CLINICAL STUDY PROTOCOL

Protocol Title: A Phase 3, Open Label, Switch Over Study to Assess the Safety, Efficacy and Pharmacokinetics of pegunigalsidase alfa (PRX-102) 2 mg/kg Administered by Intravenous Infusion Every 4 Weeks for 52 weeks in Patients with Fabry Disease Currently Treated with Enzyme Replacement Therapy: Fabrazyme® (agalsidase beta) or Replagal™ (agalsidase alfa)

Protocol PB-102-F50

Investigational Product:	pegunigalsidase alfa (PRX-102), a PEGylated crossed linked recombinant human alpha galactosidase-A
Indication:	pegunigalsidase alfa (PRX-102) is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (alpha galactosidase A deficiency)
Phase:	3
Protocol Version:	Version 1, 27 March 2017 Version 2, 06 May 2017 Version 3, 27 Oct 2017 Version 4, 2 July 2018 Version 4.1, 25 July 2018
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 Phase 3, Open Label, Switch Over Study to Assess the Safety, Efficacy and Pharmacokinetics of pegunigalsidase alfa (PRX-102) 2.0 mg/kg Administered by Intravenous Infusion Every 4 Weeks for 52 weeks in Adult Patients with Fabry Disease Currently Treated with Enzyme Replacement Therapy: Fabrazyme® (agalsidase beta) or Replagal™ (agalsidase alfa)
INVESTIGATIONAL PRODUCT: Pegunigalsidase alfa, a PEGylated crossed linked recombinant human alpha galactosidase-A
INDICATION: Pegunigalsidase alfa (PRX-102) is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Fabry disease (alpha galactosidase deficiency).
PHASE OF DEVELOPMENT: 3
INVESTIGATIONAL SITES/LOCATIONS: Multicenter
OBJECTIVES: To evaluate the safety, efficacy and pharmacokinetics of pegunigalsidase alfa (PRX-102) in patients with Fabry disease currently treated with currently commercially available ERT (agalsidase alfa or agalsidase beta).
STUDY DESIGN: This is an open-label switchover study to assess the safety, efficacy, and pharmacokinetics of pegunigalsidase alfa treatment of 2 mg/kg every 4 weeks in patients previously treated with ERT, agalsidase alfa or agalsidase beta, for at least 3 years and on a stable dose (>80% labelled dose/kg) for at least the last 6 months. Following screening, patients will be enrolled and switched from their current ERT to receive intravenous (IV) infusions of pegunigalsidase 2 mg/kg every 4 weeks for 52 weeks (total of 14 infusions). At the time of enrollment, premedication, if used for the agalsidase alfa or agalsidase beta infusions before enrollment, will be continued using the same premedication regimen during the first infusion with pegunigalsidase alfa and then will be gradually tapered down at the Investigator's discretion during the next infusions based on Appendix 8. First infusions of pegunigalsidase alfa will be administered under controlled conditions at the investigation site. Based on Appendix 8, the patients will be able to receive their pegunigalsidase alfa infusions at a home care setup once the Investigator and Sponsor Medical Monitor agree that it is safe to do so. In the case of clear clinical deterioration, the treatment may be changed to 1.0 mg/kg every 2 weeks at the Investigator's discretion and discussion with the Medical Monitor.

NUMBER OF SUBJECTS (PLANNED): Up to 30 but not less than 25. Of the enrolled patients, up to 6 of the patients will be females (~20%).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Key inclusion criteria:

Eligible subjects must fulfill the following inclusion criteria:

1. Age: 18-60 years
2. A documented diagnosis of Fabry disease
3. Males: plasma and/or leucocyte alpha galactosidase activity (by activity assay) less than lower limit of normal according to the laboratory reference ranges and one or more of the characteristic features of Fabry disease
    a. Neuropathic pain
    b. Cornea verticillata
    c. 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
    a. Neuropathic pain
    b. Cornea verticillata
    c. Clustered angiokeratoma
5. Treatment with agalsidase alfa or agalsidase beta for at least 3 years and on a stable dose (>80% labelled dose/kg) for at least 6 months
6. eGFR $\geq$ 30 mL/min/1.73 m^2 by CKD-EPI equation at screening visit
7. Availability of at least 3 historical serum creatinine evaluations since starting ERT and not more than 2 years old
8. Female patients and male patients whose co-partners are of child-bearing potential agree to use a medically accepted, highly effective method of contraception. These include combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner, or sexual abstinence
9. Patients whose clinical condition, in the opinion of the Investigator, is suitable for treatment with ERT every 4 weeks.

Key exclusion criteria:

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

1. History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase alfa or agalsidase beta
2. History of renal dialysis or transplantation

3. Linear negative slope of eGFR of ≥ 2 mL/min/1.73 m^2 based on at least 4 serum creatinine values over approximately 2 years (including the value obtained at the screening visit)
4. History of acute kidney injury in the 12 months prior to screening, including specific kidney diseases (e.g., acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (e.g., ischemia, toxic injury); as well as extrarenal pathology (e.g., prerenal azotemia and acute post renal obstructive nephropathy)
5. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated or dose changed in the 4 weeks prior to screening
6. Urine protein to creatinine ratio (UPCR) at screening > 0.5 g/g or mg/mg or 500 mg/g and not treated with an ACE inhibitor or ARB
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. Cerebrovascular event (stroke, transient ischemic attack) in the 6-month period before screening
10. 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: Upon confirmation of eligibility, patients will be switched to pegunigalsidase alfa 2 mg/kg, administered intravenously, every 4 weeks.

Infusion time with pegunigalsidase alfa changes according to the weight of the patient pending: patient tolerability, Investigator evaluation, and Sponsor Medical Monitor/Director's approval and after an attempt to taper down gradually used pre-medication as described in Appendix 8.

- For patients weighing up to (≤) 100 kg, the infusion length will be 4.5 hours and may be reduced gradually to 2 hours
- For patients weighing more than (>) 100 kg, the first infusion length will be 6 hours and may be reduced gradually to 3 hours

DURATION OF TREATMENT: 52 weeks (14 infusions) with the option to be enrolled in an open-label extension study upon completion of the study.

DISCONTINUATION FROM TREATMENT: Reasons for permanent discontinuation include the following:

- Patient experiences two or more Grade 3 toxicities or one or more Grade 4 toxicity considered by the Investigator to be associated with pegunigalsidase alfa treatment (CTCAE v. 4.03, 2010)
- Patient experiences progressive hypersensitivity or severe hypersensitivity that is not

allayed with pre-treatment

- 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.

SAFETY ENDPOINTS:

Changes from baseline in:

- Clinical laboratory tests
- Physical examination
- Assessment of the injection site
- Electrocardiogram
- Treatment-emergent adverse events
- Ability to taper off infusion premedication
- Requirement for use of premedication overall to manage infusion reactions
- Treatment-induced anti-pegunigalsidase alfa antibodies

EFFICACY EXPLORATORY ENDPOINTS:

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

PHARMACOKINETICS (PK): Blood samples from all patients will be taken for PK analysis on Day 1 and at the end of treatment at Visit 14 (week 52). Blood samples will be drawn for an additional intermediate PK analysis at Visit 7 (week 24), for all patients who signed inform consent to this version (Version 4) before reaching Visit 7 (week 24), or at Visit 11 (week 40) for patients who passed Visit 7 at the time of signing the inform consent to this version. The following (but not limited to) PK parameters will be derived from the plasma concentration *versus* time profiles to determine the PK of the study drug: C_{max}, T_{max}, $t_{1/2}$, AUC_{0-t}, and $AUC_{0-\infty}$. Blood samples will be drawn at the following time points: pre-infusion (baseline); 1 hour after the beginning of the infusion; at the end of the infusion, at 1±0.25, 2±0.25, 4±0.25, 8±0.25, 24±0.5, 48±3, and 96±3 hours post-infusion and at 14±3, 21±3 and 28±3 days post-infusion

before next infusion (a total of 13 timepoint within 28 days).

STATISTICAL ANALYSIS:

The sample size of approximately 30 patients is adequate to evaluate the safety of switching from agalsidase alfa and agalsidase beta to pegunigalsidase alfa in Fabry disease in which patient recruitment in clinical trials is difficult.

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

An interim analysis may be conducted for administrative purposes.

DOCUMENT APPROVAL

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

SPONSOR REPRESENTATIVE

25 July 2018

Signature Date

PRINCIPAL INVESTIGATOR

Signature Date

Print Name: _____

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2 LIST OF ABBREVIATIONS

ACEI	Angiotensin converting enzyme inhibitor
AE	Adverse event
AKI	Acute Kidney Injury
Alpha-GAL-A	Alpha-Galactosidase-A
ARB	Angiotensin II receptor blocker
AUC_{0-t}	Area under the concentration-time curve from baseline to a specified time (t)
$AUC_{0-\infty}$	Area under the concentration-time curve from baseline to infinity
β-hCG	β-human chorionic gonadotropin (pregnancy test) for females
BPI	Brief pain inventory
C_{ave}	Average concentration
C3	Complement C3
C4	Complement C4
CHO	Chinese hamster ovary
CKD	Chronic kidney disease
C_{max}	Maximum concentration observed
CT	Computed tomography
DP	Drug product
EC	Ethics Committee
ECG	Electrocardiography
eCRF	electronic Case Report Form
eGFR	Estimated glomerular filtration rate
ERT	Enzyme replacement therapy
FOS	Fabry Outcome Survey
Gb3	Globotriaosylceramide
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
hr	Hour
IC	Informed consent
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
kg	kilogram
LLN	Lower limit of normal
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
Lyso-Gb3	Globotriaosylsphingosine
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
PK	Pharmacokinetic(s)
PP	Per Protocol
PT	Prothrombin time
PTT	Partial Thromboplastin time
QOL	Quality of life

SAE	Serious adverse event
TIA	Transient ischemic attack
$t_{1/2}$	Terminal plasma half-life, is the time required to divide the plasma concentration by two after reaching pseudo-equilibrium
T_{max}	Time at which the concentration is the maximum value (C_{max})
USPI	United States Package Insert

3 ETHICAL CONDUCT OF THE STUDY AND REGULATORY REQUIREMENTS

3.1 Institutional Review Board (IRB)

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

3.2 Ethical Conduct of the Study

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

3.3 Subject Information and Consent

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

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

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

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

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

4 INTRODUCTION

Fabry disease is a progressive lysosomal storage disease that is seriously debilitating and ultimately life-threatening. It is caused by X-linked deficiency of the enzyme galactosidase-A (-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 et al., 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 (Thurberg et al., 2002). Progressive accumulation of Gb3 and related lipids lead 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 et al., 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 et al., 2001). A 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 hemodialysis. A study by Hughes et al., comparing men and women with Fabry disease, using data from 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 can restore enzyme function in patients, and currently two ERTs using this enzyme are available; agalsidase-alfa (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 regarding 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 et al., 2001a; 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; Weidemann et al., 2009; Germain et al., 2007; Schiffmann et al., 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 may be 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% of male patients developed these IgG antibodies within the first 6 months of treatment (Schiffmann et al., 2006; Eng et al., 2001; Eng et al., 2001a). 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 (Vedder et al., 2008; Hollak et al., 2009). However, this approach is not considered a long-term solution.

Protalix has developed pegunigalsidase alfa, a chemically modified recombinant human alpha-GAL-A expressed in plant cell culture. Because of this modification, pegunigalsidase alfa exhibits more stabilized enzymatic activity, extended circulation residence time, and enhanced bioavailability of the enzyme relative to the commercial drugs.

Pegunigalsidase alfa was studied in Fabry disease patients in a Phase 1/2 study (PB-102-F01) for 12 weeks and continued in a 9-month extension study (PB-102-F02) for a total duration of one year. The results of these studies from 16 patients who completed the extension study, 6 each in the 0.2 mg/kg and 1.0 mg/kg treatment groups and four (4) in the 2.0 mg/kg treatment group, demonstrated that after receiving one year of pegunigalsidase alfa treatment: stable cardiac and renal function with favorable trends; Gb3 inclusion in kidney peritubular capillaries was substantially reduced; a mean reduction in the total score of the Mainz Severity Score Index (MSSI; Whybra et al., 2004) for the severity of Fabry disease in general, neurological, cardiovascular, and renal systems; a stable or favorable trend in the severity and frequency of abdominal pain and frequency of diarrhea in Gastrointestinal Symptoms Assessment (GSA); and reduction in pain severity score and pain interference score with the Brief Pain Inventory (BPI) scale, indicating an improvement in general activity, walking, working, sleeping, and enjoyment in life.

The most commonly experienced all-cause adverse events (AEs) were fatigue in 6 patients, and nausea and vomiting each in 5 patients. The most commonly experienced AEs that were considered possibly related to treatment were nausea in 4 patients, chest discomfort, dizziness, maculopapular rash, and fatigue each in 2 patients. Two patients experienced a treatment-related serious adverse event (SAE): migraine and bronchospasm. The patient who experienced a Grade 3 hypersensitivity-related bronchospasm led to the patient's discontinuation from the study per protocol. Pegunigalsidase alfa PK parameters and profile in Fabry patients indicate dose dependency. The enzyme was found to be available throughout the 2-week infusion intervals with a plasma half-life of approximately 80 hrs. The data from these two studies conclude that dosing of pegunigalsidase alfa at 1.0 mg/kg every 2 weeks offers an optimal treatment regimen for attenuating disease progression in patients with Fabry disease, while indicating the option, based on the enzyme amount delivered, for the use of 2.0 mg/kg every 4 weeks to be used in patients with mild to moderate Fabry Disease currently treated with ERT.

4.1 Rationale

The rationale for this open label, switch over study is based on the enhanced PK profile of pegunigalsidase alfa. Phase 1/2 study measurements and PK projection modelling data suggest pegunigalsidase alfa 2.0 mg/kg every 4 weeks would be beneficial in patients with Fabry Disease currently treated with ERT.

The weekly projected partial AUC and average concentration (Cave) indicate that there should be measurable levels of pegunigalsidase alfa at the third and fourth weeks after infusion in the same order of magnitude as Fabrazyme® in the first week after infusion (Table 1:). Calculations enabled the evaluation/estimation of the drug availability on weeks 1, 2, 3, and 4 of pegunigalsidase alfa compared to Fabrazyme® every other week following repeated dosing. The half-life (t½) of 2.0 mg/kg pegunigalsidase alfa is ~ 80 hrs vs. ~2 hrs of Fabrazyme® and Replagal™ with Cmax values ~10x greater than those published for Fabrazyme® (Fabrazyme® USPI 2016). The estimated Cave of 2.0 mg/kg pegunigalsidase alfa every 4 weeks provides a concentration of ~90 ng/mL at the 3rd week and ~10 ng/mL at the 4th week post infusion. Both values are greater than the negligible 2nd week Cave values for Fabrazyme® (Table 1:).

Table 1: Partial AUC/ C_{ave} (by Week) – Modeling Based on Pegunigalsidase alfa Phase 1/2 Data and Fabrazyme® AUC ~700 µg•min/mL

	pegunigalsidase alfa 2 mg/kg				Fabrazyme® 1 mg/kg	
	IV every 2 weeks		IV every 4 weeks		IV every 2 weeks	
Time (week)	Partial AUC (week) (ng•hr/mL)	C_{ave} for week (ng/mL)	Partial AUC (ng•hr/mL)	C_{ave} for week (ng/mL)	Partial AUC (ng•hr/mL)	C_{ave} for week (ng/mL)
1	989,406	5,889	989,406	5,889	12,000	71.4
2	119,065	709	119,065	709	nil	nil
3	1,004,012	5,976	14,637	87	12,000	71.4
4	120,864	719	1,799	11	nil	nil
5	1,004,233	5,978	989,627	5,891	12,000	71.4
6	120,892	720	119,092	709	nil	nil
7	1,004,233	5,978	14,640	87	12,000	71.4
8	120,892	720	1,800	11	nil	nil
9	1,004,233	5,978	989,627	5,891	12,000	71.4
10	120,892	720	119,092	709	nil	nil
11	1,004,233	5,978	14,640	87	12,000	71.4
12	120,892	720	1,800	11	nil	nil

Note: Since the projection was done for repeated dosing, the different shading indicates the infusion intervals to make it easier to follow.

This treatment dose and regimen is aimed as a maintenance program for Fabry patients without severe clinical symptoms with relatively slowing disease progression. Additionally, it may address the clinical needs of early or younger diagnosed patients.

The unique PK parameters of pegunigalsidase alfa with the proposed dose and regimen have the potential to results with a comparable efficacy and safety profile with a reduced immunogenicity compared to current ERTs, with greater convenience leading to significant improvement in QOL. This has the potential to delay the risk of developing disease complication in mild to moderate patients by slow disease progression. This study will provide health care providers and patients with Fabry disease alternative treatment options based on the unique characteristics of pegunigalsidase alfa.

5 STUDY OBJECTIVES

To evaluate the safety and efficacy of 2.0 mg/kg pegunigalsidase alfa every 4 weeks in patients with Fabry disease currently treated with ERT (agalsidase alfa or agalsidase beta).

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan – Description

This will be an open-label, switch-over study to assess the safety and efficacy of pegunigalsidase alfa 2.0 mg/kg administered by intravenous infusion every 4 weeks for 12 months (52 weeks) in adult patients with Fabry disease currently treated with ERT: Fabrazyme® (agalsidase beta) or

Replagal™ (agalsidase alfa) for at least 3 years and on a stable dose (>80% labelled dose/kg) for at least the last 6 months.

Number of Subjects (Planned):

Up to 30 but not less than 25 of the enrolled patients, up to 6 of the patients will be females (~20%).

Following screening, patients will be enrolled and switched from their current ERT to receive intravenous (IV) infusions of pegunigalsidase alfa 2 mg/kg every 4 weeks for 52 weeks or 14 infusions.

At the time of enrollment, if premedication is used for the agalsidase alfa or agalsidase beta infusions before enrollment, this premedication will be continued through the first infusion with pegunigalsidase alfa and then gradually tapered down at the Investigator's discretion and based on Appendix 8.

For patients weighing up to (≤) 100 kg, the first infusions of pegunigalsidase alfa will be administered under controlled conditions at the investigation site starting at 4.5 hr with the option to reduce the IV duration gradually to 2 hr (see Appendix 8).

For patients weighing more than (>) 100 kg, the first infusions of pegunigalsidase alfa will be administered under controlled conditions at the investigation site starting at 6 hr with the option to reduce the IV duration gradually to 3 hr (see Appendix 8).

The first infusions of pegunigalsidase alfa will be administered under controlled conditions at the investigation site. The patient can receive their pegunigalsidase alfa infusions in a home care setup once the Investigator and Sponsor Medical Director/Monitor agree that it is safe to do so based on Appendix 8.

In the case of clear clinical deterioration, the treatment may be changed to 1.0 mg/kg every other week at the Investigator's discretion and discussion with the Sponsor Medical Director/Monitor.

The study will include a screening visit and 14 treatment visits, once every 4 weeks for 52 weeks starting on Day 1 (Visit 1).

6.2 Discussion of Study Design

This study design is based on the unique enhanced PK profile of pegunigalsidase alfa. The weekly projected partial AUC and C_{ave} values, based on the Phase I/II PK profile, indicate that there should be measurable levels of pegunigalsidase alfa following 2 mg/kg treatment at the third and fourth weeks after infusion in the same order of magnitude as Fabrazyme® in the first week post-infusion (Table 1:). Calculations enabled the evaluation/estimation of the drug availability on weeks 1, 2, 3, and 4 of pegunigalsidase alfa compared to Fabrazyme® every 2 weeks. The half-life ($t_{½}$) of 2.0 mg/kg pegunigalsidase alfa is ~ 80 hrs vs. ~2 hrs of Fabrazyme® and Replagal™ with C_{max} values ~10-fold higher than those found with Fabrazyme®. The estimated C_{ave} of 2.0 mg/kg pegunigalsidase alfa every 4 weeks provides an average concentration of ~90 ng/mL at 3 weeks and ~10 ng/mL at 4 weeks post infusion. Both are higher than the negligible 2nd week C_{ave} values for Fabrazyme® (Table 1:).

Subjects are required to be treated with ERT: Fabrazyme® (agalsidase beta) or Replagal™ (agalsidase alfa) for at least 3 years and on a stable dose (>80% labelled dose/kg) for at least 6 months.

This study will provide a new treatment option based on the unique characteristic of pegunigalsidase alfa for health care providers and patients with Fabry disease in pegunigalsidase alfa-treated patients.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

The subjects must fulfill the following inclusion criteria:

1. Age: 18 – 60 years
2. A documented diagnosis of Fabry disease.
3. Males: plasma and/or leucocyte alpha-Galactosidase-A activity (by activity assay) less than lower limit of normal per laboratory reference range and one or more of the characteristic features of Fabry disease
    a. Neuropathic pain
    b. Cornea verticillata
    c. 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
    d. Neuropathic pain
    e. Cornea verticillata
    f. Clustered angiokeratoma
5. Treatment with agalsidase alfa or agalsidase beta for at least 3 years and on a stable dose (>80% labelled dose/kg) for at least the last 6 months
6. eGFR $\geq$ 30 mL/min/1.73 m^2 by CKD-EPI equation at screening visit
7. Availability of at least 3 historical serum creatinine evaluations since starting agalsidase alfa or agalsidase beta 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 accepted, highly effective method of contraception. These include combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner, or sexual abstinence

9. Patients whose clinical condition, in the opinion of the Investigator, that are suitable for treatment with ERT every 4 weeks.

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 or agalsidase beta
2. History of renal dialysis or transplantation
3. Linear negative slope of eGFR of $\geq$ 2 mL/min/1.73 m^2 based on at least 4 serum creatinine values over approximately 2 years (including the value obtained at the screening visit)
4. History of acute kidney injury in the 12 months prior to screening, including specific kidney diseases (e.g., acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (e.g., ischemia, toxic injury); as well as extrarenal pathology (e.g., prerenal azotemia, and acute post renal obstructive nephropathy)
5. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated or dose changed in the 4 weeks prior to screening
6. Urine protein to creatinine ratio (UPCR) at screening > 0.5 g/g or mg/mg or 500 mg/g and not treated with an ACE inhibitor or ARB
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. Cerebrovascular event (stroke, transient ischemic attack) in the 6-month period before screening
10. 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 to be associated with pegunigalsidase alfa (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
- 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 CRF. 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 30 days following discontinuation. If circumstances prevent the subject from completing all visits, every attempt will be made to complete all procedures listed in Section 9.2.3 for Visit 14 excluding the drug infusion.

7 STUDY PRODUCT

7.1 Study Medication Supply

Protalix will provide pegunigalsidase alfa to the sites as needed.

7.2 Description and Formulation of Study Product

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

The Drug Product (DP) is provided in 15 ml clear glass vials closed with rubber stoppers and secured with aluminum flip off caps.

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

20 mg pegunigalsidase alfa (2.0 mg/mL)
0.7% NaCl
25-30 mM Sodium Citrate (pH 5.7 – 6.3).

7.3 Study Drug Dosage and Preparation

Pegunigalsidase alfa 2.0 mg/kg; the individual dose for each patient will be prepared according to the patient's weight at screening. In the case of clinical deterioration, the treatment may be changed to 1.0 mg/kg every two weeks at the Investigator's discretion and discussion with the Medical Monitor.

Dose of PRX-102 will be adjusted at visit 8 if the weight at visit 7 changes by ≥25% from screening weight

Each dose will be prepared by a pharmacist or nurse at each site. The required amount of enzyme will be adjusted with normal saline (0.9% NaCl) to a final volume of 150 mL/infusion for patients weighing at screening up to 70 kg, 250 mL/infusion for patients weighing between 70–

100 kg, and 500 mL/infusion for patients weighing more than 100 kg the volume will be adjusted only if dose is changed.

7.4 Study Drug Administration

For patients weighing up to (≤) 100 kg, the first infusion of pegunigalsidase alfa will be administered under controlled conditions at the investigation site starting at 4.5 hrs with the option to reduce the IV duration gradually to 2 hrs.

For patients weighing more than (>) 100 kg, the first infusion of pegunigalsidase alfa will be administered under controlled conditions at the investigation site starting at 6 hrs with the option to reduce the IV duration gradually to 3 hrs.

Study drug will be administered by intravenous infusion over 4.5 – 6 hrs. If well tolerated by the patient, the infusion rate may be adjusted to 2 – 3 hrs (Appendix 8) according to the individual subject's signs and symptoms (Appendix 2). All changes will be based on Investigator evaluation and Sponsor Medical Director approval.

The first infusions of pegunigalsidase alfa will be administered under controlled conditions at the investigation site. After tapering down premedication, when applicable, and reducing the infusion time and observation time (see Appendix 8), the patient can then receive the pegunigalsidase alfa infusions at a home care setup once the Investigator and Sponsor Medical Director agree that it is safe to do so.

7.5 Packaging and Labeling

The DP is provided in 15 mL clear glass vials closed with rubber stoppers and secured with aluminum flip off caps. The drug product is packaged in vials containing 20 mg pegunigalsidase alfa (2 mg/mL), 0.7% NaCl, and 25 – 30 mM Sodium Citrate (pH 5.7 - 6.3).

Study product is a liquid stored in 15 mL clear injection glass vials (Müller + Müller-Joh. GmbH + Co, Germany). Grey rubber stoppers (formulation 4432/50/Grey) are used for closure (West Pharmaceutical Services Deutschland GmbH & Co KG).

The label is presented in Appendix 1. Vial Label

7.6 Conditions for Storage and Use

The proposed storage condition for the pegunigalsidase alfa DP is 5 ± 3°C. The proposed storage condition for the infusion bag is 5 ± 3°C, RT, and at 22.5 ± 2.5°C for up to 36 hours.

7.7 Method of Assigning Subjects Identification

In this open label study, all subjects will receive 2 mg/kg pegunigalsidase alfa once every 4 weeks:

A unique screening number (formatted as xxSF50yyy [x: site number, S: screening, F50: constant indicating protocol number, y: sequential subject number in the site]) will be assigned to each screened subject. Once a subject is eligible for treatment, including successful completion

of screening, sponsor medical director approval but prior to visit 1, a subject enrollment ID number will be generated. This ID number will include the site and subject number (formatted as xx-F50yyy [xx: site number, F50: constant indicating protocol number, yyy: sequential subject number in the study]).

7.8 Dispensing, Compliance and Accountability

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

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

7.9 Prior and Concomitant Therapy

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

The following medications are strictly prohibited during the study:

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

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

8 EFFICACY AND SAFETY ASSESSMENTS

8.1 Efficacy Variables

- Estimated glomerular filtration rate ($eGFR_{CKD-EPI}$) (Appendix 5. National Kidney Foundation Guidelines for Chronic Kidney Disease
- Left Ventricular Mass Index (g/m^2) by echocardiogram
- Plasma Lyso-Gb3
- Plasma Gb3

- Urine Lyso-Gb3
- Protein/Creatinine ratio spot urine test (UPCR)
- Frequency of pain medication use
- Exercise tolerance (Stress Test)
- Short Form Brief Pain Inventory (BPI) (Appendix 7. Brief Pain Inventory- BPI (Short Form)
- Mainz Severity Score Index (MSSI) (Appendix 4. The Mainz Severity Score Index (MSSI))
- Quality of life EQ-5D-5L (Appendix 6. QOL Questionnaire - EQ-5D-5L)

8.2 Pharmacokinetic Variables

Blood samples will be taken from all patients for PK analysis on Day 1 and at the end of the study (Visit 14 at week 52). Blood samples will be drawn for an additional intermediate PK analysis at Visit 7 (week 24), for all patients who signed inform consent to this version (Version 4) before reaching Visit 7 (week 24), or at Visit 11 (week 40) for patients who passed Visit 7 at the time of signing the inform consent to this version. The following (but not restricted to) PK parameters will be derived from the plasma concentration versus time profiles to determine the pharmacokinetics of the study drug: C_{max}, T_{max}, $t_{1/2}$, AUC_{0-t}, and $AUC_{0-\infty}$. Blood samples (~6 mL) will be drawn at the following time points: pre-infusion (baseline); 1 hour after the beginning of the infusion; at the end of the infusion, at 1±0.25, 2±0.25, 4±0.25, 8±0.25, 24±0.5, 48±3, and 96±3 hours post-infusion and at 14±3, 21±3 and 28±3 days post-infusion (a total of 13 timepoint within 28 days).

8.3 Safety Variables

Safety will be assessed by changes 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-induced anti-pegunigalsidase alfa antibodies (Appendix 3. Pegunigalsidase alfa Hypersensitivity Evaluation and Treatment Algorithm)

8.3.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject participating in a clinical trial. An AE 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. If the subject enters the extension study, the first 30 days of the extension study will be considered the observation period for adverse events of this study (PB-102-F50). 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. Known pre-existing 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 AEs commonly observed and AEs 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 AE.

A treatment-emergent AE is any AE occurring after start of study medication and within the time of residual drug effect (30 days after the last administration of the study medication; please note the above provision for subjects who enter the extension study), or a pre-treatment AE or pre-existing medical condition that worsens in intensity after start of study medication and within the time of residual drug effect.

AEs 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. Pegunigalsidase alfa Hypersensitivity Evaluation and Treatment Algorithm 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 AE. However, if deemed necessary by the Investigator, a procedure can be captured along with the reason for conducting the procedure.

An overdose is not an AE 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 AE caused by an overdose or medication error is considered serious if a criterion listed in the definition above is fulfilled.

Important AEs 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.

SAEs 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 AEs and all AEs spontaneously reported by the trial subject using concise medical terminology. In addition, each trial subject will be questioned about AEs. The question asked will be "Since you began taking the study medication, have you had any health problems?"

8.3.1.1 Procedures for Assessing, Recording, and Reporting AEs and SAEs

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 AEs. All AEs (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 AE will include description of the 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.

AEs 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.

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

Severity	Definition
Mild (Grade 1)	Awareness of signs or symptoms, but no disruption of usual activity
Moderate (Grade 2)	Discomfort sufficient to interfere, but not prevent, daily activity
Severe (Grade 3)	Unable to carry out usual activity
Very severe (Grade 4)	Incapacitating, requires hospitalization, results in death
Category	Definition
Unrelated	Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under possible or probable.
Unlikely	Does not follow a reasonable temporal sequence from administration. May have been produced by the subject's clinical state or by environmental factors or other therapies administered.
Possible	Follows a reasonable temporal sequence from administration, but may have been also produced by the subject's clinical state, environmental factors or other therapies administered.
Probable	Clear-cut temporal association with administration with improvement on cessation of investigational medicinal product or reduction in dose. Reappears upon rechallenge. Follows a known pattern of response to the investigational medicinal product.
Definitely	There is evidence of exposure to the test product, for example, reliable history or acceptable compliance assessment; the temporal sequence of the AE onset relative to the drug is reasonable; the AE is most likely to be explained by the drug treatment than by another cause; the challenge is positive; re-challenge (if feasible) is positive; the AE shows a pattern consistent with previous knowledge of the drug treatment.

8.3.2 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.

- Coagulation profile: prothrombin time (PT) and partial thromboplastin time (PTT)

- Biochemistry: sodium, potassium, glucose, blood urea nitrogen, creatinine, cystatin C, calcium, phosphate (inorganic), uric acid, total protein, albumin, bilirubin (total), alkaline phosphatase, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, and creatine phosphokinase

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

- Vitamin D

8.3.3 Anti-pegunigalsidase alfa Antibodies

Anti-pegunigalsidase alfa antibodies will be assessed using a validated analytical method before dosing at screening, baseline (Day 1), Week 2 (15±3 days after 1st infusion), Visit 2 (Week 4 ± 3 days), and in Visits 4 (week 12), 7 (week 24), 11 (week 40), and V14 (week 52).

Anti-Drug IgE antibodies and tryptase will be assessed in events of hypersensitivity reaction following Sponsor request.

8.3.4 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. Refer to Missing Data for further description of how episodes of AKI will be handled in data analysis for efficacy.

9 STUDY PROCEDURES AND FLOW CHART

9.1 Study Flow Chart

Calendar (week)		Day1	2	4	8	12	16	20	24	28	32	36	40	44	48	52
Activity /Visit Number/ Inf	S	V1	2weeks	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Sign IC	x															
Assign screening number	x															
Inclusion/exclusion criteria	x	x														
Demographics	x															
Medical & Specific FD history including major clinical events	x															
Physical examination	x	x				x			x				x			x
Body weight	x	x							x							x
Body height	x															
Vital signs[5,]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
review of medications Pain medications Pre-medication Use	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Alfa-galactosidase activity in plasma	x															
Alfa-galactosidase activity in leucocytes	x															
Urine protein/creatinine ratio (UPCR)	x	x				x			x				x			x
Hematology	x	x				x			x				x			x
PT and PTT	x															
Biochemistry	x	x				x			x				x			x
Serum creatinine and Cystatin C	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Vitamin D	x															
Serum pregnancy (βHCG) for females	x															
Urine pregnancy test for females		x				x			x				x			x
Urinalysis - dipstick	x	x				x			x				x			x
HBsAg, HCV & HIV	x															
Short Form Brief Pain Inventory (BPI)		x							x							x
Anti-Drug Antibodies (IgG)[2]	x	x	x	x		x			x				x			x
Plasma PK[3]		x							x				x			x
Electrocardiography (ECG)	x	x				x			x				x			x
Chest X-ray[1]	x															

Calendar (week)		**Day1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Activity /Visit Number/ Inf	**S**	**V1**	**2weeks**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Quality of Life (5Q-5D-5L)		x							x							x
Mainz Severity Score Index (MSSI)		x														x
Request patient approval by Medical Monitor		x														
Medical Monitor approval		x														
Echocardiography		x							x							x
Cardiac function assessment (stress test)		x														x
Brain MRI		x														x
Adverse events assessments		x		x	x	x	x	x	x	x	x	x	x	x	x	x
Mutation analysis		x														
Con Meds	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Urine lyso Gb3 concentration		x				x			x				x			x
Plasma Gb3 concentration[2]		x				x			x				x			x
Plasma Lyso Gb3 concentration[2]		x				x			x				x			x
Study Drug IV infusion[8,9]		x		x	x	x	x	x	x	x	x	x	x	x	x	x
Observe Patient[6]		x		x	x	x	x	x	x	x	x	x	x	x	x	x
Call Patient [7]		x														

[1] Will be performed only for patients who have not had the test during the last 3 months before screening

[2] Will be performed pre-infusion

[3] PK Time points: pre-infusion (baseline); 1 hour after the beginning of the infusion; at the end of the infusion, at 1±0.25, 2±0.25, 4±0.25, 8±0.25, 24±0.5, 48±3, and 96±3 hours post-infusion and at 14±3, 21±3 and 28±3 days post-infusion
Patients who signed inform consent to this version (Version 4) before reaching Visit 7 (week 24), will perform PK at Visit 7; patients who signed inform consent after Visit 7 will perform PK at visit 11 (week 40).

[5] Evaluate vital signs: blood pressure, pulse, temperature and respiration rate; any time pre-infusion, every 30 (±10) minutes during the first hour of the infusion, and from the second hour, 60 (±10) minutes up to the end of the clinical observation, and at the end of the observation time, if the patient tolerates the infusion. Otherwise, evaluate vital signs every 15 minutes until achieving tolerability.

[6] According to Appendix 8

[7] 24 hours post dosing first infusion

[8] Evaluate the injection site

[9] In patients who tolerate the infusions well, the infusion rate can be adjusted according to Appendix 8.

9.2 Study Visits

9.2.1 Screening (Visit 0, Visit S, Day -30 ± 10 Days)

1. Obtain written informed consent from the subject
2. Assign screening number
3. Demographics
4. Medical history and specific Fabry disease history including major clinical events

5. Physical examination, including weight and height
6. Vital signs, including blood pressure, pulse, temperature, and respiration rate
7. Current medications including (pain medications and pre-medication use)
8. Laboratory tests
    - Hematology-Local
    - Biochemistry
    - Urinalysis - dipstick
    - Alpha galactosidase activity in plasma
    - Alpha galactosidase activity in leucocytes
    - Urine protein/creatinine ratio (UPCR) - spot urine test
    - PT and PTT
    - Serum creatinine and Cystatin C
    - Vitamin D
    - HBsAg, HCV, & HIV
    - Anti-pegunigalsidase alfa antibodies (IgG)
    - Serum pregnancy test (β-HCG) for female subjects of child-bearing potential
9. Chest X-ray (if not performed in the last 3 months)
10. Final enrollment approval will be determined after completion of screening visit and filling in Inclusion/exclusion criteria
11. ECG

9.2.2 Visit 1 (Baseline, Day 1, 1 ± 3 Days)

1. Inclusion/exclusion review
2. Request approval of patient by the Medical Monitor
3. Physical examination, including weight
4. Vital signs, including blood pressure, pulse, temperature, and respiration rate
5. Current medications (pain medications and pre-medication use)

6. Laboratory tests
    - Hematology
    - Biochemistry
    - Mutation analysis sample
    - Urine protein/creatinine ratio (UPCR) - spot urine test
    - Serum creatinine and Cystatin C
    - Urinalysis - dipstick
    - Urine lyso Gb3
    - Plasma Gb3 (pre-infusion)
    - Plasma Lyso-Gb3 (pre-infusion)
    - Urine pregnancy test for females
    - Anti-pegunigalsidase alfa antibodies (pre-infusion of visit 1)
    - Plasma PK analysis time points: pre-infusion (baseline); 1 hour after the beginning of the infusion; at the end of the infusion, at 1±0.25, 2±0.25, 4±0.25, 8±0.25, 24±0.5, 48±3, and 96±3 hours post-infusion and at 14±3, 21±3 and 28±3 days post-infusion.
7. Short Form Brief Pain Inventory (BPI) (Appendix 7. Brief Pain Inventory- BPI (Short Form))
8. ECG
9. Quality of Life: 5Q-5L-5D (Appendix 6. QOL Questionnaire - EQ-5D-5L)
10. Mainz Severity Score Index (MSSI) (Appendix 4. The Mainz Severity Score Index (MSSI))
11. Echocardiography
12. Cardiac function assessment (stress test)
13. Brain MRI
14. Adverse events
15. Study Drug IV infusion
16. Perform the following procedures at all pegunigalsidase alfa dosing:

- If the patient is typically pre-medicated, include the pre-medication prior to initiating the infusion.
- For a patient weighing up to 100 kg, the infusion length will start at 4.5 hours; for patients over 100 kg, the infusion length will start at 6 hours and can be reduced pending tolerability (Appendix 8)
- Evaluate vital signs: blood pressure, pulse, temperature and respiration rate: any time pre-infusion, every 30 (±10) minutes during the first hour of infusion, and from the second hour, every 60 (±10) minutes up to the end of the clinical observation time, and at the end of observation time, if the patient tolerates the infusion. Otherwise, evaluate vital signs every 15 minutes.
- Post dossing clinical observation will start from 4 hours length and can be reduced pending tolerability up to one hour (Appendix 8), regardless of the length of the infusion.
- Evaluate the infusion site

17. Schedule the patient for the next visit
18. Question the patient on infusion tolerability at 24 hours post-infusion by phone or at the site.

9.2.3 Week 2 (Day 15±3 days post- 1st infusion)

1. Anti-pegunigalsidase alfa antibodies

9.2.4 Visit 2 (Week 4 ± 3 days)

1. Vital signs, including blood pressure, pulse, temperature, and respiration rate
2. Serum creatinine and Cystatin C (pre-infusion)
3. Anti-pegunigalsidase alfa antibodies (pre-infusion)
4. Concomitant medications
5. Adverse events
6. Study Drug IV infusion (evaluate the injection site) and post dossing clinical observation see Appendix 8.
7. Remind the patient of the date of his/her next visit.

9.2.5 Visits 3, 5, 6, 8, 9, 10, 12, and 13 (Weeks 8, 12, 16, 20, 28, 32, 36, 44, and 48 ± 3 Days for Each Visit)

8. Vital signs, including blood pressure, pulse, temperature, and respiration rate

9. Serum creatinine and Cystatin C (pre-infusion)
10. Concomitant medications
11. Adverse events
12. Study Drug IV infusion (evaluate the injection site) and post dossing clinical observation see Appendix 8.
13. Remind the patient of the date of his/her next visit.

9.2.6 Visits 4 and 11 (Weeks 12 and 40 ± 3 Days)

1. Physical examination
2. Vital signs, including blood pressure, pulse, temperature, and respiration rate
3. Laboratory tests
    - Hematology
    - Biochemistry
    - Urine protein/creatinine ratio (UPCR) - spot urine test
    - Serum creatinine and Cystatin C (pre-infusion)
    - Urine pregnancy test for females
    - Urinalysis - dipstick
    - Urine lyso Gb3
    - Plasma Gb3 (pre-infusion)
    - Plasma Lyso-Gb3 (pre-infusion)
    - Anti-pegunigalsidase alfa antibodies (pre-infusion)
    - Visit 11 (week 40) ONLY;
        - Plasma PK analysis (For patients who signed inform consent to Version 4 **after** Visit 7) at the following time points: pre-infusion (baseline); 1 hour after the beginning of the infusion; at the end of the infusion, at 1±0.25, 2±0.25, 4±0.25, 8±0.25, 24±0.5, 48±3, and 96±3 hours post-infusion and at 14±3, 21±3 and 28±3 days post-infusion.
4. ECG
5. Concomitant medications

6. Adverse events
7. Study Drug IV infusion (evaluate the injection site) and post dossing clinical observation, see Appendix 8.
8. Remind the subject of the date of his/her next visit.

9.2.7 Visit 7 (Week 24 ± 3 Days)

1. Physical examination, including weight
2. Vital signs, including blood pressure, pulse, temperature, and respiration rate
3. Laboratory tests
   - Hematology
   - Biochemistry
   - Urine protein/creatinine ratio (UPCR) - spot urine test
   - Serum creatinine and Cystatin C (pre-infusion)
   - Urine pregnancy test for females
   - Urinalysis - dipstick
   - Urine lyso Gb3 (first morning mid-stream void performed on 2 consecutive days, pre-infusion)
   - Plasma Gb3 (pre-infusion)
   - Plasma Lyso-Gb3 (pre-infusion)
   - Anti-pegunigalsidase alfa antibodies (pre-infusion)
   - Plasma PK analysis (For patients who signed inform consent to Version 4 **before** reaching Visit 7) at the following time points: pre-infusion (baseline); 1 hour after the beginning of the infusion; at the end of the infusion, at 1±0.25, 2±0.25, 4±0.25, 8±0.25, 24±0.5, 48±3, and 96±3 hours post-infusion and at 14±3, 21±3 and 28±3 days post-infusion..
4. BPI (Appendix 7. Brief Pain Inventory- BPI (Short Form))
5. Quality of Life: 5Q-5L-5D (Appendix 6. QOL Questionnaire - EQ-5D-5L)
6. ECG
7. Concomitant medications
8. Adverse events

9. Study Drug IV infusion (evaluate the injection site) and post dossing clinical observation see Appendix 8.
10. Remind the subject of the date of his/her next visit.

9.2.8 Visit 14 (Week 52 ± 3 Days)

1. Physical examination, including weight
2. Vital signs, including blood pressure, pulse, temperature and respiration
3. Laboratory tests
   - Hematology
   - Biochemistry
   - Urine protein/creatinine ratio (UPCR) - spot urine test
   - Serum creatinine and Cystatin C (pre-infusion)
   - Urine pregnancy test for females
   - Urinalysis - dipstick
   - Urine lyso Gb3
   - Plasma Gb3 (pre-infusion)
   - Plasma Lyso-Gb3 (pre-infusion)
   - Anti-pegunigalsidase alfa antibodies (pre-infusion)
   - Plasma PK analysis time points: pre-infusion (baseline); 1 hour after the beginning of the infusion; at the end of the infusion, at 1±0.25, 2±0.25, 4±0.25, 8±0.25, 24±0.5, 48±3, and 96±3 hours post-infusion and at 14±3, 21±3 and 28±3 days post-infusion.
4. BPI (Appendix 7. Brief Pain Inventory- BPI (Short Form))
5. ECG
6. Quality of Life: 5Q-5L-5D (Appendix 6. QOL Questionnaire - EQ-5D-5L)
7. MSSI (Appendix 4. The Mainz Severity Score Index (MSSI))
8. Cardiac function assessment (stress test)
9. Echocardiography
10. Brain MRI

11. Concomitant medications
12. Adverse events
13. Study Drug IV infusion (evaluate the injection site) and post dossing clinical observation, see Appendix 8.

9.2.9 Premature Withdrawal Visit

All attempts should be made to perform all the tests for Visit 14 at the withdrawal visit for patients who may discontinue the study before completion.

10 STATISTICAL METHODS PLANNED AND SAMPLE SIZE

10.1 Determination of Sample Size

The sample size of approximately 30 subjects was determined pragmatically and is adequate to evaluate the safety of switching from agalsidase alfa or beta to 2 mg/kg pegunigalsidase alfa every 4 weeks in this orphan disease in which patient recruitment in clinical trials is difficult.

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.

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.

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

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

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

10.3.1 Efficacy Variables

For each efficacy variable, the percent change from baseline to each visit of which 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).

eGFR is calculated from the serum creatinine according to the CKD-EPI formula. Intra-patient comparison will be also evaluated.

10.3.2 Safety Analysis

10.3.2.1 Adverse Events

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

AEs will be summarized by treatment group to provide visual comparison among the treatment groups with respect to incidence of AEs (the number of subjects reporting at least one episode of a specific AE), incidence of AEs by severity within body system, incidence of AEs by attribution within body system, and incidence of AEs causing withdrawal and incidence of SAEs. 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 AE on more than one occasion.

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

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

10.3.2.2 Clinical Laboratory

Clinical Laboratory examinations will be performed prior to 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.

10.3.3 Interim Analysis

An interim analysis may be performed for administrative purposes.

10.3.4 Missing Data

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

Episodes of Acute Kidney Injury (AKI) will be considered missing data for the purposes of the efficacy analysis. AKI will be defined by a 1.5-fold increase in serum creatinine from the immediately previous laboratory value and assessment by the Investigator. However, prior to

data base lock, cases of AKI will be assessed by two independent nephrology experts. Their evaluation will include whether they agree that AKI occurred in a patient and whether serum creatinine values should be excluded from the eGFR slope calculations for the primary endpoint. Excluded serum creatinine values will be considered missing data.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Source Data and Records

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

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

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

11.2 Reporting of Results

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

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 eCRF.

Protalix Ltd. or its designee will monitor completed eCRFs. An eCRF will be completed for each screened subject.

All protocol-required information collected during the study must be entered by the Investigator, or designated representative, in the Target e*CRF™, an internet-based electronic data collection system. All details of the eCRF completion and correction will be explained to the Investigator and his team. 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 eCRF, the names, positions, and signatures of these persons must be supplied to the Sponsor.

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

The completed eCRF 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 eCRF or any other documents submitted to the Sponsor, the subjects will not be identified by their names, but by their screening and/or enrollment ID numbers (see Section 7.7) in the study. The Investigator will maintain documents not meant for submission to the Sponsor (e.g., the confidential subject identification code and the signed informed consent documents) in strict confidence.

12 REPORTING AND PUBLICATION

12.1 Confidentiality of Study Data

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

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14 APPENDICES

14.1 Appendix 1. Vial Label

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

Figure 1: Outer Package Label (Example)

Protocol #: PB-102-F50
Study drug name: pegunigalsidase alfa (PRX-102)
20 mg/vial; 10mL in each vial
Qty: N vials_____
For intravenous injections only as directed
Batch number: _____ Expiry: MM-YYYY
IND No. 110,161
Directions for use:
Store at: 2-8°C (36-46°F)
Caution: New Drug – Limited by Federal (or United States) law to investigational use.

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

Figure 2: Individual Vials Label (Example)

Study drug name: pegunigalsidase alfa 20 mg/vial for intravenous injection only as directed
10 mL in each vial
Batch number: _____ Expiry: MM-YYYY
Protocol #: PB-102-F50
Caution: New Drug – Limited by Federal (or United States) law to investigational use.
Patient number: _____
Visit number: _____
Sponsor: Protalix Ltd, 2 Snunit St., Carmiel, Israel,
Tel: +972-4-9889488

14.2 Appendix 2. Tolerability and Infusion Rate Algorithm

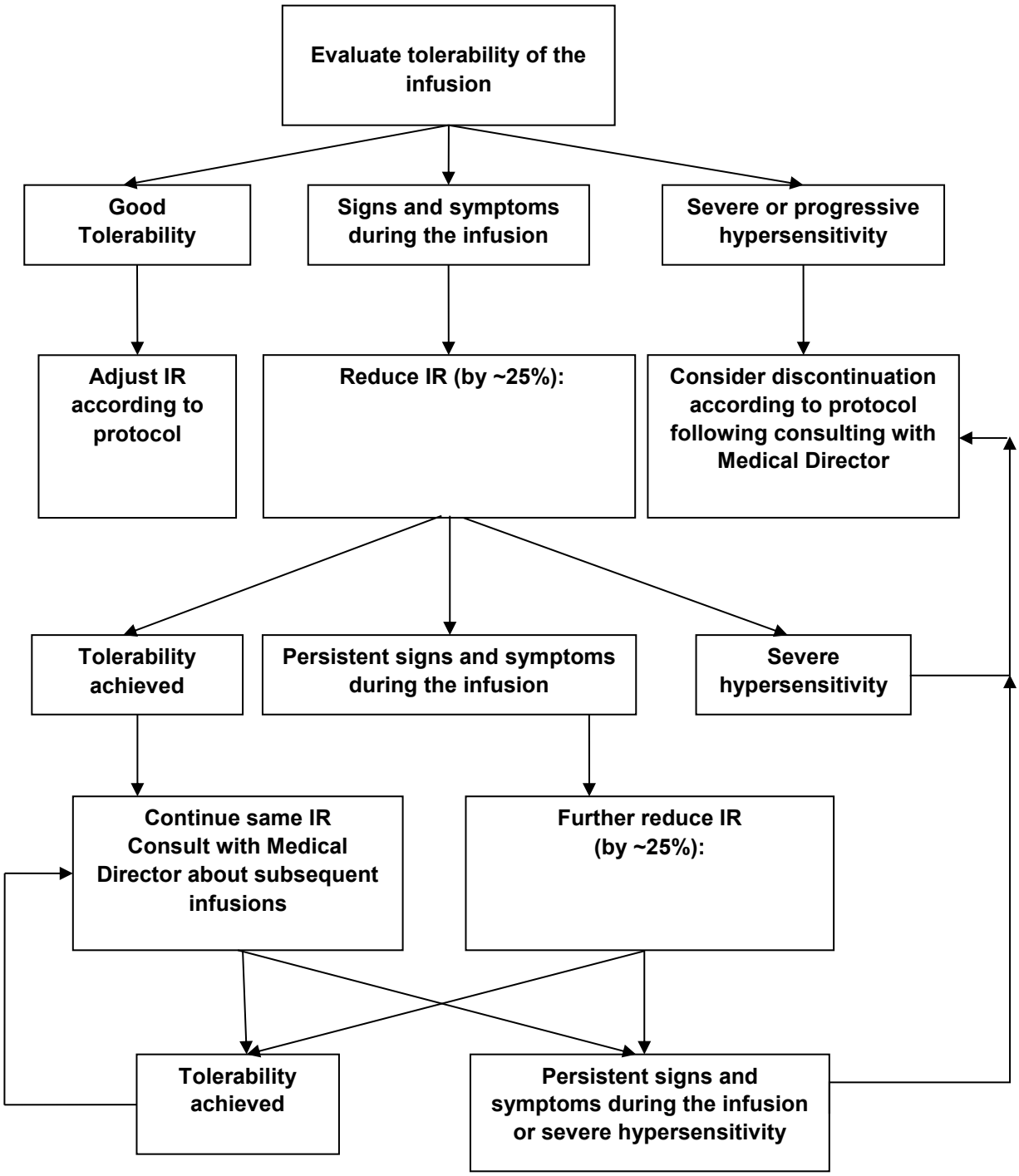
The infusion rate (IR) may be adjusted according to individual subject signs and symptoms. The assumptions with respect to adverse experiences to the infusion are:

1. Most of the subjects will tolerate the infusion without any special symptom or event.
2. Subjects presenting with signs and symptoms 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 with 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 the 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 (e.g., antihistamine for urticaria).

The specific algorithm for infusion rates to be followed:



Changes in Infusion Rates According to the Protocol

The tolerability of the infusions in patients will be determined by signs and symptoms during the infusion, observation in the hospital, and by the telephone contact the day after the first infusion. The infusion rate may be adjusted according to individual patient signs and symptoms according to the above algorithm.

For patients with good tolerability, an attempt of premedication discontinuation should be done. After that, the infusion length and the clinical observation after the infusion could be reduced according to Appendix 8.

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

14.3 Appendix 3. Pegunigalsidase alfa Hypersensitivity Evaluation and Treatment Algorithm

During and after infusion of pegunigalsidase alfa, 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.

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 given 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 pegunigalsidase alfa 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. Tolerability and Infusion Rate Algorithm for adjustment of infusion rate). The premedication will be administered according to the following steps as needed to prevent progressive hypersensitivity:

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

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

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

14.4 Appendix 4. The Mainz Severity Score Index (MSSI)

The MSSI score has been proven representative in patients with 'classic' Fabry disease and is useful for monitoring clinical improvement in patients receiving enzyme replacement therapy (Whybra et al., 2004).

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 baseline (Visit 1) and every 6 months throughout the study.

The Mainz Severity Score Index (MSSI)

General Score			**Neurological Score**		
Sign/symptom	**Rating**	**MSSI score**	**Sign/symptom**	**Rating**	**MSSI score**
Characteristic facial appearance	No	0	Tinnitus	No	0
	Yes	1		Mild	1
Angiokeratoma	None	0		Severe	2
	Some	1	Vertigo	No	0
	Extensive	2		Mild	1
Edema	No	0		Severe	2
	Yes	1	Acroparesthesia	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**		
Diarrhea/ constipation	No	0	Depression	No	0
	Yes	1		Yes	1
Hemorrhoids	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 proteinuria	0
	Thickening of wall/septum	1		Proteinuria	4
	LVH seen on ECG	6		Tubular dysfunction/low GFR or creatinine clearance	8
	Cardiomyopathy (<15)	8		End-stage renal failure (serum creatinine levels >3.5 mg/dl)	12
	Severe cardiomyopathy (>15)	12		Dialysis	18
Valve insufficiency	No	0			
	Yes	1			
ECG abnormalities	No	0			
	Yes	2			
Pacemaker	No	0			
	Yes	4			
Hypertension	No	0			
	Yes	1			
Maximum Score		**20**	**Maximum Score**		**18**

* Limitation on physical activity according to NYHA classification is as follows. Class I: none; Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea 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 ischemic attack.

14.5 Appendix 5. National Kidney Foundation Guidelines for Chronic Kidney Disease

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

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

14.5.1 Estimation of GFR:

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

14.5.2 CKD-EPI Equation:

The CKD-EPI equation (Levey et al., 2009) performed better than the MDRD (Modification of Diet in Renal Disease Study; Levey et al., 2006) equation, especially at higher GFR, with less bias and greater accuracy. When looking at NHANES (National Health and Nutrition Examination Survey) data, the median estimated GFR was 94.5 *vs.* 85.0 mL/min per 1.73 m^2, and the prevalence of chronic kidney disease was 11.5% *vs* 13.1%. The CKD-EPI equation, expressed as a single equation, is:

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

Scr: serum creatinine (mg/dL),
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.

14.6 Appendix 6. QOL Questionnaire - EQ-5D-5L

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

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

ANXIETY / DEPRESSION

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

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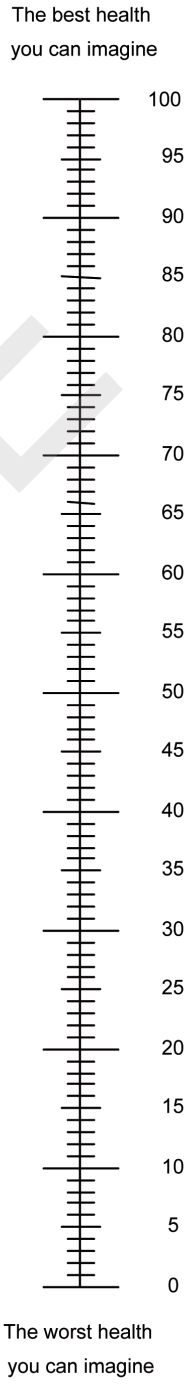
- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the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

YOUR HEALTH TODAY = ☐



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

The short form of the Brief Pain Inventory (BPI) will be performed at baseline and Visits 7 and 10. (https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/symptom-research/symptom-assessment-tools/brief-pain-inventory.html)

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: _____/_____/_____ Time: _____

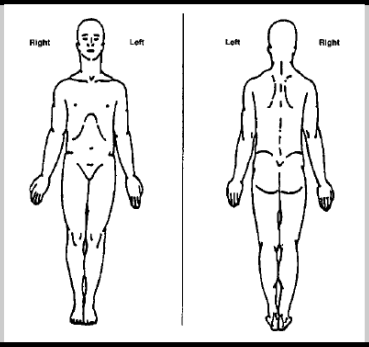
Name: _____ _____ _____

Last First Middle Initial

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

1. Yes 2. No

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



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

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

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

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

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

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

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

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

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

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

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

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

A. General Activity

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

B. Mood

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

C. Walking Ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

14.8 Appendix 8. Schedule of Premedication, Infusion Rates, and Observation Times Post-Infusion

Proposed schedule to:

1. Taper down premedication
2. Increase infusion rate
3. Reduce observation time after infusion

The schedule below, will guide the sites on the process to taper down premedication, increase the infusion rate up to minimal time of infusion allowed by the protocol based on the tolerability of the patient, and reduce the observation time after infusion. At the end of the process, the patient may be offered to continue therapy in a home care setup based on the Investigator evaluation and discussion with the Medical Director.

General considerations:

1. Patients whose weight is up to (≤)100 kg, the length of first infusion will be 4.5 hours.
2. Patients whose weight is more than (>) 100 kg, the length of first infusion will be 6 hours.
3. Clinical follow-up (observation) after the infusion in all rates will be 4 hours for the first infusion.
4. Patients who received the previous ERT with premedication will have the first infusion of pegunigalsidase alfa with the same protocol of premedication as with the previous ERT.
5. All changes can be implemented only if there is good tolerability of the previous change.
6. In the case of questionable tolerability, the continuation of the process will be discussed between the Investigator and the Medical Director.

1. Taper down premedication

The principle in the process is:

On the first infusion: the subject will continue the premedication as in previous ERT tratment. On the next infusion, one of the medications used as premedication will be removed. If well tolerated, on the next infusion, additional medication used as premedication will be removed (when applicable). This regimen will continiue up to tapering down all premedications, or best tolerability to the infusion is achieved.

2. Reduce infusion time

The principle in the process is:

Reduction in the infusion time will start after an attempt was done to taper down the premedication based on patient tolerability. The length of infusion will be reduced by 0.5 hour as described in Table 2 to achieve the best tolerated infusion length or an infusion of 2 hours (for patients ≤ 100 kg weight) or 3 hours (for patients weighing more than 100 kg).

3. Reduce observation time after infusion

The principle in the process is:

The process for reducing observation time after the infusion will start after the attempt of tapering down the premedication was finalized (when one of the results could be the patient will remain on premedication). Until then, the post-infusion observation will be 4 hours.

On the next upcoming visit, the observation time will be reduced by 0.5 hour in each infusion up to 2 hours and then reduced to 1 hour post-infusion.

4. Referring the patient to home care set-up

The patients will be able to join the home care program once the patient is clinically stable with no additional changes in premedication, infusion rate, and observation time.

The changes require discussion and approval by the Medical Monitor/Director.

Table 2 represents a proposed regimen to achieve the goal of reducing premedication, infusion length, and post infusion observation; Other regimens need to be discussed and approved by the Medical Monitor/Director.

Table 2: Proposed Regimen of Reduced Premedication, Infusion Length, and Post-Infusion Observational Period

Visit		no premed up to 100 kg	single premed up to 100 kg	2 premeds up to 100 kg	3 premeds up to 100 kg	no premed more than 100 kg	single premed more then 100 kg	2 premeds more than 100 kg	3 premeds more then 100 kg
	infusion time	4.5 H	4.5 H	4.5 H	4.5 H	6 H	6 H	6 H	6 H
	observation time	4 H	4 H	4 H	4 H	4 H	4 H	4 H	4 H
	premedication	no premed	same premed	same premed	same premed	no promed	same premed	same premed	same premed
1	home care option	NO	NO	NO	NO	NO	NO	NO	NO
	infusion time	4 H	4.5 H	4.5 H	4.5 H	5.5 H	6 H	6 H	6 H
	observation time	4 H	4 H	4 H	4 H	4 H	4 H	4 H	4 H
	premedication	no premed	remove premed	remove 1 premed	remove 1 premed	no premed	remove premed	remove 1 premed	remove 1 premed
2	home care option	NO	NO	NO	NO	NO	NO	NO	NO
	infusion time	3.5 H	4 H	4.5 H	4.5 H	5 H	5.5 H	6 H	6 H
	observation time	3.5 H	4 H	4 H	4 H	4 H	4 H	4 H	4 H
	premedication	no premed	no premed	remove premed	remove 2 premed	no premed	no premed	remove premed	remove 2 premed
3	home care option	NO	NO	NO	NO	NO	NO	NO	NO
	infusion time	3 H	3.5 H	4 H	4.5 H	4.5 H	5 H	5.5 H	6 H
	observation time	3 H	3.5 H	4 H	4 H	4 H	4 H	4 H	4 H
	premedication	no premed	no premed	no premed	remove premed	no premed	no premed	no premed	remove premed
4	home care option	NO	NO	NO	NO	NO	NO	NO	NO
	infusion time	2.5 H	3 H	3.5 H	4 H	4 H	4.5 H	5 H	5.5 H
	observation time	2.5 H	3 H	3.5 H	4 H	4 H	4 H	4 H	4 H
	premedication	no premed	no premed	no premed	no premed	no premed	no premed	no premed	no premed
5	home care option	NO	NO	NO	NO	NO	NO	NO	NO
	infusion time	2 H	2.5 H	3 H	3.5 H	3.5 H	4 H	4.5 H	5 H
	observation time	2 H	2.5 H	3 H	3.5 H	3.5 H	4 H	4 H	4 H
	premedication	no premed	no premed	no premed	no premed	no premed	no premed	no premed	no premed
6	home care option	NO	NO	NO	NO	NO	NO	NO	NO
	infusion time	2 H	2 H	2.5 H	3 H	3 H	3.5 H	4 H	4.5 H
	observation time	1 H	2 H	2.5 H	3 H	3 H	3.5 H	4 H	4 H
	premedication	no premed	no premed	no premed	no premed	no premed	no premed	no premed	no premed
7	home care option	NO	NO	NO	NO	NO	NO	NO	NO
	infusion time	2 H	2 H	2 H	2.5 H	3 H	3 H	3.5 H	4 H
	observation time	1 H	1 H	2 H	2.5 H	2 H	3 H	3.5 H	4 H
	premedication	no premed	no premed	no premed	no premed	no premed	no premed	no premed	no premed
8	home care option	YES	YES	NO	NO	NO	NO	NO	NO
	infusion time	2 H	2 H	2 H	2 H	3 H	3 H	3 H	3.5 H
	observation time	1 H	1 H	1 H	2 H	1 H	2 H	3 H	3.5 H
	premedication	no premed	no premed	no premed	no premed	no premed	no premed	no premed	no premed
9	home care option	YES	YES	YES	NO	YES	NO	NO	NO
	infusion time	2 H	2 H	2 H	2 H	3 H	3 H	3 H	3 H
	observation time	1 H	1 H	1 H	1 H	1 H	1 H	2 H	3 H
	premedication	no premed	no premed	no premed	no premed	no premed	no premed	no premed	no premed
10	home care option	YES	YES	YES	YES	YES	YES	NO	NO
	infusion time	2 H	2 H	2 H	2 H	3 H	3 H	3 H	3 H
	observation time	1 H	1 H	1 H	1 H	1 H	1 H	1 H	2 H
	premedication	no premed	no premed	no premed	no premed	no premed	no premed	no premed	no premed
11	home care option	NO	NO	NO	NO	NO	NO	NO	NO
	infusion time	2 H	2 H	2 H	2 H	3 H	3 H	3 H	3 H
	observation time	1 H	1 H	1 H	1 H	1 H	1 H	1 H	1 H
	premedication	no premed	no premed	no premed	no premed	no premed	no premed	no premed	no premed
12	home care option	YES	YES	YES	YES	YES	YES	YES	YES
	infusion time	2 H	2 H	2 H	2 H	3 H	3 H	3 H	3 H
	observation time	1 H	1 H	1 H	1 H	1 H	1 H	1 H	1 H
	premedication	no premed	no premed	no premed	no premed	no premed	no premed	no premed	no premed
13	home care option	YES	YES	YES	YES	YES	YES	YES	YES
	infusion time	2 H	2 H	2 H	2 H	3 H	3 H	3 H	3 H
	observation time	1 H	1 H	1 H	1 H	1 H	1 H	1 H	1 H
	premedication	no premed	no premed	no premed	no premed	no premed	no premed	no premed	no premed
14	home care option	NO	NO	NO	NO	NO	NO	NO	NO