# Statistical Analysis Plan
# Version 1.0
**Nov 25, 2020**

## Protocol: PB-102-F50
**Date of the final protocol (version 4.1): 25 Jul, 2018**

**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)**

**Ssponsor: Protalix Ltd.**

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**Approval**

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# 1. ABBREVIATIONS

| | |
|---|---|
| ACEi | Angiotensin-Converting Enzyme Inhibitor |
| ADA | Anti-Drug Antibodies |
| AE | Adverse Event |
| ARB | Angiotensin Receptor Blocker |
| AUC | Area Under the Curve |
| BPI | Brief Pain Inventory |
| CI | Confidence Interval |
| CKD | Chronic Kidney Disease |
| $C_{max}$ | Maximum Observed Plasma Drug Concentration |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| CV | Coefficient of Variation |
| DBL | Database Lock |
| ECG | Electrocardiography |
| eGFR | Estimated Glomerular Filtration Rate |
| ERT | Enzyme Replacement Therapy |
| FCE | Fabry Clinical Events |
| FD | Fabry Disease |
| Gb3 | Globotriaosylceramide |
| GMR | Geometric Mean Ratio |
| HBsAg | Hepatitis B Surface Antigen |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| IRR | Infusion Related Reaction |
| IV | Intravenous |
| KM | Kaplan-Meier |
| Lyso-Gb3 | Globotriaosylsphingosine |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic Resonance Imaging |
| MSSI | Mainz Severity Score Index |
| NSR | Normal Sinus Rhythm |
| PK | Pharmacokinetics |
| PrT | Prothrombin Time |
| PT | Preferred Term |
| PTT | Partial Thromboplastin Time |
| QoL | Quality of Life |
| SAE | Serious Adverse Event |

| | |
|---|---|
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |
| SE | Standard Error |
| $T_{1/2}$ | Terminal Elimination Half-life |
| TEAE | Treatment Emergent Adverse Event |
| $T_{max}$ | Time to Maximum Observed Plasma Drug Concentration |
| UPCR | Urine Protein to Creatinine Ratio |
| WHO | World Health Organization |

# 2. INTRODUCTION

The statistical analysis plan (SAP) contains the analysis information in detail on the definition of the analysis populations, derivation of variables, convention of analysis scope, and statistical methodology for the analyses of safety and efficacy of pegunigalsidase-alfa (PRX-102) 2mg/kg administered every 4 weeks based on data collected per protocol PB-102-F50. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing. Any deviations from this SAP during the actual data analysis will be documented properly in a change request or a note-to-file document, as well as in the Clinical Study Report (CSR). The SAP will be finalized before the first database lock (DBL).

Analysis of PK endpoints will be presented in a separate document.

# 3. OBJECTIVES AND ENDPOINTS

## 3.1 Objectives

To evaluate the safety, efficacy, and PK of pegunigalsidase-alfa (PRX-102) in patients with Fabry disease currently treated with currently commercially available Enzyme Replacement Therapy (ERT) (agalsidase-alfa or agalsidase-beta).

## 3.2 Endpoints

### 3.2.1 Safety Endpoints

- Treatment-emergent adverse events (TEAE)
- Infusion-related reactions (IRR)
- Infusion premedication
- Treatment-induced anti- pegunigalsidase-alfa antibodies
- Clinical laboratory tests
- Physical examinations
- Injection site reactions
- Electrocardiogram (ECG)
- Vital signs

### 3.2.2 Efficacy Endpoints (Exploratory)

- Estimated Glomerular Filtration Rate ($eGFR_{CKD-EPI}$)
- eGFR slope
- Plasma Globotriaosylsphingosine (Lyso-Gb3)
- Plasma Globotriaosylceramide (Gb3)
- Urine Lyso-Gb3
- Urine Protein/Creatinine Ratio (UPCR) spot urine test
- Left Ventricular Mass Index ($g/m^2$) by echocardiogram
- Usage of pain medication
- Stress test
- Short form Brief Pain Inventory (BPI)
- Mainz Severity Score Index (MSSI)
- Quality of Life (QoL) EQ-5D-5L
- Fabry Clinical Events (FCE)

### 3.2.3 PK Endpoints

PK endpoints will include (but not restricted to) the following endpoints:

- $C_{max}$
- $T_{max}$
- $T_{1/2}$
- $AUC_{0-t}$
- $AUC_{0-\infty}$

# 4. STUDY DESIGN

This is an open-label switch over study of pegunigalsidase alfa (PRX-102) treatment in patients previously treated with ERT (agalsidase-alfa or agalsidase-beta), for at least 3 years and on a stable dose for at least the last 6 months.

Patient age will be 18 to 60 years, with a documented diagnosis of Fabry Disease (FD), and $eGFR_{CKD-EPI}$ at screening of 30 mL/min/1.73 $m^2$ or more and linear negative slope no worse than -2 mL/min/1.73 $m^2$ /year based on at least 4 serum creatinine values over approximately 2 years (and including the value at screening).

Eligible 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. The protocol allows that in case of clinical deterioration, the dosing regimen may be changed to 1.0 mg/kg every two weeks at the Investigator's discretion. Patients will have the option to be enrolled to an open-label extension study upon completion of the study.

## 4.1 Sample Size and Statistical Power Consideration

Thirty patients participated in the study. This sample size was determined pragmatically and is adequate to evaluate the safety of switching from previous ERT every 4 weeks in this orphan disease in which patient recruitment is difficult. The sample size is not based on statistical considerations.

## 4.2 Study Diagram and Flow Chart

**Table 1: Study Assessments**

| 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 | | | | | | | | | | | | | | | |
| Quality of Life (5Q-5D-5L) | | x | | | | | | | x | | | | | | | x |
| Mainz Severity Score Index (MSSI) | | x | | | | | | | | | | | | | | x |
| Request patient approval by Medical | | 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** |
| Monitor | | | | | | | | | | | | | | | | |
| 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.

# 5. ANALYSIS POPULATIONS (ANALYSIS SETS)

## 5.1 Safety Population

The safety population consists of all subjects who received at least one dose (partial or complete) of pegunigalsidase alfa in the study. All safety analyses will be based on this population.

## 5.2 Efficacy Population

The efficacy population consists of all subjects who received any dose of pegunigalsidase alfa 2 mg/kg in the study and who have at least one post-baseline visit with an efficacy evaluation. All efficacy analyses will be based on this population.

# 6. TREATMENT DESCRIPTIONS

Unless otherwise indicated, on the summary tables, the treatment will be identified as PRX-102, where applicable.

# 7. STATISTICAL ANALYSIS METHODS AND ISSUES

## 7.1 Statistical Methods

Descriptive statistics include sample size (n), mean, Standard Deviation (SD), Standard Error (SE), median, minimum and maximum for continuous variables. For categorical variables count and percentage will be provided.

This study is descriptive in nature. Confidence Intervals (CIs) will be described in the relevant sections and should be interpreted with caution since the study was not powered.

Due to COVID-19 pandemic, the study was prolonged, beyond visit 14 for one patient (Enrollment ID: 03-F50030) who could not perform end of study visit at the site as scheduled. During this extended time, the patient continued to receive infusions and perform the relevant lab tests. AE and medications collection were continued. Procedures which should be performed on site were delayed to the end of study visit.

Information collected up to visit 14 for this patient will be tabulated as planned. Data collected beyond visit 14 will only be listed.

The protocol allows that in case of clinical deterioration, the dosing regimen may be changed to 1.0 mg/kg every two weeks at the Investigator's discretion. In such cases, additional intermediate visits will be added for infusion administration. By visit tables will only present planned visits based on the regimen every 4 weeks. Patients who switched the dosing regimen will be included in the efficacy analysis up to the planned visit in which they switched. Efficacy data collected in visits (intermediate or planned) from the visit of the switch and forward will only be listed.

By visit tables will present planned visits based on the per protocol planned visits for each procedure. Outcomes of procedures which were performed in a planned visit, but the procedure was not planned for that visit, will only be listed.

Listings will show data collected on all enrolled subjects (including screening failures), and the patients will be sorted to show treated patients first and then patients who were screening failures.

Visits within subjected will be shown chronologically based on the date of the visit. Unscheduled visits will be listed, and the visit column will show the visit as unscheduled, with no number.

## 7.2 Missing Data

Imputations of missing data associated with AE severity and relatedness are specified in Section 10.2. Below are imputations rules related to missing or incomplete dates of AE or medication. No other imputations will be made for missing safety or efficacy endpoints.

### 7.2.1 Partial or Missing Dates of Medication

The following imputations will be used in case of incomplete dates for medications :

- The middle of the month (i.e. 15$^{th}$) will be used if only the day is missing
- In case the year is not missing, but the month is missing, the month will be imputed to July. If the day is missing as well then it will be imputed to the 1$^{st}$ of July
- No imputation will be done in case the year is missing.

In some of the analyses, a flag of whether a medication was used at a certain visit is needed (e.g. use of Angiotensin-Converting Enzyme Inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB) treatment at baseline or usage of pain medication at baseline or in the last visit). In case partial start date and/or end date exist, imputation will be based on the above rule and determination of the flag will be based on the imputed dates. In case that the start date is missing the year, the determination of usage of a medication at different visits will be based on the stop date of the medication. If the year of the stop date is missing, then the determination will be based on the "Ongoing" status of the medication form as follows: if the ongoing status is Yes then it is assumed that the medication was taken throughout the study (including at baseline and last visits), and if the ongoing status is No then it is assumed the medication was stopped prior to the baseline visit.

### 7.2.2 Partial or Missing Dates of Episodes of Acute Kidney Injury

Episodes of Acute Kidney Injury (AKI) are reported by the investigators as AE. An AKI episode is defined between the start and the end date of the AKI AE. The following rules will be followed in case on incomplete start or end date of an AKI event:

- AKI start date:
    - If month and year are available and day is missing, the 1st of the month will be imputed. In case the event is during the month of the first infusion, it will be imputed to the date of 1st infusion.
    - If month is missing and year is available then if the year is the same as the year of 1st infusion then the date should be the date of 1st infusion. Otherwise the date should be set to January 1st.
    - If year is missing then the date should be imputed to date of 1st infusion.

- AKI end date:
    - If month and year are available and day is missing, the last day of the month will be imputed. In case the event is during the month of the last infusion, it will be imputed to the date of end of study.
    - If month is missing and year is available then if the year is the same as the year of last infusion then the date should me the last day in the study. Otherwise the date should be set to December 31st.
    - If year is missing then the date should be imputed to last day in the study.

Serum creatinine during episodes of acute kidney injury (AKI) will be excluded from the eGFR slope calculation and summary tables and considered to be missing.

## 7.3 Baseline Definitions

The baseline for this study is defined as the assessment made at Visit 1 prior to the first infusion of pegunigalsidase alfa. If not available, the last assessment before receiving the first treatment of pegunigalsidase alfa will be used as baseline.

## 7.4 Multiple Comparisons

No statistical tests are pre-planned in this study, which is mainly descriptive in nature and not powered for inferential analyses, hence, no adjustment for multiplicity is planned.

## 7.5 Subgroups

Subgroup analysis will be conducted based on baseline characteristics and demographic for selected efficacy and safety endpoints and in case that the size of at least one of the groups is less than 5, it may be decided to skip the subgroup. The sections which describes the analysis of efficacy and safety endpoints will define the selected subgroups from the following list:

- Gender (Male or Female).
- Anti-Drug Antibodies (ADA) status at baseline (Negative; Positive). Determination of status is based on IgG positive to pegunigalsidase alfa at baseline – see Section 10.3.
- FD classification (Classic/Non-Classic). In order to be classified as FD classic, a patient should have ≤ 5% mean of lab normal ranges residual enzymatic activity in plasma or leukocytes at baseline visit and at least one Fabry specific symptom: Cornea Verticillata, Acroparesthesias, and/or Angiokeratomas. In case of missing information for the symptoms or residual activity, which does not allow for clear classification as classic or non-classic, the FD classification will be missing and the subject will be excluded from the sub-group analysis (for example, if a patient meets the symptoms requirement and have a plasma residual activity of 10% but the leukocytes residual activity is missing then the classification will be missing and the patient will be excluded from the subgroup analysis. As another example, if a patient meets the symptoms requirement and have a plasma residual activity of 3% and the leukocytes residual activity is missing, it is still possible to classify the patient as Classic and the patient will be included in the subgroup analysis).
- Baseline eGFR (≤ and > 60 ml/min/1.73m$^2$).
- Previous ERT treatment (agalsidase-alfa or agalsidase-beta) defined as the ERT taken before the switch.
- Use of Angiotensin-Converting Enzyme Inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB) treatment at baseline (Yes/No). The usage of ACEi or ARB is based on the classification in the CM form in the eCRF. Based on this form it is possible to identify patients who received ACEi or ARB at baseline. All other patients will be classified as “no” for this subgroup.

## 7.6 Interim Analysis

No interim analysis will be performed.

# 8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

## 8.1 Subject Disposition

The number and percentage of subjects who were screened, enrolled, treated, completed, and discontinued will be summarized. The documented reasons for screen failures will be tabulated. The number and percentage of subjects who discontinued will also be summarized for each reason of discontinuation. The number of subjects in each of the analysis sets will be presented. The number of patients who switched dosing regimen will be presented, as well as the number of subjects with study prolongation due to COVID-19.

The listing of disposition will indicate subjects who were affected by COVID-19. Protocol violations will be listed.

## 8.2 Demographics

Patient demographics (age, gender, race, and ethnicity) will be summarized using descriptive statistics overall and for subgroups defined in Section 7.5. The analysis will be done for the safety set.

## 8.3 Baseline Characteristics

Baseline characteristics will be summarized by descriptive statistics overall and for subgroups defined in Section 7.5. The analysis will be done for the safety set.

Baseline characteristics include the following variables:

- Weight
- Height
- Age started Fabry therapy
- Previous ERT (agalsidase-alfa or agalsidase-beta) is the ERT taken just before the switch
- % residual enzyme activity in leukocyte (defined as the value in leukocyte × 100/83.5, where 83.5 nmol/hr/mg protein is the mean of reference range)
- % residual enzyme activity in plasma (defined as the value in plasma ×100/12.95, where 12.95 nmol/ hr/mL is the mean of reference range)

- eGFR
- pre-switch eGFR annualized slope
- Plasma Lyso-Gb3
- Fabry disease (FD) classification (classic / non-classic) (See Section 7.5)
- Presence of Severe Proteinuria (UPCR ≥ 0.5 gr/gr /) (Yes/No)
- Treatment with ACEi or ARB (yes/no)
- Premedication use for ERT infusion prior to enrollment (yes / no)
- Anti pegunigalsidase-alfa antibodies status (ADA positive or ADA negative). The determination of the status is based on the results of the IgG at baseline for PRX-102 – see Section 10.3.
- Anti-drug antibodies for agalsidase-alfa (ADA positive or negative). This will be presented only for patients who were treated with agalsidase-alfa prior to the switch. The determination of the status is based on the results of the IgG at baseline for agalsidase-alfa.
- Anti-drug antibodies for agalsidase-beta (ADA positive or negative). This will be presented only for patients who were treated with agalsidase-beta prior to the switch. The determination of the status is based on the results of the IgG at baseline for agalsidase-beta.

## 8.4 Fabry Disease Medical History

Fabry Disease Medical history data by body system and conditions will be tabulated, overall and for subgroups defined in Section 7.5. The analysis will be conducted for the safety set.

Data collected in the Fabry disease medical history Case Report Form (CRF), Fabry disease diagnosis CRF and Fabry disease past treatment CRF will be listed in a single listing.

## 8.5 Other Medical History

Other medical history will be summarized by descriptive statistics overall and for subgroups defined in Section 7.5. The analysis will be done for the safety set.

## 8.6 Treatment Compliance

Treatment compliance will be assessed by dividing the actual number of partial or complete infusions, over the expected number of infusions during the patient duration in the study. For patients who terminated early, the expected number of infusions will be based on their treatment start date and date of discontinuation. This will be done regardless of reason of discontinuation. For patients who switched dosing regimen from monthly infusions to infusions every other week, the expected number of infusions should be adjusted from the time of the switch until Visit 14 (or early termination, as above).

Compliance will be summarized using descriptive statistics for the efficacy set. Patient compliance will be summarized also by the following categories: < 60%; ≥ 60% and < 80%; ≥80%.

# 9. ANALYSIS OF EFFICACY ENDPOINTS

All the analyses presented in this section will be done using the efficacy population. This study is descriptive in nature and sample size is not based on statistical ground.

## 9.1 eGFR

eGFR will be calculated based on the value of the serum creatinine values according to the CKD-EPI formula:

$$eGFR\ (mL/min/1.73\ m^2) = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black / African American}]$$

where Scr is serum creatinine (mg/dL), $\kappa$ is 0.7 for females and 0.9 for males, $\alpha$ is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/$\kappa$ or 1, and max indicates the maximum of Scr/$\kappa$ or 1.

Serum creatinine can be recorded in two units, µmol/L and mg/dL. In calculation of eGFR or summary of creatinine, the value in µmol/L needs to be converted to mg/dL using the following conversion formula: 1 mg/dL = 88.4 µmol/L.

The age should be the actual age when the subject's serum creatinine is collected. The calendar age at each timepoint should be used in the formula to be consistent with that in the Electronic Data Capture system.

The results of the serum creatinine test at the screening visit appears twice in the data-base: once as part of the data transferred from the central laboratory and once in the eCRF (once the site receives from the central laboratory, the value is entered into the eCRF to check the eligibility in terms of eGFR value and the eGFR slope). These two values should be identical. In the listings, by-visit tables of eGFR and slope calculations, the value entered to eCRF should be used.

Episodes of Acute Kidney Injury (AKI) are reported by the investigators as AE (The associated System Organ Class (SOC) is Renal and urinary Disorders and Preferred Term (PT) is Acute Kidney Injury. Serum creatinine measurements, if any, during an AKI episode will be excluded from the eGFR summary tables and any analysis related

to eGFR. An AKI episode is defined between the start and the end date of the AKI AE. The imputation of date in case of a partial dates are provided in Section 7.2.

eGFR values during an AKI episode will only be listed.

eGFR will be summarized descriptively by visit overall.

A shift from baseline to Week 52 or early termination, between the following eGFR categories will be presented:

- eGFR $\geq$ 90 mL/min/1.73 $m^2$,
- 60 mL/min/1.73 $m^2$ $\leq$ eGFR < 90 mL/min/1.73 $m^2$,
- eGFR < 60 mL/min/1.73 $m^2$.

eGFR over time will be plotted for each patient. The mean eGFR ± Standard Error (SE) will be plotted over time.

## 9.2 eGFR Slope

For each patient, the following linear regression using all the available eGFR values after, and including, the baseline visit will be used to compute the eGFR slope after the switch to PRX-102:

$$eGFR = \alpha + \beta \times [\text{time in year}]$$

The slope $\beta$ (mL/min/1.73 $m^2$ / year) will be an estimate of the subject's annualized change in eGFR. The "[time in year]" in the formula is the time, in year, from "baseline" to the respective visit, and will be estimated by (date of the visit – date of baseline)/365.25. In case of study prolongation due to COVID-19, only data collected up to Week 52 (Visit 14) will contribute to the slope calculation. In case of switching dosing regimen, the slope calculations will be based on eGFR measured up to (including) the visit of the switch.

The slope prior to the switch will be calculated in a similar manner, using the historical serum creatinine values as well as screening and the baseline serum creatinine value. Any eGFR data obtained more than 730 days (approximately 24 months) prior to Screening visit will not be used in estimating the pre-switch annualized slope.

The screening slope which is based on the historical serum creatinine values as well as screening serum creatinine, and is documented in the eCRF.

The serum creatinine at baseline is used in the two slopes calculations (pre- and post-switch).

Note that the resulting slope will include the baseline serum creatinine which is not used for the evaluation of inclusion/exclusion. It may be that the slope with the baseline (prior to the switch) will be different from the slope at screening.

The eGFR slopes pre and post switch as well as the screening slope will be summarized descriptively. The summary of the slope post switch will include also a 95% Confidence Interval (CI) for the mean slope based on a t-distribution.

This analysis will be repeated for all the subgroups defined in Section 7.5.

For the sub-groups, a 95% CI, for the mean difference in slope post switch between the two categories within each sub-group, will be constructed based on t-distribution.

The sub-groups will be summarized graphically by box-plots.

## 9.3 Plasma Lyso-Gb3

Descriptive statistics of plasma Lyso-Gb3 concentration (nM) will be summarized at each visit that it was collected, as well as the change from baseline and percent change from baseline. The summary will include also a 95% Confidence Interval (CI) for the mean change from baseline and percent change from baseline based on t-distribution.

The summaries will be repeated for the following sub-groups (see Section 7.5): ADA; Gender; Previous ERT; FD classification. For the sub-groups a 95% CI for the mean difference between the average percent change from baseline for the levels of each subgroup will be constructed based on t-distribution.

Plasma Lyso-Gb3 levels over time will be presented graphically by a spaghetti plot, for individual subjects (separate plots for male and female). The mean ± SE of the change from baseline over time will be presented graphically. The change from baseline to week 52, for the subgroups, will be presented graphically using box-plots.

The number and percentage of patients who deteriorated or did not deteriorated will be summarized at each visit overall and for the above sub-groups. A deterioration is defined as an increase > 10% in the lyso Gb3 compared to baseline and an increase > 10 nM in lyso Gb3 concentration compared to baseline.

## 9.4 Plasma Gb3

Descriptive statistics of plasma Gb3 concentration (nM) will be summarized at each visit, as well as the change from baseline and percent change from baseline. The summary will include also a 95% CI for mean percent change from baseline and for the 95% CI for the mean change from baseline based on t-distribution. The summaries will be presented overall and by gender.

## 9.5 Urine Lyso-Gb3

Descriptive statistics of urine lyso-Gb3 concentration (pM/mM Creatinine) will be summarized at each visit, as well as the change from baseline and percent change from baseline. The summary will include also a 95% CI for mean percent change from baseline and the 95% CI for the mean change from baseline based on t-distribution. The summaries will be presented overall and by gender.

## 9.6 Urine UPCR

Urine protein/creatinine ratio (UPCR), by spot urine test will be classified into three categories, based on the Kidney Disease Improving Global Outcomes (KDIGO) guidelines:

- Normal to mildly increased, in case UPCR < 0.15 gr/gr,
- Moderately increased, in case 0.15 ≤ UPCR < 0.5 gr/gr,
- Severely increased, in case 0.5 ≥ UPCR gr/gr

The limit of detection for protein is 4 mg/dL, and for a large number of the measurements, the protein is undetectable, resulting in a UPCR of < x gr/gr (calculated by 4 divided by the measured level of creatinine). Any such observation will be classified to one of the above categories, ignoring the '<' sign in the

observation. This is considered a conservative assignment to categories.

UPCR will be summarized at each visit based on the above 3 categories overall and for the following sub-groups: ADA; Gender; Previous ERT; Use of ACEi/ARB; and FD classification.

The shift from baseline to Week 52 or early termination, between UPCR categories, will be summarized overall. The tables will show the number and percentage of patients in each cell. The analysis will be repeated for the subgroup Use of ACEi/ARB.

UPCR listing will include the actual observation (i.e. '<' sign will not be removed) as well as the assigned category.

## 9.7 Echocardiogram Report

The echocardiography evaluations are done with substantial variations, therefore only data listing will be provided. LVMI (units: $g/m^2$) will be listed LVMI is based on the Left Ventricular Mass (LVM; units of g; collected as part of the echocardiography) and BSA (Body Surface Area) as follows:

$$LVMI = LVM / BSA.$$

Du Bois and Du Bois (1916) will be used to calculate BSA:

$$BSA = 0.007184 \times W0.425 \times H0.725,$$

where H is the height measured in cm (at screening visit) and W is the weight measured in Kg and taken from the same visit the echocardiography was performed. In case that weight at the visit is missing, the last available weight prior to the visit will be used. Qualitative assessments (normal / other) regarding Aortic, Mitral, Tricuspid, and Pulmonic will be presented by a shift table from baseline overall.

## 9.8 Pain Medication

See Section 10.8 regarding coding of pain.

Pain medication will be identified based on the classification on the eCRF. Pain medications will be summarized by the count and percentage of the subjects with each medication by standardized medication name within medication class.

The number of patients who used pain medication at any time during the study will be summarized by count and percentage by the number of medications they used (0, 1, 2, up

to the maximum, where the medications with identical standard name is counted once and 0 represent patient who did not take any pain medication during the study).

The change from baseline to the last visit in the number of different pain medications used will be examined by a shift table with the following categories for the number of pain medications used: 0, 1, and 2+. The tables will be presented overall and will be repeated for the subgroups of FD classification and previous ERT. For patient who terminated early, the table will show their shift to their last assessment prior to discontinuation. This analysis will be based on the pain medication used on the day of the baseline visit, and the day of last visit.

## 9.9 Stress Test

The qualitative evaluation (yes / no) of symptoms (chest pain, shortness of breath, Dizziness, palpitations, and other) and the overall impression: normal stress test (yes / no) will be summarized by count and percentage at each visit overall.

A shift from baseline will be presented overall impression: normal stress test (yes / no). For patient who terminated early, the table will show their shift to their last assessment prior to discontinuation.

## 9.10 Brief Pain Inventory (BPI)

Pain severity will be summarized descriptively by visit, for each of the severity domains (worst, least, right now and average in the last 24 hours). Change from baseline will be presented as well as a 95% CI for the mean change from baseline, based on t-distribution. The analysis for the average pain over the last 24 hours will be done also for the following subgroups (Section 7.5): ADA; Gender; Previous ERT; FD classification.

The proportion of patients whose average pain severity in the last 24 hours did not change or improved compared to baseline (the difference from baseline is $\leq 0$) and the proportion of patients whose average pain severity in the last 24 hours deteriorated compared to baseline will be summarized by visit.

Pain interferences will be summarized descriptively by visit, by each of the interference domains together with their change from baseline and a 95% CI for the mean change from baseline, based on t-distribution.

## 9.11 MSSI (Mainz Severity Score Index)

The change from baseline for each of the domains (general, neurological, cardiovascular, renal dysfunction, and overall score (sum of these four scores) will be summarized by descriptive statistics at each visit the MSSI is evaluated. A 95% CI, based on t-distribution, will be presented for the mean change from baseline.

A total MSSI score < 20 is considered as mild; a score 20 ≤ and ≤ 40 is considered moderate and > 40 is considered severe (Beck, 2006). A shift table from baseline to week 52 between the three categories will be presented.

For patients who discontinue early, their value at their last assessment will be used for the MSSI analyses.

## 9.12 Quality of Life EQ-5D-5L

The count and percentage of patients for each of the categories in the qualitative assessments regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression will be summarized at each visit.

The overall health score (Visual Analog Score, from 0 to 100) will be summarized by descriptive statistics at each visit together with the change from baseline and a 95% CI for mean change from baseline based on t-distribution.

## 9.13 Fabry Clinical Events

Fabry clinical events (FCE) are classified into four categories: renal, cardiac, cerebrovascular and non-cardiac death. The adjudicated decisions will be made by the Sponsor medical monitor, based on reported adverse events and clinical information included in the data base.

The criteria for FCE are the following and based on Hopkin (2016):

1. Renal events:

    - First occurrence of either initiation or chronic dialysis (>40 days),

- Renal transplantation.

2. Cardiac events:

- Cardiac related death,
- Myocardial infarction,
- First time congestive heart failure,
- Atrial fibrillation,
- Ventricular tachycardia,
- Evidence of progressive heart disease severe enough to require pacemaker,
- Implantation of pacemaker,
- Bypass surgery,
- Coronary artery dilatation,
- Implantation of defibrillator.

3. Cerebrovascular events:

- Hemorrhagic or ischemic stroke,
- Transient Ischemic Attack.

4. Non-cardiac related Death.

The number and percentage of patients with FCE (regardless of type of event) and by type will be presented. For the number of FCE (regardless of type of event) patients who had more than one type will be counted once.

FCE listing will show the categories by SOC and PT and the time to event measured from Visit 1.

# 10. ANALYSIS OF SAFETY ENDPOINTS

All the analyses presented in this section will be done using the Safety set.

## 10.1 Extent of Exposure

To account for infusions which are 4 weeks apart, the exposure (in months) for subject is defined as

((date of last infusion) – (date of first infusion) + 1)*12/365.25

For a subject that received one infusion, the exposure is 1 day or 0.03 months.

The exposure duration (in months) will be summarized by descriptive statistics overall and for all the subgroups defined in Section 7.5.

In addition, the cumulative exposure (over all subjects) in person-months will be provided.

The number of partial or complete infusions that a patient received will be summarized overall and by location of administration (home/site). Summary of infusion duration (HH:MM) by visit will be presented overall and by patient weight (≤ 100 kg; > 100kg) using descriptive statistics.

Listing of infusion should include whether the infusion was interrupted or not and whether the complete dose was administered or not.

## 10.2 Adverse Events

### 10.2.1 AE Overall

Adverse events (AE) will be coded by the Medical Dictionary for Drug Regulatory Activities (MedDRA) version 19.0 or higher.

Pre-treatment AEs include all AEs collected prior to the first pegunigalsidase alfa infusion. Pre-treatment AE will only be listed.

Treatment-emergent adverse event (TEAE) is any AE occurring after the start of the first infusion of pegunigalsidase alfa. In case the date of onset is completely unknown,

the AE will be classified as TEAE. In case the date is partially known and the month is earlier than the month of first infusion, the event will be classified as pre-treatment AE.

The number and percentage of patients with at least one TEAE and the number of TEAEs will be reported in an overall table for the following parameters: Any TEAE; Related (possibly, probably or definitely related) TEAEs; Mild or moderate TEAEs; Related mild or moderate TEAEs; Severe TEAEs; Related severe TEAEs; Serious TEAEs; Non-serious TEAEs; Related serious TEAEs; TEAEs leading to withdrawal; Related TEAEs leading to withdrawal; TEAEs leading to death; and related TEAEs leading to death.
In the analysis by severity, subjects whose event was classified as "Very Severe" or "Fatal" will be presented in the "Severe" category.
This analysis will be repeated for the following sub-groups: ADA; Gender; Previous ERT; FD classification.
This overall analysis will be repeated for injection site reaction TEAEs.

TEAE summary tables by the MedDRA System Organ Class (SOC) and Preferred Term (PT) will present the number and percentage of subjects with at least one TEAE and the number of TEAEs. These tables will be generated overall; by severity; and by relationship to study drug.
Similar tables by SOC and PT will be generated for serious TEAEs overall and by relationship to study drug.

In the summaries of severity and relationship to study drug, the most extreme outcome (highest severity and closest relationship to study drug) will be used for those subjects who experience the same TEAE (per PT) more than once.
Missing values associated with TEAEs will be treated as missing except for causality, intensity, and outcome of a TEAE: for these variables a "worst case" approach will be taken in the analysis. Thus:

- If the causality is missing, the TEAE will be regarded as related to pegunigalsidase alfa.

- If the intensity is missing, the intensity of the AE will be regarded as severe.
- If the outcome is missing and the stop date is not provided, the outcome will be regarded as "ongoing".

If the seriousness is missing, all efforts should be made prior to database lock to make sure that this information is available, if still missing, the worst-case scenario will be assumed.

If there are any TEAEs leading to withdrawal or death, these cases will be presented by patient.

Listing of TEAEs will include also the TEAE onset and end date and start date relative to first pegunigalsidase alfa infusion.

### 10.2.2 Infusion Related Reactions (IRR)

IRRs are those TEAEs which occur during the infusion or within 2 hours after the completion of the infusion and their causality is definitely, probably, or possibly related.

Classification rules for assignment of patients with TEAEs during the infusion or within 2 hours after the infusion are described below.

Injection site reactions with SOC and PT listed in Table 2 are not considered IRR and should be excluded from the IRR analysis.

**Table 2: Injection Site Reaction SOC and PT Not Considered as IRR**

| MedDRA SOC | MedDRA Preferred Term |
|---|---|
| General disorders and administration site conditions | Infusion site discomfort |
| | Injection site discomfort |
| | Infusion site pain |
| | Injection site pain |
| | Infusion site hematoma |
| | Injection site hematoma |
| | |
| Injury poisoning and procedural complications | Contusion |
| | Procedural site reaction |
| | Procedural pain |
| | |
| Vascular disorders | Vein rupture |

The number and percentage of patients with at least one IRR and the number of IRRs will be reported in an overall table with the following parameters: Any IRR; Mild or moderate IRRs; Severe IRRs; Serious IRRs; IRRs leading to withdrawal; IRRs leading to death.

This analysis will be repeated for the following sub-groups: ADA; Gender; Previous ERT; FD classification. An additional sub-group will be the location of administration (Home or Site).

IRR summary tables by SOC and PT will present the number and percentage of subjects with at least one IRR and the number of IRRs. The tables for the IRRs will be presented overall and by severity.

**TEAE occurring during the infusion or within 2 hours after the infusion:**

To determine whether a TEAE occurred within this time frame, information collected in two CRF forms will be considered: AE form (fields of onset date and time) and Drug Administration form (fields of administration date; start and end times; question 1 "Did the patient experience an AE during or after the infusion?" and the sub-questions in case the answer is Yes. The sub-questions are 1a: "During the infusion", 1b: "Within 2 hours after the infusion" or 1c: "Up to 24 hours after the infusion"). Events which meet one of the following criteria will be considered to occur during infusion or within 2 hours after the infusion:

- Date and time for both TEAE and infusion are complete, and the onset of the TEAE is during the infusion or within 2 hours from its completion (stop time), regardless of the answer to question 1 above;
- The answer to question 1 above is Yes, and the options selected are either 1a or 1b.

All other events will not be classified into this time category.

## 10.3 Anti-Drug Antibodies (ADA)

A summary table for IgG and Neutralizing antibody will present the number and percentage of patients who are positive or negative by visit. In case that IgG was tested twice on the same visit (for example, due to hypersensitivity) only the 1st test will be

part of the summary by visit. The table will also show the overall ADA status post-treatment where post-treatment positive is defined as positive in at least one visit post baseline (Visit 1), or negative if negative at all post-baseline visits, regardless of status at baseline.

Note that only patients who were tested positive for IgG ADA will be tested for Neutralizing Antibody. ADA characterization. i.e., IgG titer and positivity to other unique PRX-102 epitopes will be listed.

The decision about ADA status at each visit is based on sequential evaluation as follows:

1. If the IgG screening is negative then ADA at that visit is reported as "negative" (and no more evaluations).
2. If the IgG screening is "Presumptive Pos", the next evaluation is the IgG Immunodepletion
    a. If IgG Immunodepletion is negative then the ADA status at the visit is reported as "negative"
    b. If IgG Immunodepletion is positive then the ADA status at the visit is reported as "positive"

Patients are considered treatment emergent ADA positive if they satisfy one of the following conditions:

1. Titer boosted: patients who were IgG positive to PRX-102 at baseline and boosted post treatment (i.e., titer increase by at least 4-fold from baseline. See Shankar et al. 2014 and FDA Guidance for Industry, January 2019: Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection).
2. Treatment Induced: patients who were IgG negative to PRX-102 at baseline and positive in at least one timepoint post first infusion

The number and percentage of patients who are Treatment emergent ADA (yes/no) will be presented. For treatment emergent ADA, the table will indicate to which of the two groups a patient belongs (titer boosted or treatment induced).

A shift table from ADA status at baseline (positive or negative) to overall status post baseline (positive if positive in at least one visit post baseline, or negative if negative at all post-baseline visits).

## 10.4 Vital Signs

The vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiration rate) will be summarized overall by visit. Within each visit, vital signs will be reported for pre-dose, 30 minutes from start of infusion, 60 min from start of infusion and then every hour up to 6 hours, and in addition the vital sign taken at the at the end of observation will be presented, regardless of the actual time they were taken (i.e. before or after 360 minutes).At each visit the change from pre-dose to each post dose will be presented. For the time points before 360 minutes, the analysis will use the nominal time in relation to the time of infusion.

In case that measurements are taken every 30 minutes or 60 minutes, but not at the planned times then only observations at 30, 60, 120… will be included in the analysis and the other will be listed (e.g. if measurements are taken at 15, 30, 45, 75, 105 minutes then the measurements at 15, 45, 75 and 105 will only be listed).

In case that patients do not tolerate the infusion, vital signs are taken every 15 minutes. These evaluations will only be listed.

In case the clinical visit lasted for more than 6 hours and vital signs were taken for more than 6 hours then these vital signs will only be listed.

## 10.5 Laboratory Test Results

The following laboratory test results will be summarized overall by descriptive statistics at the scheduled visits, and for continuous results also including the change from baseline:

1. Hematology: Hemoglobin, Platelets, Total white blood cell count
2. Coagulation Profile: Partial thromboplastin time (PTT), Prothrombin time (PrT)
3. Vitamin D
4. Urinalysis: Dipstick for presence of blood, Dipstick for presence of glucose, Dipstick for presence of ketones, Dipstick for presence of Protein
5. Biochemistry: Alanine transaminase, Albumin, Alkaline phosphatase, Aspartate transaminase, Bilirubin (total), Blood urea nitrogen, Calcium, Creatinine, Creatine phosphokinase, Cystatin c, Gamma-glutamyl transferase, Glucose,

Lactate dehydrogenase, Phosphate (inorganic), Potassium, Sodium, Total protein and Uric acid

Note: serum creatinine can be recorded in two units, µmol/L and mg/dL. In calculation of eGFR or summary of creatinine, the value in µmol/L needs to be converted to mg/dL using the following conversion formula: 1 mg/dL = 88.4 µmol/L.

Note: Serum creatinine can be entered in two fields in the Study Data Tabulation Model (SDTM) (CHEMISTRY and ENZYMATE). When the results from same sample is entered at both fields, then the value is identical. In such cases, only one of them will be taken in the analysis

In case that blood sample is taken twice at the same visit, only the results of the fist blood sample (based on the time the blood sample was taken) will be listed and used in the analyses.

All laboratory results will be listed (also parameters that are not tabulated).

For parameters for which, there are test results which are below the level of detection and reported with '<' sign, the change from baseline analysis will not be presented. The analysis of actual values at the visit will be based only on the values for which the true value was observed, and the summary will indicate the number of observations that were below the limit of detection. In the listings, these observations will be presented with the '<' sign.

## 10.6 Physical Examination

The physical examination results (normal / abnormal / not done) will be summarized overall by body system and by visit.

## 10.7 Electrocardiography (ECG)

Descriptive statistics for the following quantitative and qualitative ECG parameters will be summarized by visit overall. For quantitative parameters, the change from baseline will be summarized as well.

1. Quantitative ECG parameters: Mean Heart Rate, PR Interval (Aggregate), QRS duration (Aggregate), QT Interval (Aggregate)

2. Qualitative ECG parameters: Rhythm – Normal Sinus Rhythm (NSR), Conduction abnormalities, Left ventricular hypertrophy, Supraventricular tachycardia, Premature atrial contraction, Atrial flutter, Atrial fibrillation, Premature ventricular contraction, Ventricular tachycardia, and Any clinically abnormal findings (i.e. any abnormal condition as listed above).

## 10.8 Prior and Concomitant Medication

Prior and concomitant medications reported during the study will be coded by World Health Organization (WHO) Drug Dictionary Version 20160601E. Prior and concomitant medication will be tabulated overall by count and percentage with each medication by standardized medication name within medication class. Medication class will be listed alphabetically.

Listing of medication will include start and end date and whether the drug was taken prior to 1st infusion of pegunigalsidase alfa. If the date is incomplete, the following rules will be used to flag that the drug was taken prior to 1st infusion:

- If the month and/or day are missing, and the year is earlier than year the 1st infusion
- If the day of the month is missing, the year is the same year as 1st infusion and the month is earlier than the month of 1st infusion.

In all other cases, it will be assumed that the drug was taken after the 1st infusion.

### 10.8.1 ACEi and ARB

Usage of ACEi and/or ARB while on pegunigalsidase alfa will be identified based on the classification on the concomitant medication eCRF. The number of patients treated with ACEi and/or ARB at any time point after (including) the baseline visit will be summarized by descriptive statistics overall.

### 10.8.2 Infusion Premedication

Usage of infusion premedication (administrated before or during an infusion) will be identified based on the classification on the concomitant medication eCRF.

The number of patients with or without premedication use will be summarized by visit overall.

A shift table, to identify how many patients changed the number of infusions premedication medication classes from baseline to the last visit (Visit 14 or the last assessment before discontinuation) will be presented (note that in this analysis infusion premedication at baseline which belong to the same medication class will be counted as 1. A value of 2 means that medications from 2 medication classes were used. Similarly for Visit 14). This analysis will be based on infusion premedication use on the day of baseline visit, and the day of last visit. The shift table will include the following categories: 0, 1, 2, 3+.
A separate listing will be provided for infusion premedication.

### 10.9 Chest X-ray

Chest x-ray results will be listed.

## 11. ANALYSIS OF PK ENDPOINTS

PK concentration will be listed. The rest of the PK analysis, derivation of parameters and PK summary statistics will be described in a separate Pharmacokinetic Analysis Plan.

## 12. DIFFERENCES FROM PROTOCOL

The statistical section of the protocol is short and was not meant to provide detailed information for the analysis. Some of the changes in the planned analysis of PB-102-F50 are due to knowledge and insights gained in the overall clinical program of PRX-102.

The main changes in the analysis plan compared to protocol are as follows:

1. The following endpoints were added: Infusion Related Reaction (IRR) and Fabry clinical events.
2. Analysis sets: the protocol defined the Intent-to-Treat as the main efficacy set. The SAP revised the main efficacy set to be called Efficacy population. It differs from the Intent-to-Treat proposed in the protocol that requires that a patient should have at least one post

baseline observation. The Per-Protocol set was removed since there is no primary end-point and no sensitivity analysis is planned.

3. Efficacy variables: the protocol specified that the percent change from baseline will be used for quantitative efficacy endpoints. The SAP revised this, and depending on the endpoint, either a change from baseline or percent change from baseline or both are being used. For some of the efficacy end-point, only a shift table is presented.
4. Descriptive statistics for all variables include: mean (SE), SD, median, minimum and maximum. The interquartile range is not presented.
5. No shift tables are used for safety variables.
6. Evaluation of Acute Kidney Injuries is based on AE reporting and clinical judgment of the investigator and not by independent nephrologists.
7. 95% CI; Shift tables were added for some efficacy.
8. The statistical section of the protocol stated that hypersensitivity will be analysed as AE of special interest. Since IRR is a wider analysis which was added (see item 1 in this list), then the analysis of hypersensitivity will be part of the IRR evaluation.

# 13. LIST OF TABLES AND DATA LISTINGS

## 13.1 Statistical Tables

The statistical tables are to be generated using SAS version 9.4. In general, the sample size (n) is to be presented by whole number; minimum, and maximum are to be presented based on the number of decimal points of the reported value and other parameters with one more decimal point. The count will be the whole number. The percentage will be presented to one decimal place.

| Number | Title | Population |
|---|---|---|
| 14.1.1 | Patients Disposition | All |
| 14.1.2.1 | Patients Demographics Overall, by Gender and by ADA status | Safety |
| 14.1.2.2 | Patients Demographics by Fabry Disease Classification and by Previous ERT | Safety |
| 14.1.2.3 | Patients Demographics by eGFR and by Use of ACEi/ARB | Safety |
| 14.1.3.1 | Baseline Characteristics Overall, by Gender and by ADA status | Safety |
| 14.1.3.2 | Baseline Characteristics by Fabry Disease Classification and by Previous ERT | Safety |
| 14.1.3.3 | Baseline Characteristics by eGFR and by Use of ACEi/ARB | Safety |
| 14.1.4.1 | Fabry Disease Medical History Overall, by Gender and by ADA status | Safety |
| 14.1.4.2 | Fabry Disease Medical History by Fabry Disease Classification and by Previous ERT | Safety |
| 14.1.4.3 | Fabry Disease Medical History by eGFR and by Use of ACEi/ARB | Safety |
| 14.1.5.1 | Other Medical History Overall, by Gender and by ADA status | Safety |
| 14.1.5.2 | Other Medical History by Fabry Disease Classification and by Previous ERT | Safety |
| 14.1.5.3 | Other Medical History by eGFR and by Use of ACEi/ARB | Safety |
| 14.1.6 | Treatment Compliance | Efficacy |
| 14.2.1.1 | Kidney Functions - eGFR Summary – Overall and by Gender | Efficacy |
| 14.2.1.2 | Kidney Functions – Shift in eGFR Categories from Baseline to Week 52 or Early Discontinuation | Efficacy |
| 14.2.1.3.1 | Kidney Functions (eGFR Slope) Overall, by Gender and by ADA status | Efficacy |
| 14.2.1.3.2 | Kidney Functions (eGFR Slope) by FD Classification and by Previous ERT | Efficacy |
| 14.2.1.3.3 | Kidney Functions (eGFR Slope) by eGFR and by Use of ACEi/ARB | Efficacy |
| 14.2.2.1.1 | Plasma Lyso-Gb3 Concentrations Overall, by Gender and by ADA status | Efficacy |
| 14.2.2.1.2 | Plasma Lyso-Gb3 Concentrations by FD Classification and previous ERT | Efficacy |
| 14.2.2.2.1 | Plasma Lyso-Gb3 Concentrations – Deterioration Compared to Baseline Overall, by Gender and by ADA Status | Efficacy |
| 14.2.2.2.2 | Plasma Lyso-Gb3 Concentrations - Deterioration Compared to Baseline by FD Classification and previous ERT | Efficacy |
| 14.2.3 | Plasma Gb3 Concentrations Overall and by Gender | Efficacy |
| 14.2.4 | Urine Lyso-Gb3 Concentrations Overall and by Gender | Efficacy |

| | | |
|---|---|---|
| 14.2.5.1 | UPCR Categories Overall, by Gender and by ADA Status | Efficacy |
| 14.2.5.2 | UPCR Categories or by FD classification and by Previous ERT | Efficacy |
| 14.2.5.3 | UPCR Categories by Usage of ACEi/ARB | Efficacy |
| 14.2.5.4 | UPCR - Shift from Baseline to Week 52 or Early Discontinuation | Efficacy |
| 14.2.5.5 | UPCR - Shift from Baseline to Week 52 or Early Discontinuation by usage of ACEi/ARB | Efficacy |
| 14.2.6 | Echocardiogram Qualitative Assessments – Shift from Baseline | Efficacy |
| 14.2.7.1 | Number of Subjects Used Pain Medications at Any Time During the Study | Efficacy |
| 14.2.7.2 | Number of Different Pain Medications That a Subject Received During the Study | Efficacy |
| 14.2.7.3 | Pain Medication Use – Shift from Baseline to Last Visit | Efficacy |
| 14.2.7.4 | Pain Medication Use – Shift from Baseline to Last Visit by FD Classification | Efficacy |
| 14.2.7.5 | Pain Medication Use – Shift from Baseline to Last Visit by Previous ERT | Efficacy |
| 14.2.8.1 | Stress Test Quantitative Assessments | Efficacy |
| 14.2.8.2 | Stress Test Overall Impression - Shift from Baseline | Efficacy |
| 14.2.9.1 | Short Form Brief Pain Inventory (BPI) Severity Domains | Efficacy |
| 14.2.9.2.1 | Short Form Brief Pain Inventory (BPI)- Average Pain Over the Last 24 Hours by Gender and ADA Status | Efficacy |
| 14.2.9.2.2 | Short Form Brief Pain Inventory (BPI)- Average Pain Over the Last 24 Hours by FD Classification and by Previous ERT and by ADA Status | Efficacy |
| 14.2.9.2.3 | Short Form Brief Pain Inventory (BPI) - Average Pain Severity Improvement or No Change Compared to Baseline | Efficacy |
| 14.2.9.3 | Short Form Brief Pain Inventory (BPI) Interference Domains | Efficacy |
| 14.2.10.1 | Mainz Severity Score Index (MSSI) | Efficacy |
| 14.2.10.2 | Mainz Severity Score Index (MSSI) Overall Score - Shift from Baseline | Efficacy |
| 14.2.11.1 | Quality of Life EQ-5D-5L - Overall Health Score | Efficacy |
| 14.2.11.2 | Quality of Life EQ-5D-5L Qualitative Assessments | Efficacy |
| 14.2.12 | Number of Subjects with Fabry Clinical Events | Efficacy |
| 14.3.1.1 | Exposure Overall, by Gender and by ADA status | Safety |
| 14.3.1.2 | Exposure by FD Classification and by Previous ERT | Safety |
| 14.3.1.3 | Exposure by eGFR and by Use of ACEi/ARB | Safety |
| 14.3.2.1 | Number of Infusions Administered at Home, on Site and Overall | Safety |
| 14.3.2.2 | Infusions Duration (hours) Overall and By Patient Weight | Safety |
| 14.3.3.1.1 | Summary of TEAE | Safety |
| 14.3.3.1.2 | Summary of TEAE by Gender by ADA Status | Safety |
| 14.3.3.1.3 | Summary of TEAE by FD Classification and by Previous ERT | Safety |
| 14.3.3.2 | Summary of Injection Site Reaction | Safety |
| 14.3.3.3.1 | TEAE by MedDRA SOC and PT | Safety |
| 14.3.3.3.2 | TEAE by MedDRA SOC and PT and Severity | Safety |
| 14.3.3.3.3 | TEAE by MedDRA SOC, PT and Relationship to Study Drug | Safety |
| 14.3.3.4.1 | Serious TEAE by MedDRA SOC and PT | Safety |
| 14.3.3.4.2 | Serious TEAE by MedDRA SOC, PT and Relationship to Study Drug | Safety |
| 14.3.3.5.1 | Summary of IRR by Overall and by Location of Administration | Safety |

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| 14.3.3.5.2 | Summary of IRR by Gender and by ADA | Safety |
| 14.3.3.5.3 | Summary of IRR by FD Classification and by Previous ERT | Safety |
| 14.3.3.6.1 | IRR by MedDRA SOC and PT | Safety |
| 14.3.3.6.2 | IRR by MedDRA SOC, PT and Severity | Safety |
| 14.3.4.1 | Anti-Drug Antibodies | Safety |
| 14.3.4.2 | ADA Status - Shift from Baseline | Safety |
| 14.3.5 | Vital Signs | Safety |
| 14.3.6.1 | Laboratory Test Results – Biochemistry | Safety |
| 14.3.6.2 | Laboratory Test Results – Hematology | Safety |
| 14.3.6.3 | Laboratory Test Results – Urinalysis | Safety |
| 14.3.6.4 | Laboratory Test Results – Coagulation Profile at Screening | Safety |
| 14.3.6.5 | Laboratory Test Results – Vitamin D at Screening | Safety |
| 14.3.7 | Physical Examinations | Safety |
| 14.3.8.1 | Electrocardiography (ECG) Quantitative Parameters | Safety |
| 14.3.8.2 | Electrocardiography (ECG) Qualitative Parameters | Safety |
| 14.3.9.1 | Prior and Concomitant Medications | Safety |
| 14.3.9.2 | Subjects Treated with ACEi and/or ARBs | Safety |
| 14.3.9.3.1 | Infusion Premedication | Safety |
| 14.3.9.3.2 | Shift from Baseline to Last Visit in the Number of Infusion Premedication | Safety |

## 13.2 Figures

| Number | Title | Population |
|---|---|---|
| 15.2.1.1 | Spaghetti Plot of eGFR over Time | Efficacy |
| 15.2.1.2 | Mean eGFR +/-SE Over Time | Efficacy |
| 15.2.1.3 | eGFR Slopes - Boxplots for Subgroups | Efficacy |
| 15.2.2.1 | Spaghetti Plot of Plasma Lyso-Gb3 Concentrations over Time (Male Subjects) | Efficacy |
| 15.2.2.2 | Spaghetti Plot of Plasma Lyso-Gb3 Concentrations over Time (Female Subjects) | Efficacy |
| 15.2.2.3 | Mean Plasma Lyso Gb3 +/-SE Over Time | Efficacy |
| 15.2.2.4 | Plasma Lyso Gb3 Change from Baseline - Boxplots for Subgroups | Efficacy |

## 13.3 Data Listings

Data listings will be show first treated patients followed by screen failures, and within these two groups, it will be sorted by subject ID. The listings will present all data collected, for all subjects.

| Number | Title |
|---|---|
| 16.1.1 | Subject Disposition |
| 16.1.2 | Protocol Deviations |
| 16.1.3 | Subjects Demographics |
| 16.1.4 | Fabry Disease Medical History |
| 16.1.5 | Other Medical History |
| 16.1.6 | Treatment Compliance |
| 16.1.7 | Body Measurements |
| 16.2.1 | Kidney Functions (eGFR and eGFR Slope) |
| 16.2.2 | Gb3 Concentration (Plasma GB3, Plasma Lyso-Gb3 and Urine Lyso-Gb3) including Change from Baseline |
| 16.2.3 | Echocardiogram |
| 16.2.4 | Stress Test |
| 16.2.5 | Brief Pain Inventory (BPI) |
| 16.2.6 | Mainz Severity Score Index (MSSI) |
| 16.2.7 | Quality of Life EQ-5D-5L |
| 16.2.8 | Fabry Clinical Events |
| 16.3.1 | Exposure |
| 16.3.2.1 | Pre-treatment Adverse Events |
| 16.3.2.2 | Treatment Emergent Adverse Events |
| 16.3.2.3 | Treatment-Emergent Adverse Events Leading to Withdrawal or Death |
| 16.3.2.4 | Infusion Related Reactions |
| 16.3.3 | Vital Signs |
| 16.3.4.1.1 | Laboratory – Anti Drug Antibodies: IgG for PRX-102 |
| 16.3.4.1.2 | Laboratory: Anti-Drug Antibodies: IgG for Agalsidase Beta |
| 16.3.4.1.3 | Laboratory: Anti-Drug Antibodies: IgG for Agalsidase Alfa |
| 16.3.4.1.4 | Laboratory: Anti-Drug Antibodies: IgE |
| 16.3.4.2 | Laboratory– Hematology |
| 16.3.4.3 | Laboratory– Coagulation Profile |
| 16.3.4.4 | Laboratory– Vitamin D |
| 16.3.4.5 | Laboratory– Urinalysis (Dipstick) |
| 16.3.4.6 | Laboratory– Biochemistry, Serum Creatinine and Cystatin C |
| 16.3.4.7 | Laboratory– Spot Urine |
| 16.3.4.8 | Laboratory– Serology |
| 16.3.4.9 | Laboratory: Pregnancy |
| 16.3.5 | Physical Examination |
| 16.3.6 | Electrocardiography (ECG) |
| 16.3.7.1 | Prior and Concomitant Medications |
| 16.3.7.2 | Infusion Premedication During Study |

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|---|---|
| 16.3.8 | Chest X-rays |
| 16.3.9 | Brain MRI |
| 16.3.10 | PK Concentrations |

# 14. SHELLS

Tables and listings shells will be provided in a separate document and provide a framework of the statistical analysis for the study and final shells may be slightly different in appearance. As long as the same information is presented, this is considered to be in alignment with the shells below.

# 15. REFERENCES

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