CLINICAL STUDY PROTOCOL

Protocol Title: An Open Label Study of the Safety and Efficacy of PRX-102 in Patients with Fabry Disease Currently Treated With REPLAGAL® (Agalsidase alfa)

Protocol Number PB-102-F30

Study 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 1.0, 11 August 2016 Version 2.0, 4 December 2016 Version 3.0, 06 June 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: An Open Label Study to Assess the Safety and Efficacy of PRX-102 in Patients with Fabry Disease Currently Treated with REPLAGAL® (Agalsidase alfa)

INVESTIGATIONAL PRODUCT: Pegunigalsidase alfa (PRX-102), a chemically modified 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 in patients with Fabry disease currently treated with agalsidase alfa

STUDY DESIGN: This is an open label switch over study to assess the safety and efficacy of PRX-102. Patients treated with agalsidase alfa for at least 2 years and on a stable dose (>80% labelled dose/kg) for at least 6 months. Patients will be screened and evaluated over 3 months while continuing on agalsidase alfa. Following the screening period, the patient will be enrolled and switched from their agalsidase alfa treatment to receive intravenous (IV) infusions of PRX-102 1 mg/kg every two weeks for 12 months. No more than 25% of treated patients will be female.

At the time of enrolment, premedication, if used for the agalsidase alfa infusions before enrolment, will be continued through the first infusion with PRX-102 and then will be gradually tapered at the investigator's discretion during the first 2 months. The first infusions of PRX-102 will be administered under controlled conditions at the investigation site. The patient can receive their PRX-102 infusions at a home care setup once the investigator and Sponsor Medical Director agree that it is safe to do so.

NUMBER OF SUBJECTS (PLANNED): 22

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Inclusion criteria:

Eligible patients must fulfill the following inclusion criteria:

1. Age: 18-60 years
2. A documented diagnosis of Fabry disease.

3. Males: plasma and/or leucocyte alpha galactosidase activity (by activity assay) less than lower limit of normal according to laboratory range and one or more of the characteristic features of Fabry disease
    i. Neuropathic pain
    ii. Cornea verticillata
    iii. Clustered angiokeratoma
4. Females: historical genetic test results consistent with Fabry mutations, or in the case of novel mutations a first degree male relative with Fabry disease, and one or more of the characteristic features of Fabry disease
    i. Neuropathic pain
    ii. Cornea verticillata
    iii. Clustered angiokeratoma
5. Treatment with agalsidase alfa for at least 2 years and on a stable dose (>80% labelled dose/kg) for at least 6 months
6. eGFR $\geq$ 40 ml/min/1.73 m^2 by CKD-EPI equation
7. Availability of at least 2 historical serum creatinine evaluations since starting agalsidase alfa treatment and not more than 2 years
8. Female patients and male patients whose co-partners are of child-bearing potential agree to use a medically acceptable method of contraception, not including the rhythm method

Exclusion criteria:

1. History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase alfa
2. History of renal dialysis or transplantation
3. 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)
4. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated or dose changed in the 4 weeks prior to screening
5. Urine protein to creatinine ratio (UPCR) > 0.5 g/g and not treated with an ACE inhibitor or ARB
6. Known history of hypersensitivity to Gadolinium contrast agent that is not managed by the use of premedication
7. Females who are pregnant, planning to become pregnant during the study, or are breast feeding
8. Cardiovascular event (myocardial infarction, unstable angina) in the 6 month period before screening
9. Congestive heart failure NYHA Class IV
10. Cerebrovascular event (stroke, transient ischemic attack) in the 6 month period before screening
11. 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(S), DOSE AND MODE OF ADMINISTRATION: During the first 3 months (Screening period), patients will be on agalsidase alfa according to their previous regimen (dose, frequency and rate of infusion). Upon confirmation of eligibility, patients will be switched to PRX-102 1 mg/kg, intravenously to be administered over 3 hours, every 2 weeks. After the first 2 months of treatment with PRX-102, infusion time may be reduced gradually to 1.5 hours pending patient tolerability, investigator evaluation, and Sponsor Medical Monitor/Director approval.

STUDY DURATION: Total 15 months, with 3 months Screening while on agalsidase alfa and 12 months Treatment on PRX-102, with the option to be enrolled in an extension study upon completion of this study.

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 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

SAFETY ENDPOINTS:

Change from baseline in:

- Clinical laboratory tests
- Physical examination
- Assessment of the injection site
- Electrocardiogram
- Treatment-emergent adverse events
- Ability to taper off infusion premedication throughout the first 2 months of the study
- Requirement for use of premedication overall to manage infusion reactions
- Treatment-emergent anti-PRX-102 antibodies

EFFICACY ENDPOINTS:

- Mean annualised change in estimated glomerular filtration rate ($eGFR_{CKD-EPI}$)

- Left Ventricular Mass Index (g/m^2) preferably by MRI (echocardiogram can be used as an alternative)
- 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

STATISTICAL ANALYSIS:

The sample size of 22 patients is adequate to evaluate the safety of switching from agalsidase alfa to PRX-102 in this orphan disease in which patient recruitment in clinical trials is difficult.

The study endpoints will be evaluated by various summary analyses by study visit and by change from baseline data for each efficacy endpoint. Safety and efficacy endpoints will be compared to baseline using summary statistics. Data will not be analysed by inferential statistics.

An interim analysis may be conducted for administrative purposes.

DOCUMENT APPROVAL

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

SPONSOR REPRESENTATIVE

June 6, 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
BPI	Brief pain inventory
CKD	Chronic kidney disease
C_{max}	Maximum concentration observed
CRF	Case report form
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
PP	Per Protocol
PT	Prothrombin time
PTT	Partial Thromboplastin time
SAE	Serious adverse event
TIA	Transient ischaemic attack

3. ETHICAL CONDUCT OF THE STUDY AND REGULATORY REQUIREMENTS

3.1 Institutional Review Board (IRB)

The study protocol and any amendments will be reviewed by an Institutional Review Board (IRB). The IRB will review the informed consent form, their updates (if any), and any written materials given to the subjects. A list of all IRBs 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 form 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 patient will receive a copy of the patient information and the signed informed consent.

The patient 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 2009a).

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 2009a). 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 2009a). 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., 2009b; 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., 2009b; 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 2009b). 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). Schiffmann (2007) showed that increasing the frequency of dosing with agalsidase alfa from every other week to weekly in a subgroup of patients with Fabry disease whose eGFR continued to decline at rapid rate while being treated every other week significantly slowed the rate of decline in eGFR. Nine (82%) of 11 patients demonstrated

either a positive eGFR slope (n = 3, 27%) or a slowing in their rate of decline (*i.e.*, less negative eGFR slope; n = 6, 55%) after switching to weekly administration of agalsidase alfa.

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. This extended exposure of the target organs to enzyme may be important for improving efficacy similar to what Schiffmann et al., (2007) showed with weekly compared to every other week agalsidase alfa.

The most commonly experienced AEs in PRX-102 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 an appropriate treatment regimen for attenuating disease progression.

5. STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of this trial is to evaluate the safety of PRX-102 in patients with Fabry disease currently treated with agalsidase alfa.

5.2 Secondary Objectives

The secondary objective of this trial is to evaluate the efficacy of PRX-102 in patients with Fabry disease currently treated with agalsidase alfa.

6. INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan – Description

This is an open label switch over study to assess the safety and efficacy of PRX-102. Patients treated with agalsidase alfa for at least 2 years and on a stable dose (>80% labelled dose/kg/) for at least 6 months. Patients will enter the study for 3 month Screening period for baseline data generation. Eligible patients will be switched from their agalsidase alfa treatment to receive intravenous (IV) infusions of PRX-102 1 mg/kg every two weeks for 12 months. No more than 25% of treated patients will be female.

At the time of enrolment, premedication, if used for the agalsidase alfa infusions before study entry, will be continued during the Screening period and to the first infusion with PRX-102 treatment and then gradually tapered at the investigator's discretion during the first 2 months. The first infusions of PRX-102 will be administered under controlled conditions at the investigation site. The patient can receive their PRX-102 infusions at a home care setup once the investigator and Sponsor Medical Director agree that it is safe to do so.

6.2 Discussion of Study Design and Choice of Control Group(s)

This is a Phase 3, open-label, switchover study to assess the safety and efficacy of PRX-102 (pegunigalsidase alfa) in patients with Fabry disease who have been treated with agalsidase alfa (Replagal®) ERT. The dose of pegunigalsidase alfa is 1 mg/kg and switching from agalsidase alfa is an appropriate study design in this rare disease population.

PRX-102 and agalsidase alfa are different products and immunogenicity and hypersensitivity may be different between the products. Premedication to prevent adverse reactions during infusion is administered in some patients receiving agalsidase alfa. Because the requirements for premedication may be different between the two products, premedication will be tapered off, as tolerated, over the initial 2 months of infusions under careful observation after switching to PRX-102. Premedication to prevent infusion reactions can be maintained or re-introduced as required.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

The subjects must meet the following inclusion criteria:

1. Age: 18-60 years
2. A documented diagnosis of Fabry disease

3. Males: plasma and/or leucocyte alpha galactosidase activity (by activity assay) less than lower limit of normal according to laboratory range and one or more of the characteristic features of Fabry disease
    i. Neuropathic pain
    ii. Cornea verticillata
    iii. Clustered angiokeratoma
4. Females: historical genetic test results consistent with Fabry mutations, or in the case of novel mutations a first degree male relative with Fabry disease, and one or more of the characteristic features of Fabry disease
    i. Neuropathic pain
    ii. Cornea verticillata
    iii. Clustered angiokeratoma
5. Treatment with agalsidase alfa for at least 2 years and on a stable dose (>80% labelled dose/kg) for at least 6 months
6. eGFR $\geq$ 40 ml/min/1.73 m^2 by CKD-EPI equation
7. Availability of at least 2 historical serum creatinine evaluations since starting agalsidase alfa treatment and not more than 2 years
8. Female patients and male patients whose co-partners are of child-bearing potential agree to use a medically acceptable method of contraception, not including the rhythm method

6.3.2 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 alfa
2. History of renal dialysis or transplantation
3. 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)
4. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated or dose changed in the 4 weeks prior to screening
5. Urine protein to creatinine ratio (UPCR) > 0.5 g/g and not treated with an ACE inhibitor or ARB
6. Known history of hypersensitivity to Gadolinium contrast agent that is not managed by the use of premedication
7. Females who are pregnant, planning to become pregnant during the study, or are breast feeding
8. Cardiovascular event (myocardial infarction, unstable angina) in the 6 month period before screening
9. Congestive heart failure NYHA Class IV
10. Cerebrovascular event (stroke, transient ischemic attack) in the 6 month period before screening

11. 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

6.3.3 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 (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 27.

6.3.4 Replacement Policy

Withdrawn patients will not be replaced.

7. STUDY PRODUCT

7.1 Study Medication Supply

Protalix will provide PRX-102 to the sites as needed.

7.2 Description 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 10.2 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 Study drug dosage and preparation

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

Dose of PRX-102 will be adjusted at visit 14 (6 months on pegunigalsidase alfa treatment) if the weight changes by 25% from first infusion.

Each dose will be prepared by a pharmacist or nurse at each site.

The required amount of PRX-102 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 the dosage adjustment was performed.

7.4 Study Drug Administration

PRX-102 will be administered by intravenous infusion over 3 hours (0.83 mL/min). 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. The patient will be clinically observed for 2 hours post dosing when under PRX-102. Observation period may be shorten to 1 hour pending patient tolerability per investigator discretion and after Medical Monitor approval.

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

7.5 Packaging and Labeling

PRX-102 is packed in vials containing 20 mg (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).

Sample Vial labels are provided in Appendix 1.

7.6 Conditions for Storage and Use

PRX-102 is stored at 2-8°C (36-46°F).

7.7 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.

7.8 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 treatment period:

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

The use of premedication to prevent infusion reactions associated with agalsidase alfa 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 two months after switching to PRX-102 The rate of down titration/removal of the premedication will be at the investigator's discretion and recurrence of infusion reactions. Re-institution of premedication to manage infusion reactions will be allowed (see also Appendix 3 and 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 prohibited unless the subject develops proteinuria and the Protalix Medical Director approves. ACEI or ARB therapy may not be initiated for the treatment of hypertension in the absence of proteinuria.

8. EFFICACY AND SAFETY ASSESSMENTS

8.1 Safety Variable(s)

- Safety will be assessed by the frequency, severity, and duration of treatment-emergent AEs (see Section 8.3, 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) IgG antibodies will be assessed before dosing with PRX-102 at baseline (Visit 1). Anti-PRX IgG antibodies will be assessed 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, anti-PRX-102 antibodies will be assessed 1 and 3 months after last infusion
- Anti-Drug IgE antibodies will be assessed in events of hypersensitivity reaction following Sponsor request
- Ability to taper off infusion premedication at the start of the study
- Requirement for use of premedication overall to manage infusion reactions

8.1.1 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

8.2 Efficacy Variables

- Mean annualised change in estimated glomerular filtration rate ($eGFR_{CKD\text{-}EPI}$) (See Appendix 6)
- Left Ventricular Mass Index (g/m^2) preferably by MRI (echocardiogram can be used as an alternative) (See Appendix 4)
- 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) (See Appendix 7)
- Mainz Severity Score Index (MSSI) (See Appendix 5)

- Quality of life EQ-5D-5L (See Appendix 9)

8.3 Adverse Events

8.3.1 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 30 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, 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.

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 unfavourable 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 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 coded to one of the following intensity categories below:

Severity	**Definition**
Mild	Awareness of signs or symptoms, but no disruption of usual activity
Moderate	Event sufficient to affect usual activity (disturbing)
Severe	Event causes inability to work or perform usual activities (unacceptable)

Events will be coded into one of the following causality categories as defined below:

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.

Adverse events with the causality assessed as unrelated or unlikely are categorized as not related to study medication.

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.

8.3.3 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.

9. STUDY PROCEDURES AND FLOW CHART

	Screening Period		Visits Treatment Period PRX-102 (Pegunigalsidase alfa)						
Activity	Screening Visit (-3 Month)	Visit A (-2 Month) and B (-1 Month)	Visit 1	Visits 2, 4, 6, 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26	Visits 3, 5, 9, 11	Visits 7, 20 (Months 3 and 9)	Visit 14 (Month 6)	Visits 16, 18, 22, 24	Visit 27 (Month 12)
Sign IC	x								
Assign screening number	x								
Medical history	x								
Demographics	x								
Alpha-galactosidase activity in plasma and leucocytes	x								
Historical serum creatinine	x								
Vital signs (blood pressure, pulse, temperature and respiration)	x		x	x	x	x	x	x	x
Body weight	x		x			x	x		x
Body height	x								
Physical examination	x		x			x	x		x
Concomitant medications (including pain and premedications)	x	x	x	x	x	x	x	x	x
Hematology	x		x			x	x		x
Biochemistry	x		x			x	x		x
Serum Creatinine and Cystatin C	x	x	x		x	x	x	x	x
Urinalysis - dipstick	x		x			x	x		x
Protein/Creatinine ratio spot urine test	x	x	x			x	x		x
HbsAg, HCV & HIV	x								
Serum pregnancy test (beta HCG)	x		x						

Activity	Screening Period		Visits Treatment Period PRX-102 (Pegunigalsidase alfa)						
	Screening Visit (-3 Month)	Visit A (-2 Month) and B (-1 Month)	Visit 1	Visits 2, 4, 6, 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26	Visits 3, 5, 9, 11	Visits 7, 20 (Months 3 and 9)	Visit 14 (Month 6)	Visits 16, 18, 22, 24	Visit 27 (Month 12)
Urine Lyso Gb3 concentration	x		x			x	x		x
Plasma Lyso Gb3	x		x			x	x		x
Plasma Gb3	x		x			x	x		x
Anti PRX-102 Antibodies (IgG)			x		x	x	x		x
Electrocardiography (ECG)	x		x			x	x		x
Chest X-ray	x								
Cardiac function assessment (echocardiography and stress test)	x		x				x		x
Cardiac MRI			x						x
Inclusion/exclusion criteria	x								
Request for subject approval	x								
Enrolment approval		x[1]							
Mutation analysis			x						
PT, PTT	x								
C3, C4	x								
Vit D	x								
Short Form Brief Pain Inventory (BPI)			x			x	x		x
Brain MRI			x						x
Mainz Severity Score Index (MSSI)			x				x		x
EQ-ED-5L			x				x		x
PRX-102 infusion+clinical observation			x	x	x	x	x	x	x
Adverse event assessments		x	x	x	x	x	x	x	x

[1] After Visit B

9.1 Study Visits

9.1.1 Screening Visit S1 (3 Months ±7days before Visit 1)

The following procedures will be performed:

- Administration of informed consent
- Assign Screening number
- Medical history, including Fabry disease history
- Demographics
- Alpha-galactosidase activity in plasma and leucocytes
- Historical serum creatinine values
- Vital signs (blood pressure, pulse, temperature and respiration rate)
- Body weight and height
- Physical examination
- Concomitant medications , including review of pain medication and premedication
- Clinical laboratory
    - Hematology
    - Biochemistry
    - Serum Creatinine and Cystatin C
    - Urinalysis by dipstick
    - Spot urine test for proteinuria
    - HbsAg, HCV, HIV
    - Serum pregnancy test (beta HCG)
    - Vit D
    - PT, PTT
    - C3, C4
    - Urine Lyso Gb3 concentration
    - Plasma Lyso Gb3
    - Plasma Gb3
- Electrocardiogram
- Chest X-ray – an X-ray from the previous three months is acceptable
- Cardiac function assessment with echocardiography and stress test
- Review of inclusion and exclusion criteria
- Request subject approval

Schedule the patient for the next visit.

9.1.2 Visits A and B (2 and 1 Month ±7 days before Visit 1)

The following procedures will be performed:

- Clinical laboratory
    - Serum Creatinine and Cystatin C
    - Spot urine test for proteinuria
- Concomitant medications including review of pain medication and premedication
- Adverse event assessment

Final enrolment approval will be determined after Visit B.

Schedule the patient for the next visit.

9.1.3 Visit 1(±7Days)

The initial PRX-102 infusion will occur at this visit and will take place at the clinic and will continue every two weeks. Vital signs will be measured at every infusion.

The following procedures will be performed:

- Vital signs (blood pressure, pulse, temperature and respiration rate)
- Body weight
- Physical examination
- Concomitant medications, including review of pain medication and premedication
- Clinical laboratory
    - Hematology
    - Biochemistry
    - Serum Creatinine and Cystatin C
    - Urinalysis by dipstick
    - Protein/Creatinine ratio spot urine test
    - Serum pregnancy test (beta HCG)
    - Antidrug antibodies(pre-infusion) (PRX-102)
    - Mutation analysis
    - Urine Lyso Gb3 concentration
    - Plasma Lyso Gb3
    - Plasma Gb3
- Electrocardiogram
- Cardiac function assessment with echocardiography and stress test
- Cardiac MRI
- Mainz Severity Score Index
- Quality of Life EQ-5D-5L
- Short Form Brief Pain Inventory
- Adverse event assessment
- PRX-102 infusion
- Brain MRI

The following procedures will be performed after all infusions:

1. Patients will be observed clinically for a minimum of 2 hours after dosing.
2. Vital signs will be evaluated every 30 minutes for the first hour, then every hour and at the end of clinical observation , if the patient tolerates the infusion.
3. The injection site will be evaluated.

A follow up telephone call with the patient will be held the day after the first infusion.

Schedule the patient for the next visit.

9.1.4 Visits 2, 4, 6, 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26 (±3 Days)

Taper of premedication will start at Visit 2 and occur over the next two months at the investigator's discretion.

The following procedures will be performed:

- Vital signs (blood pressure, pulse, temperature and respiration rate)
- Concomitant medications, including review of pain mediciation and premedication
- Adverse event assessment
- PRX-102 infusion
- Post dosing clinical observation

Schedule the patient for the next visit.

9.1.5 Visits 3, 5, 9, 11 (±3 Days)

Premedication tapering will complete by visit 5 (Appendix 8). The following procedures will be performed:

- Vital signs (blood pressure, pulse, temperature and respiration rate)
- Concomitant medications, including review of pain medication and premedication
- Serum Creatinine and Cystatin C
- Antidrug antibodies (pre-infusion) (PRX-102)
- Adverse event assessment
- PRX-102 infusion
- Post dosing clinical observation

Schedule the patient for the next visit.

9.1.6 Visits 7, 20 (±7 days)

PRX-102 infusions continue every 2 weeks. At Visit 7 if infusions are tolerated, infusion duration can be decreased to 1.5 hours as described in Appendix 2

The post dosing clinical observation length can be shortened to 1 hour pending patient tolerability per investigator discreation and after Medical Monitor approval when the patient has reached a stable infusion duration. Vital signs will be measured every 30 minutes when post dosing observation is reduced to 1 hour.

The following procedures will be performed:

- Vital signs (blood pressure, pulse, temperature and respiration rate)
- Physical examination
- Body weight
- Concomitant medications, including review of pain medication and premedication
- Clinical laboratory
    - Hematology
    - Biochemistry
    - Serum Creatinine and Cystatin C
    - Urinalysis by dipstick
    - Protein/Creatinine ratio spot urine test
    - Urine Lyso Gb3 concentration
    - Plasma Lyso Gb3
    - Plasma Gb3
    - Antidrug antibodies (pre dose) (PRX-102)
- Electrocardiogram
- Short Form Brief Pain Inventory
- Adverse event assessment
- PRX-102 infusion
- Post dosing clinical observation

Schedule the patient for the next visit.

9.1.7 Visit 14 (±7 days)

The following procedures will be performed:

- Vital signs (blood pressure, pulse, temperature and respiration rate)
- Body weight
- Physical examination
- Concomitant medications, including review of pain medication and premedication
- Clinical laboratory
    - Hematology
    - Biochemistry
    - Serum Creatinine and Cystatin C
    - Urinalysis by dipstick
    - Protein/Creatinine ratio spot urine test
    - Urine Lyso Gb3 concentration

  - Plasma Lyso Gb3
  - Plasma Gb3
  - Antidrug antibodies (pre dose) (PRX-102)
- Electrocardiogram
- Cardiac function assessment with echocardiography and stress test
- Short Form Brief Pain Inventory
- Mainz Severity Score Index
- Quality of Life EQ-5D-5L
- PRX-102 infusion
- Adverse event assessment
- Post dosing clinical observation

Schedule the patient for the next visit

9.1.8 Visits 16, 18, 22, 24 (±3 Days)

The following procedures will be performed:

- Vital signs (blood pressure, pulse, temperature and respiration rate)
- Concomitant medications, including review of pain medication and premedication
- Adverse event assessment
- Serum Creatinine and Cystatin C
- PRX-102 infusion
- Post dosing clinical observation

Schedule the patient for the next visit.

9.1.9 Visit 27 (±7 days) or Premature Withdrawal

The following procedures will be performed:

- Vital signs (blood pressure, pulse, temperature and respiration rate)
- Body weight
- Physical examination
- Concomitant medications, including review of pain medication and premedication
- Clinical laboratory
  - Hematology
  - Biochemistry
  - Serum Creatinine and Cystatin C
  - Urinalysis by dipstick
  - Protein/Creatinine ratio spot urine test
  - Urine Lyso Gb3 concentration
  - Plasma Lyso Gb3

  - Plasma Gb3
  - Antidrug antibodies(pre dose) (PRX-102)
- Electrocardiogram
- Cardiac function assessment with echocardiography and stress test
- Cardiac MRI
- Brain MRI
- Short Form Brief Pain Inventory
- Mainz Severity Score Index
- Quality of Life EQ-5D-5L
- PRX-102 infusion
- Adverse event assessment
- Post dosing clinical observation

10. STATISTICAL METHODS PLANNED AND SAMPLE SIZE

10.1 Determination of Sample Size

The sample size of 22 patients is adequate to evaluate the safety of switching from agalsidase alfa to PRX-102 in this orphan disease in which patient recruitment in clinical trials is difficult.

10.2 Subject Populations

The safety population will be all subjects receiving at least one partial dose of PRX-102. The efficacy population will be all subjects with at least one endpoint evaluation after the first PRX-102 infusion.

10.3 Subject Disposition

The number and percentage of subjects who were enrolled, treated, completed, and withdrawn, as well as the reason(s) for withdrawal will be summarized.

10.4 Safety Analysis

Safety will be assessed by evaluation of adverse events and clinical laboratory results.

10.4.1 Adverse Events

Adverse events will be coded to system organ class and preferred term using MedDRA version 15.0 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 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.

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

Summary statistics of all central and local laboratory test results (biochemistry, hematology, and urinalysis) will be presented for each visit. The change from baseline (Visit 1) to each post-treatment visit will also be presented.

If the test results were classified (e.g., low, normal, high), the frequency count and percentage will be presented for each visit, and shift table from baseline will be provided as well.

10.5 Efficacy Analysis

Descriptive statistics of measurements by visit, change and percent change from baseline will be presented for Left Ventricular Mass Index, plasma lyso-Gb3, plasma Gb3, urine Lyso-Gb3, and protein/creatinine ratio spot urine test. Descriptive statistics will be presented for the mean annualised $eGFR_{CKD\text{-}EPI}$. 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.

Descriptive statistics for the Brief Pain Inventory regarding pain severity, and pain interference will be summarized at baseline, 3-month, 6-month and 12-month treatments. The change of the assessments will be examined using a shift table from baseline for individual qualitative items, and by change from baseline for individual scores and composite scores. This will be done according to the Brief Pain Inventory User Guide.

Descriptive statistics of the qualitative assessments regarding the sign/symptom in general, neurological, cardiovascular, renal dysfunction and the total change in each score will be summarized.

10.6 Interim Analysis

An interim analysis may be conducted for administrative purposes.

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 patient's medical record. The CRF must be kept current to reflect patient status during the course of the study. Only a patient screening and randomization number and patient initials will be used to identify the patient.

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.

SPONSOR or CRO will monitor completed Case Report Forms (CRFs). A case report form will be provided for each screened patient.

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 patient 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 initials and 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-F30
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-F30
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

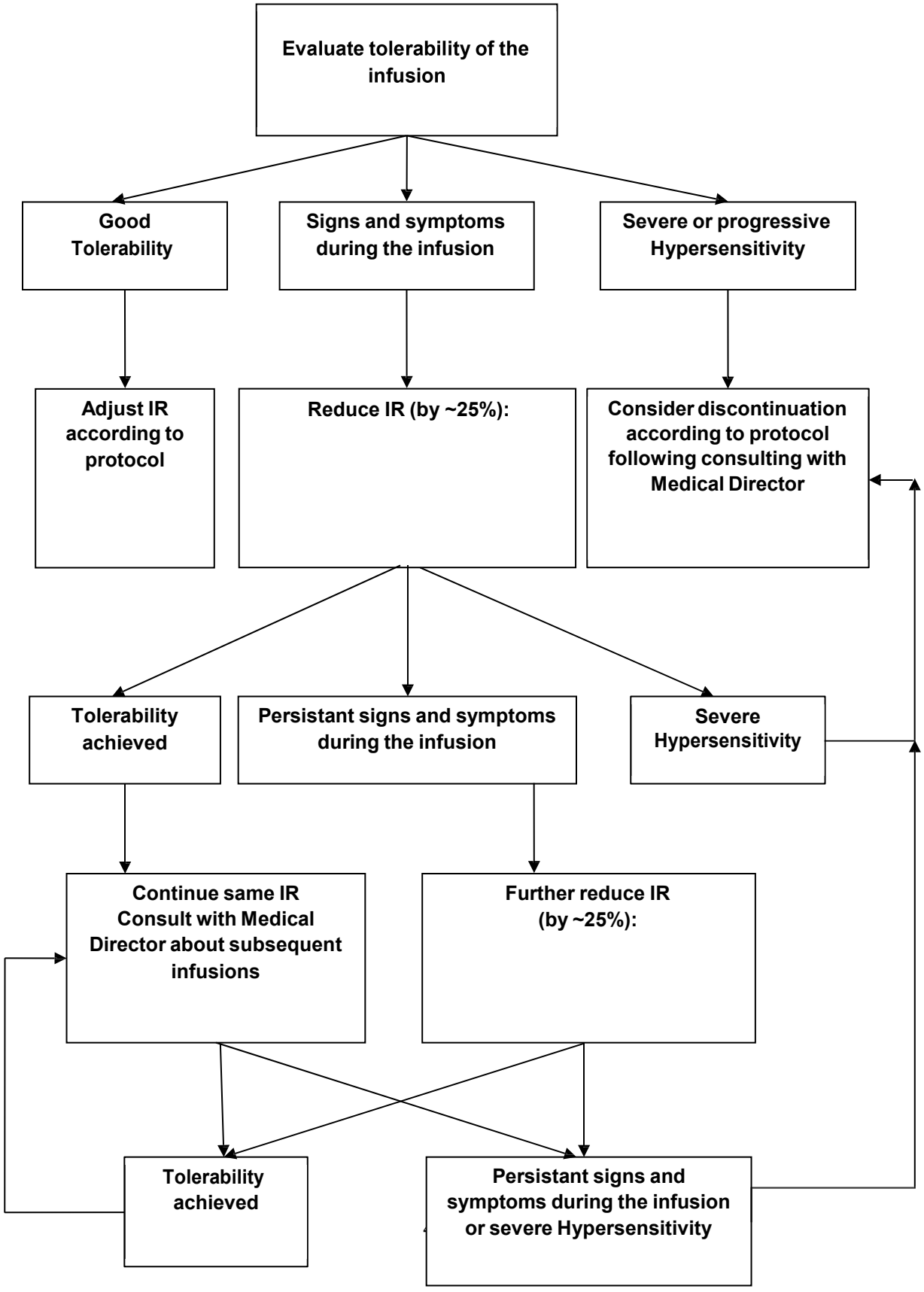
The infusion rate (IR) may be adjusted according to individual subject symptoms and signs. The infusion rate will be adjusted according to Section 7.4 Study Drug Administration under the direction of the Investigator and Protalix Medical director. Premedications if given when under agalsidase alfa will be tapered gradually during the first 2 months when under PRX-102 under the direction of the Investigator and Protalix Medical Director (See Appendix 8). 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:


Evaluate tolerability of the infusion
Good Tolerability
Signs and symptoms during the infusion
Severe or progressive Hypersensitivity
Adjust IR according to protocol
Reduce IR (by ~25%):
Consider discontinuation according to protocol following consulting with Medical Director
Tolerability achieved
Persistant signs and symptoms during the infusion
Severe Hypersensitivity
Continue same IR Consult with Medical Director about subsequent infusions
Further reduce IR (by ~25%):
Tolerability achieved
Persistant signs and symptoms during the infusion or severe Hypersensitivity

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 2 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 or other 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, cetrizine, 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

Twenty-two 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 14.4.4.1) 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 (Weidemann et al, 2009).

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 Visit 1 and then every 6 months (Visits 1, 14 and 27).

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	No	0

			level		
	Yes	2		Yes	1
New York Heart Association (NYHA) classification*	No	0			
	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: ____

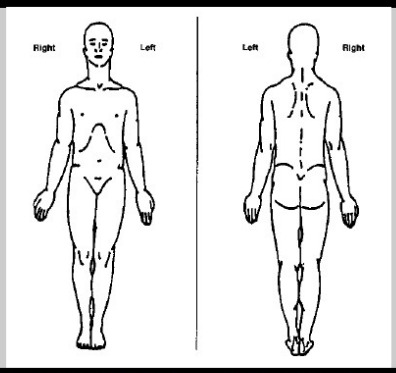
Name: _____ _____ _____

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

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

A. General Activity

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

B. Mood

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

C. Walking Ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

14.8 Appendix 8. Premedication Discontinuation Guide

Patients on agalsidase alfa can be included in the study when under premedication to diminish the side effects to the drug.

During the first 2 months of PRX-102 treatment (5 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 7 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 = ☐