.

For each cardiac MRI to be conducted throughout the study, the test will be performed only after the Investigator reviews the patient's kidney function.

For patients who may present one of the following conditions the performance of the Cardiac MRI will be discussed with Protalix Medical Director:

- GFR < 30 mL/min/1.73m^2 based on the last Serum Creatinine value

or

- Suspected Acute Kidney Injury

Gadolinium warnings from USPI:

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
See full prescribing information for complete boxed warning

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.1).**

14.4.2 Magnetic Resonance Imaging (MRI) data

Each patient enrolled in this trial will have a cardiac MRI at baseline (Visit 1) as a reference for further MRI evaluations in the study. A set of ECG gated cine and delayed contrast enhanced MRI sequences (SSFP resp. Inversion recovery Gradient echo) will be acquired. A Gadolinium based contrast agent will be used during image acquisition of the delayed contrast enhanced scan.

The sequences will be defined based on the equipment and ability to provide sufficient image quality and contrast for myocardium and fibrosis detection and quantification in Fabry's disease patients.

14.4.3 MRI evaluation parameters

The following MRI parameters will be evaluated during this trial:

- Number and location of left ventricular segments with fibrosis
- Percentage and mass of cardiac fibrosis (in grams)
- Left ventricular myocardial mass (in grams)

14.4.4 Sites and image data management

All image management activities will be centralized and conducted by an independent imaging Contract Research Organization (imaging CRO) with operational capabilities in Europe and the United States in compliance with all regulatory requirements. An overview of the main activities performed by the imaging CRO is provided in the next sections.

14.4.4.1 Standardization of image acquisition, initial site qualification

The image acquisition procedure will be standardized by the imaging CRO among all participating sites. The same image acquisition and management procedure will be used by all sites. This procedure will be defined by the imaging CRO and approved by the Sponsor. The sites will be trained and qualified by the imaging CRO prior to start of patient enrolment. Each site will provide test MRI scan(s) during the initial site qualification phase. The source of the test scan(s) will be (in order of preference) a patient volunteer, a healthy volunteer, or the screening image from the first patient tested at the site. No contrast agent will be used for the test scans except when the first image from the first patient is used. All images will be anonymized by the sites (in order to remove any patient-related nominative information) and provided in digital format (DICOM). Only digital images will be centrally processed by the imaging CRO.

14.4.4.2 Subject Sedation

Subjects may require sedation in order to obtain the high quality images required. Sites may use standard sedation protocols approved by the institution.

14.4.4.3 Quality control of image data and site Quality Assurance

The image data will be collected and quality controlled by the imaging CRO for checking the technical adequacy, the compliance of data acquisition with the study imaging protocol, the anonymization of the images and the diagnostic quality of the images (their appropriateness for centralized evaluations). If any quality-related issue is detected by the imaging CRO, specific queries will be sent to the sites to implement appropriate corrective (including potential repeat scans if needed) and preventive actions.

14.4.5 Image processing and centralized analysis

14.4.5.1 Cardiac MRI assessment

Analysis of the cine short-axis and delayed contrast enhanced images of the left ventricle will be performed with dedicated MRI quantification software.

Myocardial contours will be detected semi-automatically and manually edited and quality controlled by an expert technician at the imaging CRO.

The left ventricular contours will be submitted for final approval to an independent and blinded reader.

Based on approved contours, the left ventricular mass and % and mass of the fibrotic area are calculated automatically by the software algorithm.

14.4.5.2 Centralized and Blinded Image Review by Independent Readers

The MRI data will be centrally evaluated in a fully blinded manner by an independent reader. The reading sessions will be organized at the imaging CRO site. The same image evaluation procedure will be used for all patients' MRI scans in this trial.

Expertise of independent readers, training sessions

The reader will be a Cardiologist with a significant experience in cardiac MRI. The reader will be trained prior to start of centralized image review sessions.

He/she will be provided with a Read Rules document and will be given a training on the use of the software. Test cases representing non-study Fabry patients (as described in section 14.3.4.4.1) will be used for the training. Main consensus issues (contour detection in apical and basal LV slices, trabeculae and papillary muscles, threshold for delayed enhanced areas, etc.) will be discussed with the reader and documented.

Conduct of centralized image review sessions

The reader will be fully blinded with regard to Treatment Groups, patient's ID and site number. The images will have been pre-analyzed by experienced image analysis technologists from the imaging CRO.

The image review sessions by the cardiologist will include:

Efficacy Image Review:

MRI analysis results at baseline as a reference for further MRI evaluations in the study will be evaluated by the reader.

14.4.6 Data and report transfers to Sponsor

- Efficacy image Review sessions will be exported to the Sponsor using a predefined, standardized and secure data transfer procedure.
- The final Study database will be submitted to the Sponsor in digital format.

14.4.7 Direct access to Study data

- A Direct access to Study data will be made possible by the imaging CRO for audit purposes.
- Such Study data include:

- Information related to interactions between the imaging CRO and the sites (Queries, Data Clarification Forms, test data submitted by the sites, etc.)
- Native MRI data
- Data processed and generated by the imaging CRO
- Data generated by the blinded reader
- Audit trails

14.4.8 Unevaluable MRI:

Unevaluable MRI data can result from poor quality image, due to patient motion, improper left ventricular coverage, technical problems with the image transmission to the imaging CRO, etc. The imaging CRO procedures for ensuring quality images are meant to reduce or eliminate such poor quality images (Section 14.4.4.3 above).

If an adequate patient image cannot be obtained for a given time point in the study, the problem with the image will be documented at the imaging CRO. In addition, the imaging CRO will document all attempted corrective actions with the investigative site imaging centre.

14.5 Appendix 5. The Mainz Severity Score Index (MSSI)

The MSSI score has been proven representative in patients with 'classic' Fabry disease and is useful for monitoring clinical improvement in patients receiving enzyme replacement therapy.

The MSSI scoring system is composed of four sections that cover the general, neurological, cardiovascular and renal signs and symptoms of Fabry disease. Each section includes a group of signs and symptoms that are associated with Fabry disease.

The MSSI will be performed only at baseline (visit 1) and every 6 months throughout the study.

The Mainz Severity Score Index (MSSI):

General Score			**Neurological Score**		
Sign/symptom	**Rating**	**MSSI score**	**Sign/symptom**	**Rating**	**MSSI score**
Characteristic facial appearance	No	0	Tinnitus	No	0
	Yes	1		Mild	1
Angiokeratoma	None	0		Severe	2
	Some	1	Vertigo	No	0
	Extensive	2		Mild	1
Oedema	No	0		Severe	2
	Yes	1	Acroparaesthesia	No	0
Musculoskeletal	No	0		Occasional	3
	Yes	1		Chronic	6
Cornea verticillata	No	0	Fever pain crisis	No	0
	Yes	1		Yes	2
Diaphoresis	Normal	0	Cerebrovascular	No	0
	Hypo/Hyper	1		Ischemic lesions (in MRI/CT)	1
	Anhidrosis	2		TIA/migraine etc.	3
Abdominal pain	No	0		Stroke	5
	Yes	2	**Psychiatric/ psychosocial**		
Diarrhoea/ constipation	No	0	Depression	No	0
	Yes	1		Yes	1
Haemorrhoids	No	0	Fatigue	No	0
	Yes	1		Yes	1
Pulmonary	No	0	Reduced activity level	No	0
	Yes	2		Yes	1
New York Heart	No	0			

General Score			Neurological Score		
Association (NYHA) classification*					
	Class I	1			
	Class II	2			
	Class III	3			
	Class IV	4			
Maximum Score		**18**	**Maximum Score**		**20**

Cardiovascular Score			Renal Score		
Sign/symptom	**Rating**	**MSSI score**	**Sign/symptom**	**Rating**	**MSSI score**
Changes in cardiac muscle thickness	No	0	Evidence of renal dysfunction	No proteinuria	0
	Thickening of wall/septum	1		Proteinuria	4
	LVH seen on ECG	6		Tubular dysfunction/low GFR or creatinine clearance	8
	Cardiomyopathy (<15)	8		End-stage renal failure (serum creatinine levels >3.5 mg/dl)	12
	Severe cardiomyopathy (>15)	12		Dialysis	18
Valve insufficiency	No	0			
	Yes	1			
ECG abnormalities	No	0			
	Yes	2			
Pacemaker	No	0			
	Yes	4			
Hypertension	No	0			
	Yes	1			
Maximum Score		**20**	**Maximum Score**		**18**

* Limitation on physical activity according to NYHA classification is as follows. Class I: none; Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain, but echocardiography reveals heart involvement. Class II: slight; comfortable at rest, but

ordinary physical activity results in fatigue, etc. Class III: marked; comfortable at rest, but less than ordinary physical activity causes fatigue, etc. Class IV: unable to carry out any physical activity without discomfort; symptoms of cardiac insufficiency or of anginal syndrome may be present even at rest and physical activity increases discomfort.

Abbreviations:

CT, computed tomography; ECG, electrocardiogram; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; TIA, transient ischaemic attack.

14.6 Appendix 6. National Kidney Foundation Guidelines for Chronic Kidney Disease

Stages of Chronic kidney disease (National Kidney Foundation 2002):

- Stage 1- Kidney damage with normal or elevated GFR (≥ 90)
- Stage 2- Kidney damage with mild reduction in GFR (60-89)
- Stage 3- Kidney damage with moderate reduction in GFR (30-59)
- Stage 4- Kidney damage with severe reduction in GFR (15-29)
- Stage 5- Kidney failure (<15 or dialysis)

14.6.1 Estimation of GFR:

Estimates of GFR are the best overall indices of the level of kidney function. The level of GFR should be estimated from prediction equations that take into account the serum creatinine concentration and some or all of the following variables: age, gender, race, and body size. Among adults, the CKD-EPI equation provides a clinically useful estimate of GFR (Levey et al., 2009). This equation provides estimate of GFR standardized for body surface area.

14.6.2 CKD-EPI Equation:

The CKD-EPI equation performed better than the MDRD (Modification of Diet in Renal Disease Study) equation, especially at higher GFR, with less bias and greater accuracy. When looking at NHANES (National Health and Nutrition Examination Survey) data, the median estimated GFR was 94.5 mL/min per 1.73 m^2 vs. 85.0 mL/min per 1.73 m^2, and the prevalence of chronic kidney disease was 11.5% versus 13.1%. The CKD-EPI equation, expressed as a single equation, is:

$GFR = 141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa,1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] * 1.159 [if black/African American]

Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

14.7 **Appendix 7. Brief Pain Inventory- BPI (Short Form)**

(www.mdanderson.org/education-and-research/symptom-assessment-tools/BPI User Guide pdf)

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

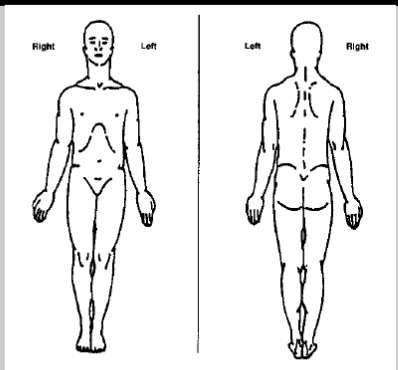
Date: ____/____/____ **Time:** ____

Name: _____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% No Relief	10%	20%	30%	40%	50%	60%	70%	80%	90%	100% Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

B. Mood

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

C. Walking Ability

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

E. Relations with other people

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

F. Sleep

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

G. Enjoyment of life

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

14.8 **Appendix 8. Premedication Discontinuation Guide**

Patients on agalsidase beta can be included in the study when under premedication to diminish the side effects to the drug. After randomization, patients are assigned in a blinded manner to PRX-102 or to continue on agalsidase beta. To keep the blind in those patients who were under premedication first infusion will be given under the regular premedication the patients were when on agalsidase beta.

During the next 3 months (6 infusions), the Investigator will manage a stepwise discontinuation of the premedication based on the appropriate tolerability of the patient to the changes. Premedication will resume in the case that the patient will present signs and symptoms of non-tolerability of the infusion.

All cases of non-tolerabilty and need of premedication will be discussed between the Investigator and the Medical Director before reaching infusion 8 and evaluating the reduction of infusion rate, see also Appendix 2.

14.9 Appendix 9. EQ-5D-5L

Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

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- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐