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

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.

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

- 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.

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

- 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:

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 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

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.

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:

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.

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 ($eGFR_{CKD-EPI}$)

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

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).

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						

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:

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

  - 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

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.

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.

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.

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.