NCT01981720

CLINICAL STUDY PROTOCOL

Protocol Title: A Multi Center Extension Study of PRX-102 Administered by Intravenous Infusions Every 2 Weeks for up to 60 Months to Adult Fabry Patients

Protocol Number: PB-102-F03

Investigational Product:	PRX-102, a chemically modified human alpha galactosidase, expressed in plant cells
Indication:	PRX-102 is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (alpha galactosidase deficiency)
Phase:	Phase 1/2
Protocol Version:	Version 2 Version 3 , 15 Jan 2015 Version 3B, 26 Jan 2015 (Dallas only) Version 3C, 28 Jan 2015 (Virginia and Iowa only) Version 3E, 18 Jan 2015 (Spain only) Version 4, 05 Jan 2016
Name and Affiliation of Principal Investigator:	A list of the Principal Investigators is maintained in the trial master file
Name and Address of Sponsor:	Protalix Ltd. 2 Snunit Street Science Park Carmiel 20100, Israel
GCP Statement:	This study will be performed in compliance with GCP, including the archiving of essential documents.

1 SYNOPSIS

TITLE: A Multi Center Extension Study of PRX-102 Administered by Intravenous Infusions Every 2 Weeks for up to 60 Months to Adult Fabry Patients
INVESTIGATIONAL PRODUCT: PRX-102, a chemically modified human alpha galactosidase, expressed in plant cells
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: Phase 1/2
INVESTIGATIONAL SITES/LOCATIONS: Multicenter
OBJECTIVES: To evaluate the ongoing safety, tolerability, and efficacy parameters of PRX-102 in adult Fabry patients who have successfully completed treatment with PRX-102 in studies PB-102-F01 and PB-102-F02
STUDY DESIGN: Patients will be enrolled to receive PRX-102 at the dose of, 1.0 mg/kg, as an intravenous infusion every 2 weeks (+/- 3 days). The duration of treatment will be up to 60 months or until PRX-102 is commercially available to the subject at the discretion of the Sponsor and no less than 36 months.
NUMBER OF SUBJECTS (PLANNED): up to 16 adult (males and females) Fabry patients (≥18 yrs) who completed study PB-102-F02
MAIN CRITERIA FOR INCLUSION AND EXCLUSION: *Key inclusion criteria:* Eligible patients must fulfill the following inclusion criteria: 1. Completion of study PB-102-F02 2. The patient signs informed consent 3. Female patients of child-bearing potential agree to use a medically acceptable method of contraception, not including the rhythm method. Acceptable methods of contraception include hormonal products, intrauterine device, or male or female condoms. Contraception should be used throughout the duration of the study and for 3 months after termination of treatment.. *Key exclusion criteria:* The presence of any of the following excludes a patient from study enrollment: 1. Presence of any medical, emotional, behavioral or psychological condition that, in the judgment of the Investigator and/or Medical Director, would interfere with the patient's compliance with the requirements of the study

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION: PRX-102 indoses of 1.0 mg/kg, intravenously, every 2 weeks. For each patient that received 0.2 or 2 mg/kg in study PB-102-F02, the dose will be adapted gradually to 1 mg/kg. Study drug will be administered at the study clinic or infusion center unless the Medical Director and Investigator approve for home care set up, based on the clinical condition of the subject and local practices and regulations.

DURATION OF TREATMENT: up to 60 months or until the product is commercially available to the subject at the discretion of the Sponsor and no less than 36 months.

DISCONTINUATION FROM TREATMENT:

Reasons for permanent discontinuation include the following:

- The patient experiences two or more Grade 3 toxicities or one or more Grade 4 toxicity that are considered by the investigator to be associated with PRX-102 treatment (U.S. Department of Health and Human Services, 2010)
- The patient experiences progressive hypersensitivity or severe hypersensitivity - to be treated appropriately and withdrawn from the study
- The patient requests to discontinue treatment
- The Investigator feels that it is not in the best interest of the patient to continue treatment and/or if the investigator believes that the patient can no longer be compliant with the requirements of the study
- Marketing approval is obtained and the drug is available at the patient country or at the discretion of the sponsor

EXPLORATORY EFFICACY ENDPOINTS:

- Gb3 concentrations in plasma sediment at baseline (will be the values from the last infusion of study PB-102-F02) and every 3 months up to 24 months and then every 6 months up to end of study.
- Globotriaosylsphingosine (Lyso-Gb3) concentration in plasma at baseline (will be the values from the last infusion of study PB-102-F02) and every 3 months up to 24 months and then every 6 months up to end of study.
- Assessment of gastrointestinal symptoms at baseline (will be the values from the last infusion of study PB-102-F02) and every 3 months up to 24 months and then every 6 months up to end of study. Questionnaire for Evaluation Gastrointestinal Symptoms (Dehout et al., 2004) used until Protocol version 4 is approved and maybe substituted by the IBS-SSS questionnaire when available
- Kidney functions (eGFR and proteinuria) at baseline (will be the values from the last infusion of study PB-102-F02) and every 3 months up to 24 months and then every 6 months up to end of study.
- Short Form Brief Pain Inventory (BPI) at baseline (will be the values from the last infusion of study PB-102-F02) and every 3 months up to 24 months and then every 6

months up to end of study.

- Left ventricular mass (LVM) and myocardial fibrosis assessment by cardiac MRI every 12 months during the study. (Baseline value will be the evaluation performed at the last visit of study PB-102-F02
- Cardiac function assessment by echocardiography and stress test every 12 months during the study. Baseline value will be the evaluation performed at last visit of study PB-102-F02
- Mainz Severity Score Index (MSSI) every 6 months during the study. (Baseline value will be the evaluation performed at last visit of study PB-102-F02.

SAFETY ENDPOINTS:

Changes from baseline in:

- Clinical laboratory tests
- Physical examination
- Assessment of the injection site reactions
- ECG
- Treatment-emergent adverse events (TEAEs)
- Anti-PRX-102 antibodies
- Cerebrovascular disease assessment (clinical and MRI evaluation) at visit 24 M and 60 M (total treatment of 3 years and 6 years).

STATISTICAL ANALYSIS:

Patients who received at least one dose of study drug will be included in the safety analysis.. Results of safety evaluations (including TEAEs, injection site reactions, physical examinations, ECG, and laboratory analyses) will be summarized and described.

No formal statistical analyses will be performed in this study. Quantitative data will be summarized across dose groups by presenting sample size, mean and its standard error, standard deviation, median, minimum, and maximum values for both actual and change from baseline results. Qualitative data will be summarized across dose groups by showing frequency and percentage within each category.

DOCUMENT APPROVAL

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

SPONSOR REPRESENTATIVE

_____ _____

Signature Date

PRINCIPAL INVESTIGATOR

_____ _____

Signature Date

Print Name: _____

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2 LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
AE	Adverse event
Alpha-GAL-A	Alpha galactosidase-A
ARB	Angiotensin receptor blocker
AUC_0-t	Area under the concentration-time curve from baseline to a specified time (t)
AUC_0-∞	Area under the concentration-time curve from baseline to infinity
BPI	Brief pain inventory
C3	Complement C3
C4	Complement C4
CHO	Chinese hamster ovary
CKD	Chronic kidney disease
C_{max}	Maximum concentration observed
CRF	Case report form
CT	Computed tomography
EC	Ethics Committee
ECG	Electrocardiography
eGFR	Estimated glomerular filtration rate
ERT	Enzyme replacement therapy
Gb3	Globotriaosylceramide
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IC	Informed consent
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
LLN	Lower limit of normal
LVH	Lt. ventricular hypertrophy
LVM	Lt. ventricular mass
Lyso-Gb3	Globotriaosylsphingosine
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
PK	Pharmacokinetics
PP	Per Protocol
SAE	Serious adverse event
SPM	Study Procedures Manual
TIA	Transient ischaemic attack
$t_{1/2}$	Time at which the concentration is half of the maximum value (C_{max})

3 ETHICAL CONDUCT OF THE STUDY AND REGULATORY REQUIREMENTS

3.1 Institutional Review Board (IRB)

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

3.2 Ethical Conduct of the Study

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

3.3 Subject Information and Consent

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

The investigator will explain that the patients 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 forms.

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

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

4 INTRODUCTION

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

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

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

As Fabry disease is an X-linked disorder, the prevalence of the mutation is predicted to be two times higher in women than in men. There is considerable variation in phenotype in heterozygous females. However, despite the X-linked nature of the disease, heterozygous and therefore tissue-mosaic females can be as severely affected by Fabry disease as hemizygous males, experiencing progressive, multi-organ involvement, reduced quality of life and reduced life expectancy. Case-finding studies have reported mutations that are known to be associated with Fabry disease in 0.3-2.4% of women who had unexplained stroke, hypertrophic cardiomyopathy, or renal failure requiring haemodialysis. A recent study by Hughes et al, that compared men and women with Fabry disease, using data from the Fabry Outcome Survey

(FOS), 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).

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 and Guffon et al., 2001; Germain et al., 2007; Schaefer et al., 2009). In addition, ERT with both products leads to improvement in quality of life, reduction or stabilization of cardiac mass, preservation of renal function, and slowing down the decline of glomerular function (Wilcox et al., 2004; Schiffmann et al., 2006; Germain et al., 2007; Schiffmann 2009). Although these findings are encouraging, the clinical effects of the current treatment of Fabry patients are not as robust as anticipated and show only limited clinical improvement (Schaefer et al., 2009; Lidove et al., 2010; El Dib et al., 2011).

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 and Banikazemi et al., 2001; Eng and 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 enzymatic activity, extended circulation residence time and enhanced bioavailability of the enzyme relative to the commercial drug.

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. 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.

5 STUDY OBJECTIVES

To evaluate the ongoing safety, tolerability and efficacy parameters of PRX-102 in adult Fabry patients who have successfully completed treatment with PRX-102 in studies PB-102-F01 and PB-102-F02.

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan – Description

This will be an open-label, dose ranging study to evaluate the ongoing safety, tolerability and efficacy parameters of PRX-102 in adult Fabry patients (≥18 years of age).

Patients will be enrolled to receive 1.0 mg/kg of PRX-102 as an intravenous infusion every 2 weeks (+/- 3 days) for up to 60 months and no less than 36 months.

All disease parameters but GB3 in urine, kidney and skin biopsies, which were evaluated during study PB-102-F02 will continue to be assessed in this extension protocol (study PB-102-F03).

6.2 Discussion of Study Design

The extension study may provide additional information on safety, tolerability and clinical outcome in PRX-102-treated patients.

An interim analysis may be performed after all subjects have completed Month 12, 24, 36 and/or 48 months. In these analyses, descriptive statistics methods will be used to summarize available efficacy and safety parameters.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

The patients must fulfill the following inclusion criteria:

1. Completion of study PB-102-F02
2. The patient signs informed consent
3. 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. Acceptable methods of contraception include hormonal products, intrauterine device, or male or female condoms. Contraception should be used throughout the duration of the study and for 3 months after termination of treatment..

6.3.2 Exclusion Criteria

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

1. 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 patient experiences two or more Grade 3 toxicities or one or more Grade 4 toxicity considered by the investigator to be associated with PRX-102 treatment (U.S. Department of Health and Human Services, 2010)
- The patient experiences progressive hypersensitivity or severe hypersensitivity - to be treated appropriately and withdrawn from the study
- The patient requests to discontinue treatment
- Investigator feels that it is not in the best interest of the patient to continue treatment and/or if the Investigator believes that the patient can no longer be compliant with the requirements of the study
- Marketing approval is obtained and the drug is available at the patient country or at the discretion of the sponsor

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 patient for the full duration of the study or at least for 60 days following discontinuation. If circumstances prevent the patient from completing all visits, every attempt will be made to complete all procedures listed in Section 9 for last visit (60 months).

7 STUDY PRODUCT

7.1 Study Medication Supply

The Sponsor will provide the study drug to the study sites as needed.

7.2 Description and Formulation of Study Product

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

Each vial contains 10.2 mL of the following contents in liquid form:

20 mg PRX-102 (2.0 mg/mL)
0.7% NaCl
25-30 mM Sodium Citrate (pH 5.7 - 6.3)

7.3 Study Drug Dosage and Preparation

PRX-102 1.0 mg/kg PRX-102 vials are stored in liquid formulation at 2-8°C (36-46°F).

The drug concentration is 2.0 mg/mL.

The individual dose for each patient will be prepared according to patient's weight and assigned dose. The patient's weight is measured approximately every 6 months up to the end of study (Visits Months: 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60), in order to adjust the amount of drug that should be administered. If there has been a change in the patient's weight, the new measured weight will be used to calculate the amount of drug required, as from the following infusion visit.

The dose will be prepared by a pharmacist or nurse at the study site or at a home care setup in the case of home care. The required amount of enzyme will be adjusted with normal saline (0.9% NaCl) to a final volume of 150 mL/infusion. For subjects weighing more than 100kg, if the clinical conditions permit it, the final volume should be between 250 ml/infusion to 500 ml/infusion.

7.4 Description of Comparator Product

Not applicable.

7.5 Study Drug Administration

Patients will continue to receive 1 mg/kg PRX-102, administered bi-weekly every 2 weeks (+/- 3 days)

For each patient that received 0.2 or 2 mg/kg in study PB-102-F02, the dose will be adapted gradually:

The change in dose will be implemented at the study site only.

Patients that were treated in group I, 0.2mg/kg, the dose will be increased by 0.2 mg/kg in every third infusion up to the dosage of 1 mg/kg.

Patients that were treated in group III, 2mg/kg, the dose will be decreased by 0.25 mg/kg in every third infusion up to the dosage of 1 mg/kg. Pre-medication implemented per protocol in this treatment group can be discontinued if according to the investigator evaluation the patient tolerability to the infusion permit so. Discontinuation of pre-medication should occur towards the accommodation of the new dose, at the discretion of the investigator in a stepwise manner.

During the period of adaptation to the new dose the patient will maintain the same rate of the last infusion, and clinical follow up will be at least 2 hours.

After adjustment to the new dose, when applicable, study drug will be administered at the study clinic or infusion center unless the Medical Director and Investigator approve that the patient can receive the treatment at a home care setup, based on the clinical condition of the subject and local practices and regulations.

Infusion rate can be adjusted according to patient tolerability (see Appendix 2); All changes in infusion rate or volume including the programmed in the protocol, should be agreed between the Investigator and the Medical Director

If the infusions are well tolerated, the infusion rate can be increased by shortening of 30 minutes every third infusion, up to 1.5 hours infusion time and not less than that.

7.6 Packaging and Labeling

The drug product is packed in vials containing 20 mg PRX-102 (2.0 mg/mL), 0.7% NaCl and 25-30 mM Sodium Citrate (pH 5.7 - 6.3).

Liquid drug is 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) are sealed with aluminium seals.

The label for the study drug is presented in Appendix 1.

7.7 Conditions for Storage and Use

The study product is stored at 2-8°C (36-46°F).

7.8 Method of Assigning Subjects to Treatment Groups

The dose of all patients will be 1mg/kg so will be only one treatment group.

For each patient recieving 0.2 or 2 mg/kg in study PB-102-F02, the dose will be adapted gradually to 1 mg/kg according to the description in paragraph 7.5.

Patient number will continue to be as assigned in Study PB-102-F02.

7.9 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 IDP (Investigational Drug Product) 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 IDP 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.

7.10 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:

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

8 EFFICACY AND SAFETY ASSESSMENTS

8.1 Efficacy Variables

The following efficacy endpoints evaluated in Study PB-102-F02 will continue to be measured in this extension study. Baseline values for this extension study will be the values from the last infusion of study PB-102-F02.

- Gb3 concentrations in plasma at baseline and every 3 months up to visit 24 months, and then every 6 months up to end of study
- Globotriaosylsphingosine (Lyso-Gb3) concentration in plasma at baseline and every 3 months up to visit 24 months, and then every 6 months up to end of study
- Assessment of gastrointestinal symptoms at baseline and every 3 months up to visit 24 months, and then every 6 months up to end of study. Questionnaire for Evaluation Gastrointestinal Symptoms (Appendix 6-Dehout et al., 2004) will be used until Protocol version 4 is approved and may be substituted by the IBS-SSS questionnaire when available (Appendix 7).
- Kidney functions (eGFR and proteinuria) at baseline and every 3 months up to visit 24 months, and then every 6 months during the rest of the study
- Short Form Brief Pain Inventory (BPI) at baseline and every 3 months up to visit 24 months, and then every 6 months up to end of study (Appendix 8)
- Left ventricular mass and myocardial fibrosis assessment by cardiac MRI at baseline and every 12 months during the study
- Cardiac function (assessed by echocardiography) and stress test at baseline and every 12 months during the study
- Mainz Severity Score Index (MSSI) at baseline and every 6 months during this study

8.2 Safety Variables

Safety will be assessed by the frequency, severity, and duration of treatment-emergent adverse events (TEAEs), including clinically significant laboratory abnormalities, ECG changes from baseline test, brain MRI changes from baseline, physical examination findings, assessment of the injection site reactions and existence of Anti PRX-102 antibodies after administration of the study drug.

8.2.1 Clinical Laboratory

- Hematology: complete blood count; total white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils), total red blood cells (hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration), and platelets
- Biochemistry: sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, phosphate (inorganic), uric acid, total protein, albumin, bilirubin (total), alkaline

phosphatase, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, and creatine phosphokinase

- Urinalysis: dipstick for presence of blood, glucose, ketones, and protein

8.2.2 Anti-PRX-102 Antibodies

Anti-PRX-102 antibodies, including neutralizing antibodies in patients having a positive IgG antibody response, will be assessed using a validated analytical method.

Anti-PRX-102 antibodies will be assessed every 3 months up to visit 24 months, and then every 6 months up to end of the study, and 3 months after last infusion.

8.2.3 Adverse Events

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

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

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

A treatment emergent adverse event is any adverse event occurring after start of study medication and within the time of residual drug effect (30 days after the last administration of the study medication), or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after start of study medication and within the time of residual drug effect.

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

Note that death is not an event, but the cause of death is. An exception is the event of sudden death of unknown cause. Note that hospitalization is not an event; however, the reason for hospitalization is. Procedures are not events; the reasons for conducting the procedures are. In general, only the reason for conducting the procedure will be captured as an adverse event.

However, if deemed necessary by the Investigator, a procedure can be captured along with the reason for conducting the procedure.

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

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

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

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

Important adverse events that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient'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 patient using concise medical terminology. In addition, each trial patient will be questioned about adverse events. The question asked will be "Since you began taking the study medication, have you had any health problems?"

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

Throughout the duration of the study, the Investigator will closely monitor each patient 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 patient, 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 patient died, and if treatment was required.

Events will be coded to one of the following intensity categories below:

Severity	Definition
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabeling;limiting self care ADL**
Grade 4	Life threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.***

*Activities of Daily Living (ADL)- Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, using the toilet, taking medications, and not bedridden.
***Grade 5 (Death) is not appropriate for some AEs

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 patient'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 patient's clinical state, environmental factors or other therapies administered.
Probable	Clear-cut temporal association with administration with improvement on cessation of investigational medicinal product or reduction in dose. Reappears upon rechallenge. Follows a known pattern of response to the investigational medicinal product.
Definitely	There is evidence of exposure to the test product, for example, reliable history or acceptable compliance assessment; the temporal sequence of the AE onset relative to the drug is reasonable; the AE is most likely to be explained by the drug treatment than by another cause; the challenge is positive; re-challenge (if feasible) is positive; the AE shows a pattern consistent with previous knowledge of the drug treatment.

Adverse events with the causality assessed as 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 (972-4-9028162) or Safety Monitor (212-681-2100) to notify the Sponsor of the event.

SAEs will be reported to all IECs/IRBs according to local requirements and applicable health authorities in accordance with applicable regulatory requirements.

The sponsor shall notify the appropriate regulatory authorities as required and all participating Investigators of any adverse event associated with the use of the drug that is both serious and unexpected. The Investigator must also notify the IECs/IRBs.

8.2.3.3 Pregnancy

Although pregnancy as such is not considered an AE or SAE, it is the responsibility of the Investigator to report to Protalix, by telephone immediately, any pregnancy occurring in a female study patient or female partner of a male study patient either during the study or within 42 days following the last dose of study drug. Protalix will provide the Investigator with a Pregnancy Tracking Form that is to be completed by the study site on a periodic basis and faxed to Protalix. The Investigator will follow the pregnancy until the end of the pregnancy. If the pregnancy continues to term (delivery), the health of the infant must also be reported to Protalix

9 STUDY PROCEDURES AND FLOW CHART

9.1 Study Flow Chart

Activity	Screening visit (Day 1)	Infusions visits 1-131(±3days)	Visit 2 M (±6days)	Visits: 3M 9 M 15 M 21 M (±6days)	Visits: 6M 18 M 30 M 42 M 54M (±6days)	Visits : 12 M 36M 48 M (±6days)	Visits: 24 M 60M (±6 days)	3 Months after last infusion[4] (±6 days)
Review Inclusion/ exclusion criteria	x							
Sign ICFs	x							
Concomitant medications[3]	x[1]	x	x	x	x	x	x	x
Vital signs[3]	x[1]	x	x	x	x	x	x	
Body weight	x[1]				x	x	x	
Physical examination	x[1]			x	x	x	x	
Adverse events assessments[3]	x[1]	x	x	x	x	x	x	x
Blood Chemistry	x[1]			x	x	x	x	
Blood count	x[1]			x	x	x	x	
Urinalysis	x[1]			x	x	x	x	
Spot urine test for proteinuria	x[1]			x	x	x	x	
Plasma Gb3 concentration	x[1]			x	x	x	x	
Plasma Lyso Gb3 concentration	x[1]			x	x	x	x	
Anti PRX-102 Antibodies (IgG)	x[1]		x	x	x	x	x	x
Electrocardiography (ECG)	x[1]				x	x	x	
Short form Brief Pain Inventory (BPI)	x[1]			x	x	x	x	
Gastrointestinal symptoms	x[1]			x	x	x	x	
Cardiac function assessment (echocardiography and stress test)						x	x	
Cardiac MRI						x	x	
Brain MRI							x	
Mainz Severity Score Index (MSSI)	x[1]				x	x	x	
IV infusion[2]		x[2]						
Plasma PRX-102 level (PK)[4]		x[4](only on infusion 1)						

[1] values for these evaluations will be transferred from Visit 20 of study PB-102-F02

[2] during all the study, infusions are administered every 2 weeks

[3] should be performed at all visits

[4] Blood sample for last PK timepoint of last infusion (Visit 20) of protocol PB-102-F02 will be drawn pre-infusion

9.2 Study Visits

Study visits schedule described below may not correspond in time with the every two weeks infusions schedule, particularly if the subject is being infused at an infusion center or at a home set up**.**

9.2.1 Infusion visits

PRX-102 will be administered by IV infusion every 2 weeks (±3 days) for up to 60 months (131 infusion visits)

At each infusion, the following activities will be performed:

1. Concomitant medications
2. Adverse events
3. The subjects will be observed clinically for a minimum of 1 hour after dosing
4. Vital signs will be evaluated before starting the infusion every 30 minutes during the infusion and at the end of clinical observation
5. The injection site will be evaluated

9.2.1.1 Additional Actions to be performed in Specific infusion visits

Infusion visit 1 (± 3 days)

1. Blood sample for last PK timepoint of last infusion (Visit 20) of protocol PB-102-F02 will be drawn pre-infusion

9.2.2 Study Visits

9.2.2.1 Screening Visit, Day 1 (Visit 20 of Study PB-102-F02)

1. Confirm eligibility by review of inclusion/exclusion criteria
2. Obtain written informed consent from the patient

9.2.2.2 Visit 2M (± 6 days)

1. Blood sample for assessing anti PRX-102 Antibodies will be drawn pre-infusion

9.2.2.3 Visit 3M, 9M, 15M and 21M (± 6 days)

1. Physical examination
2. Laboratory tests
   - Hematology
   - Biochemistry
   - Urinalysis
   - Spot urine sample for proteinuria
   - Plasma Gb3 (pre-infusion)
   - Plasma Lyso-Gb3 (pre-infusion)
   - Anti-PRX-102 antibodies (pre-infusion)
3. Short Form Brief Pain Inventory (BPI) (Appendix 8)

4. Gastrointestinal symptoms assessment questionnaire(Appendix 6) or IBS-SSS when available (Appendix 7)

9.2.2.4 Visit 6M, 18 M, 30M, 42M, 54M (±6 days)

1. Physical examination, including body weight
2. Laboratory tests
   - Hematology
   - Biochemistry
   - Urinalysis
   - Spot urine sample for proteinuria
   - Plasma Gb3 (pre-infusion)
   - Plasma Lyso-Gb3 (pre-infusion)
   - Anti-PRX-102 antibodies (pre-infusion)
3. ECG
4. Short Form Brief Pain Inventory (BPI) (Appendix 8)
5. Gastrointestinal symptoms assessment questionnaire (Appendix 6) or IBS-SSS when available (Appendix 7)
6. Mainz Severity Score Index (MSSI) (Appendix 6)

9.2.2.5 Visit 12 M, 36 M, 48 M (± 6 days)

1. Physical examination, including body weight
2. Laboratory tests
   - Hematology
   - Biochemistry
   - Urinalysis
   - Spot urine sample for proteinuria
   - Plasma Gb3 (pre-infusion)
   - Plasma Lyso-Gb3 (pre-infusion)
   - Anti-PRX-102 antibodies (pre-infusion)
3. ECG
4. Cardiac MRI
5. Cardiac Function assessment (echocardiography and stress test)
6. Short Form Brief Pain Inventory (BPI) (Appendix 8)
7. Gastrointestinal symptoms assessment questionnaire (Appendix 6) or IBS-SSS when available (Appendix 7)
8. Mainz Severity Score Index (MSSI) (Appendix 6)

9.2.2.6 Visit 24 M, 60 M (± 6 days)

1. Physical examination, including body weight
2. Laboratory tests

- Hematology
- Biochemistry
- Urinalysis
- Spot urine sample for proteinuria
- Plasma Gb3 (pre-infusion)
- Plasma Lyso-Gb3 (pre-infusion)
- Anti PRX-102 antibodies (IgG)

3. ECG
4. Gastrointestinal symptoms assessment questionnaire (Appendix 6) or IBS-SSS when available (Appendix 7)
5. Short Form Brief Pain Inventory (BPI) (Appendix 8)
6. Cardiac MRI
7. Mainz Severity Score Index (MSSI) (Appendix 6)
8. Cardiac Function assessment (echocardiography and stress test)
9. Brain MRI

9.2.2.7 Three months after last infusion (±6 days)

Anti PRX-102 Antibodies

9.2.2.8 Premature Withdrawal Visit

All attempts should be made to perform all the tests for last Visit for patients withdrawing before this Visit (including Anti-PRX-102 antibodies three months after last infusion).

10 STATISTICAL METHODS PLANNED AND SAMPLE SIZE

10.1 Determination of Sample Size

The sample size was determined pragmatically since the number of patients that can be recruited in a reasonable period of time for this rare disease is limited. In addition, sample size in this extension study depends upon the number of patients who complete Study PB-102-F02 and enroll into this study

10.2 Subject Populations

10.2.1 Intent-to-Treat (ITT) Population

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

10.2.2 Per Protocol (PP) Population

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

10.2.3 Safety Population

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

10.3 Analysis

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

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

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

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

Efficacy Variables. For each efficacy variable, the percent change from baseline to each visit the specific variable is measured will be calculated and summarized with descriptive statistics (n, mean and its standard error, median, standard deviation, range, and interquartile range).

Efficacy evaluation will include:

- Gb3 in plasma median percentage change and interquartile range from baseline to Month 12 , 24, 36, 48 and 60 months (total treatment of 2, 3, 4, 5 and 6 years respectively)
- Lyso-Gb3 in plasma median percentage change and interquartile range from baseline to Month 12 , 24, 36, 48 and 60 months (total treatment of 2, 3, 4, 5 and 6 years respectively)
- Improvement in gastrointestinal symptoms from baseline to Month 12 , 24, 36, 48 and 60 months (total treatment of 2, 3, 4, 5 and 6 years respectively)
- Proteinuria median percentage change and interquartile range from baseline to Month 12, 24, 36, 48 and 60 months (total treatment of 2, 3, 4, 5 and 6 years respectively)
- eGFR median percentage change and interquartile range from baseline to Month 12 and , 24, 36, 48 and 60 months (total treatment of 2, 3, 4, 5 and 6 years respectively)
- Descriptor scores for the Short Form Brief Pain Inventory (BPI) will be summarized for baseline, Month 12 , 24, 36, 48 and 60 months (total treatment of 2, 3, 4, 5 and 6 years respectively)
- MSSI scores at baseline, Month 12 , 24, 36, 48 and 60 months (total treatment of 2, 3, 4, 5 and 6 years respectively)
- Left ventricular mass and myocardial fibrosis severity will be summarized for Baseline of Study PB-102-F01, Months 3 and 9 of PB-102-F02 (total treatment of 6 and 12 months respectively) and Months 12 , 24, 36, 48 and 60 months (total treatment of 2, 3, 4, 5 and 6 years respectively)
- Cardiac function, evaluated by echocardiography and stress test, will be summarized for Baseline of Study PB-102-F01, Months 3 and 9 of PB-102-F02 (total treatment of 6 and 12 months respectively) and Months 12 , 24, 36, 48 and 60 months (total treatment of 2, 3, 4, 5 and 6 years respectively)

10.4 Safety Analysis

Safety will be assessed by evaluation of adverse events, injection site reactions, clinical laboratory results brain MRI and anti-PRX-102 antibodies.

10.4.1 Adverse Events

Adverse events will be coded to system organ class and preferred term using MedDRA version 14.1. All adverse events occurring after the initiation of the study treatment (treatment emergent adverse events) will be reported, including events present at baseline that worsened during the study.

Adverse events will be summarized by treatment group to provide visual comparison among the treatment groups with respect to incidence of adverse events (the number of patients 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 patients who experience the same adverse event on more than one occasion.

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

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

10.4.2 Clinical Laboratory

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

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

10.5 Interim Analysis

An interim analysis may be performed after all subjects have completed months 12, 24, 36 and/or 48 months. In these analyses, descriptive statistics methods will be used to summarize available efficacy and safety parameters.

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 patient 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 treatment number and patient initials will be used to identify the patient. In countries in which subject initials is confidential information, pseudo initials will be used.

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

Protalix Ltd. or their designee will monitor completed Case Report Forms (CRFs). A case report form will be provided for each screened 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. In countries in which subject initials is confidential information, pseudo initials will be used. 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.

13 Appendices

13.1 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-F03
Study drug name: 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: PRX-102
20 mg/vial for intravenous injection only as directed
10mL in each vial
Batch number: _____ Expiry: MM-YYYY
Protocol #: PB-102-F03
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

13.2 Appendix 2. Infusion Rate Algorithm

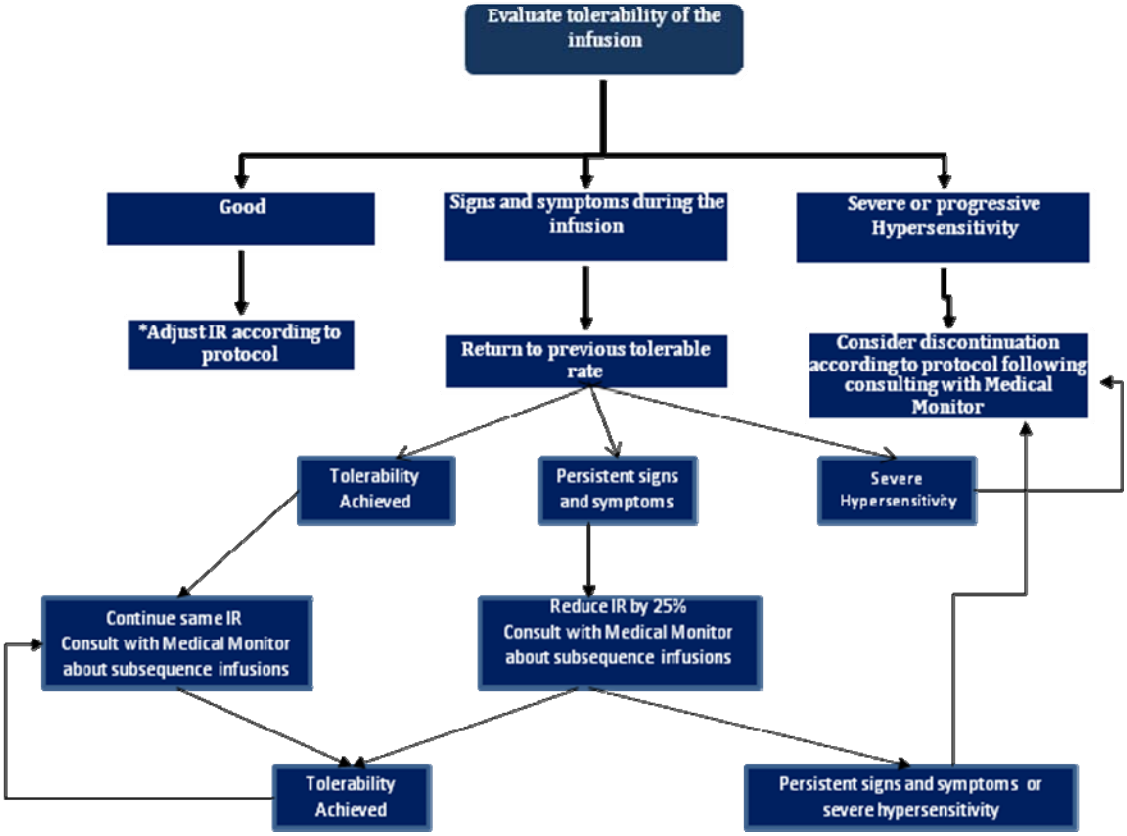
The infusion rate (IR) may be adjusted according to individual subject symptoms and signs. The assumptions with respect to adverse experiences to the infusion are:

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 infusion rates to be followed:



* For patients with a good tolerability the time of infusion will be decreased by 30 minutes every third infusion, up to a minimum infusion time of 1.5 hours.

Infusion rate can 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

13.3 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 and withdraw the patient from the study.

Treat as follows:

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

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

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

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

Bronchospasm

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

Laryngeal edema

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

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

Premedication

Premedication for subsequent PRX-102 infusions may be considered at the discretion of the investigator and Medical Director for patients 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.

All infusions of patients in Treatment Group III (2mg/kg) will be given with premedication: H1 (diphenhydramine, hydroxyzine, cetrizine, loratadine, desloratidine) blocker plus H2 blocker (ranitidine, cimetidine, famotidine) at standard doses 12 ±2 hours and 2 ±0.5 hours before the start of the infusion.

13.4 Appendix 4. Cardiac MRI

13.4.1 Patients and Sites

Up to eighteen (18) patients will be enrolled in this trial in several sites worldwide.

13.4.2 Magnetic Resonance Imaging (MRI) Data

Each patient enrolled in this trial had a cardiac MRI at baseline of Protocol PB-102-F01 for screening and as a reference for further MRI evaluations in protocol PB-102-F02 and in this protocl (12 and 24 Months of this study, respectively). 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.

13.4.3 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)

13.4.4 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.

13.4.4.1 Standardization of Image Acquisition, Initial Site Qualification

In general, this trial will use the same imaging procedures already established and validated in Protocol PB-102-F01 and in protocol PB-102-F02.

The image acquisition procedure will be standardized by the imaging CRO among allparticipating 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. 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.

13.4.4.2 Subject Sedation

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

13.4.4.3 Quality Control of Image Data and Site Quality Assurance During the Course of the Trial

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.

13.4.5 Image Processing and Centralized Analysis

13.4.5.1 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.

13.4.5.2 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.

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 efficacy analysis results at 12 and 24 Months of this study (total treatment of 2 and 3 years). Reference for these evaluations will be the cardiac MRI prformed at baseline And in study PB-102-F02.

13.4.6 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.

13.4.7 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

13.4.8 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 13.4.4.3 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.

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

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

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

The MSSI will be performed at 12 and 24 month visits in this protocol (total treatment of 2 and 3 years respectively).

Evaluation of the presence of Cornea Verticillata will be done by the PI or by referral to an Ophthalmologist

13.5.1 The Mainz Severity Score Index (MSSI)

General Score			Neurological Score		
Sign/symptom	**Rating**	**MSSI score**	**Sign/symptom**	**Rating**	**MSSI score**
Characteristic facial appearance	No	0	Tinnitus	No	0
	Yes	1		Mild	1
Angiokeratoma	None	0		Severe	2
	Some	1	Vertigo	No	0
	Extensive	2		Mild	1
Oedema	No	0		Severe	2
	Yes	1	Acroparaesthesia	No	0
Musculoskeletal	No	0		Occasional	3
	Yes	1		Chronic	6
Cornea verticillata	No	0	Fever pain crisis	No	0
	Yes	1		Yes	2
Diaphoresis	Normal	0	Cerebrovascular	No	0
	Hypo/Hyper	1		Ischemic lesions (in MRI/CT)	1
	Anhidrosis	2		TIA/migraine etc.	3
Abdominal pain	No	0		Stroke	5
	Yes	2	**Psychiatric/ psychosocial**		
Diarrhoea/constipation	No	0	Depression	No	0
	Yes	1		Yes	1
Haemorrhoids	No	0	Fatigue	No	0
	Yes	1		Yes	1
Pulmonary	No	0	Reduced activity level	No	0
	Yes	2		Yes	1
New York Heart 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	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			
Maximun Score		**20**	**Maximun 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.

13.6 Appendix 6. Questionnaire for Evaluation Gastrointestinal Symptoms

(Dehout et al., 2004)

Patients will be asked to rate the severity of abdominal pain on a 5-point numerical scale as:

0 (no pain), representing the absence of any abdominal pain;

1 (mild pain), representing discomfort;

2 (moderate pain), representing pain that results in slowing of normal activity;

3 (severe pain), representing pain that results in cessation of all activity; and

4 (very severe pain), representing pain requiring medical intervention.

Patients will be asked to rate the frequency of the occurrence of both abdominal pain and diarrhoea as:

0 (never), representing the absence of the symptom;

1 (rarely), representing an occurrence rate of less than once a month;

2 (monthly), representing an occurrence rate of at least once a month;

3 (weekly), representing an occurrence rate of at least once a week; and

4 (daily), representing an occurrence rate of at least once a day.

13.8 Appendix 7. IBS SSS

IBS QUESTIONNAIRE

Name: _____ **G.P. Name:** _____

Address: _____ **Address:** _____

_____ _____

_____ _____

Telephone: _____ **Telephone:** _____

Date of birth: _____

Marital status: Single / Married / Divorced / Widowed / Co-Habit

Occupation: _____ **Sex:** M F

Ethnic background: Caucasion (white) / Afro-Carribean / Asian / Oriental

Fathers Occupation (even if retired): _____

INSTRUCTIONS

This form is designed to enable us to record and monitor the severity of your IBS. It is to be expected that your symptoms might vary over time, so please try and answer the questions based on how you currently feel (ie over the last 10 days or so). All information will be kept in **strict** confidence.

1. For questions where a number of different responses are a possibility please circle the response appropriate to you.
2. Some questions will require you to write in an appropriate response.
3. Some questions require you to put a cross on a line which enables us to judge the severity of a particular problem.

For example:

How severe was your pain?

Please place your cross (X) anywhere on the line between 0-100% in order to indicate as accurately as possible the severity of your symptom.

This example shows a severity of approximately 90%.

0% no pain — not very severe — quite severe — severe — very severe — 100%

1

PART 1 : SEVERITY SCORE

1. a) ***Do you currently suffer from abdominal (tummy) pain?*** YES NO *Circle appropriate box* — *For office use only SCORE*

   b) ***If yes, how severe is your abdominal (tummy) pain?***

   0% — no pain — not very severe — quite severe — severe — very severe — 100%

   c) ***Please enter the number of days that you get the pain in every 10 days.***
   For example if you enter 4 it means that you get pain 4 out of 10 days. If you get pain every day enter 10

   Number of days with pain _____ x10

2. a) ***Do you currently suffer from abdominal distension* (bloating, swollen or tight tummy)*** YES NO *Circle appropriate box*
   *(*women, please ignore distension related to your periods)*

   b) ***If yes, how severe is your abdominal distension/tightness***

   0% — no distension — not very severe — quite severe — severe — very severe — 100%

3. ***How satisfied are you with your bowel habit?***

   0% — very happy — quite happy — unhappy — very unhappy — 100%

4. ***Please indicate with a cross on the line below how much your Irritable Bowel Syndrome is affecting or interfering with your life in general***

   0% — not at all — not much — quite a lot — completely — 100%

IBS SEVERITY SCORE: _____

2

PART 2 : OTHER IBS DATA

BOWEL HABIT

5. a) ***What is the most number of times you open your bowels per day/week/month?***

   Number of times _____ per day / week / month *(Circle appropriate)*

   Note: For some people the answer to part a and b could be the same

   b) ***What is the least number of times you open your bowels per day/week/month?***

   Number of times _____ per day / week / month *(Circle appropriate)*

6. In the following questions you may circle more than one answer:

   Are your motions ever:

   a) ***normal*** often / occasionally / never *(Circle appropriate)*
   b) ***hard*** often / occasionally / never *(Circle appropriate)*
   c) ***very thin (like string)*** often / occasionally / never *(Circle appropriate)*
   d) ***in small pieces (like rabbit pellets)*** often / occasionally / never *(Circle appropriate)*
   e) ***mushy (like porridge)*** often / occasionally / never *(Circle appropriate)*
   f) ***watery*** often / occasionally / never *(Circle appropriate)*

7. In the following questions you may circle more than one answer:

   Do you ever: *Circle appropriate box*

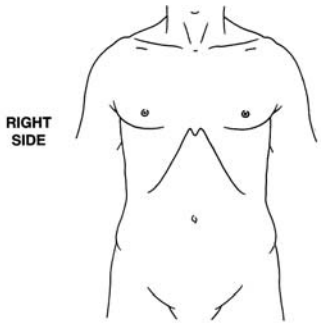
   a) ***pass mucus (or slime or jelly) with your motions*** YES NO
   b) ***pass blood with your motions*** YES NO
   c) ***have to hurry/rush to the toilet to open your bowels*** YES NO
   d) ***strain to open your bowels*** YES NO
   e) ***feel you haven't emptied your bowel completely after you have passed a motion*** YES NO

3

PART 2 : Continued

SITE OF PAIN

Please mark with a cross (x) on the diagram below where you get your pain *(use more than one x if necessary)*



8. ***Do you ever:***

   a) ***notice your stools are more frequent or loose when you get pain*** YES NO *Circle appropriate box*

   b) ***notice whether the pain is frequently eased by opening your bowels*** YES NO *Circle appropriate box*

9. ***In the last year on approximately how many weeks were you:***

   i) ***absent from work due to IBS*** _____
   (enter 52 if you have given up completely work because of IBS)

   ii) ***at work suffering from IBS*** _____

4

13.9 Appendix 8. Brief Pain Inventory- BPI (Short Form)

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

The short form of the Brief Pain Inventory (BPI) will be performed Every 3 months in this study.

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

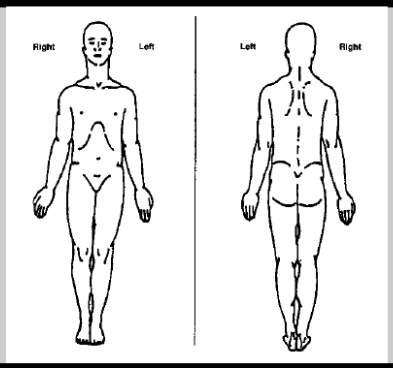
Name: _____ _____ _____

Last First Middle Initial

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

1. Yes 2. No

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



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

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

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

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

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

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

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

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

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

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

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

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

A. General Activity

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

B. Mood

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

C. Walking Ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

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