Study Title

Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Pegunigalsidase Alfa (PRX-102) in Patients with Fabry Disease

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STATISTICAL ANALYSIS PLAN

Chiesi Farmaceutici S.p.A.

STUDY CODE No. CLI-06657AA1-04 (Previously PB-102-F60)

Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Pegunigalsidase Alfa (PRX-102) in Patients with Fabry Disease

Version No.: [redacted]

Date: [redacted]

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Contents

List of Abbreviations

ADA	Anti-drug antibody
ADaM	Analysis Data Model
AE	Adverse event
AKI	Acute kidney injury
BLA	Biologics license application
BPI	Brief pain inventory
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CPK	Creatine Phosphokinase
CRL	Complete Response Letter
CSR	Clinical Study Report
DBL	Database lock
DD	Drug Dictionary
ECG	Electrocardiogram
E2W	Every 2 Weeks
EOS	End of Study
eCRF	Electronic Case Report Form
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EQ-5D-5L	5-level EuroQol 5-Dimension Questionnaire
ERT	Enzyme Replacement Therapy
FCE	Fabry Clinical Event
FD	Fabry Disease
FDA	United States Food and Drug Administration
Gb3	Globotriaosylceramide
ICF	Informed consent Form
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IRR	Infusion Related Reaction
ISR	Injection Site Reaction
ITT	Intention to Treat
IV	Intravenous
KM	Kaplan-Meier
LVM	Left Ventricular Mass

LVMI	Left Ventricular Mass Index
Lyso-Gb3	Globotriaosylsphingosine
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MSSI	Mainz Severity Score Index
nM	nanomole/liter
PT	Preferred Term
Q1	25th percentile or first quartile
Q3	75th percentile or third quartile
SADR	Serious Adverse Drug Reaction
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
UPCR	Urinary Protein to Creatinine Ratio
US	United States
VAS	Visual Analog Score
WHO	World Health Organization

Version History

Version	Date	Change History
1.0	09 JUNE 2022	Interim SAP
2.0	03 JULY 2024	Final Draft
3.0	14 APRIL 2025	Final Version

1. Introduction

This document presents the Statistical Analysis Plan (SAP) for Chiesi Farmaceutici S.p.A. protocol CLI-06657AA1-04: *Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Pegunigalsidase Alfa (PRX-102) in Patients with Fabry Disease (previously PB-102-F60).*

This analysis plan is based on the last final protocol (version [redacted]) and electronic case report form (eCRF) (version [redacted]). Study PB-102-F60* is a phase 3 extension study of studies PB-102-F03, PB-102-F20, and PB-102-F30 sponsored by Protalix Ltd. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing.

A pre-planned interim analysis occurred to support a biologics license application (BLA) re-submission to the FDA with a clinical data cut-off date of [redacted]. This version of the SAP describes the planned analyses for the final analyses which will occur when the last patient completes the PB-102-F60 study.

Any deviations from this SAP during the actual data analysis will be documented in the Clinical Study Report (CSR). The SAP will be finalized before the database lock (DBL) for the final analysis.

Chiesi will perform the statistical analyses and is responsible for the production and quality control of all outputs described in this document.

2. Study Design

The study is an interventional, multi-center, open-label, phase 3 study of infusions every other week (+/-3 days) of 1 mg/kg pegunigalsidase alfa (PRX-102) in adult Fabry disease patients (≥18 years of age) who have completed studies PB-102-F20 or PB-102-F30 or completed at least 48 months in study PB-102-F03.

The duration of treatment will be until pegunigalsidase alfa is commercially available to the patient or at the Sponsor's discretion. The end of the study will be the last patient's last visit.

Disease parameters evaluated during PB-102-F20, PB-102-F30, and PB-102-F03 studies are continued to be assessed in this extension study.

Data will be integrated in a longitudinal manner over studies and patients will be identified by the first study in which they were exposed to PRX-102. Unless stated otherwise, the treatment duration considered in the SAP will be from the start of treatment with PRX-102, either in the parent study or in the current study for patients who did not receive PRX-102 in the parent study. Table 1 shows the paths between studies, starting from 1st exposure to PRX-102.

To simplify the writing, throughout this document, studies will be identified by the suffix of the protocol number (e.g., F03, F30, F20 and F60).

* *PB-102-F60 was the study number assigned by Protalix Ltd., the original study sponsor. Due to change of sponsorship to Chiesi on 28 February 2023, PB-102-F60 was replaced with CLI-06657AA1-04. PB-102-F60 will, however, continue to be used throughout this SAP.*

Table 1: Flow Between Studies

Study	1st Exposure to PRX-102	Extensions
F03 (All patients)	F01 Visit 1	F01*→ F02* → F03 → F60
F20 (PRX-102 arm)	F20 Visit 1	F20→ F60
F20 (agalsidase beta arm)	F60 Visit 1	
F30 (All patients)	F30 Visit 1	F30→ F60

* *Studies F01 and F02 included 3 doses: 0.2 mg/kg, 1 mg/kg and 2 mg/kg E2W. Patients from the 0.2mg/kg or 2 mg/kg who continued to study F03 switched to 1mg/kg E2W.*

The study plan and scheduled assessments in F60 are summarized in **Table 2**.

Table 2: F60 Study Flow Chart Based on Protocol Version 6.0

Visit Number / Activity	Screening	Visits: 1 to 209	Visits: 3 and 10	Visits: 20, 33, 46 ,60, 72, 86, 99, 112,124, 137, 150, 163, 176, 189, and 202	Visit: 7	Visits: 14, 40, 66, 92,118, 144, 170 and 196	Visit: 20	Visits: 27,79, 131 and 183	Visits: 53, 105, 157 and 209 or Last Visit
Sign IC	X								
Inclusion/Exclusion Criteria	X								
Physical Examination	X[1]				X[3]	X		X	X
Body Weight	X[1]					X		X	X
Vital Signs	X[1]	X							
Current Medications / Pain Medications / Pre-Medications Use	X[1]	X							
Review of Adverse Events	X[1]	X							
Urine Protein/Creatinine Ratio (UPCR)	X[1]				X[3]	X		X	X
Local Hematology	X[1]				X[3]	X		X	X
Central Biochemistry[4]	X[1]				X[3]	X		X	X
Serum Creatinine and Cystatin C[4]	X[1,7]		X[3]		X[3]	X	X[3]	X	X

Visit Number / Activity	Screening	Visits: 1 to 209	Visits: 3 and 10	Visits: 20, 33, 46 ,60, 72, 86, 99, 112,124, 137, 150, 163, 176, 189, and 202	Visit: 7	Visits: 14, 40, 66, 92,118, 144, 170 and 196	Visit: 20	Visits: 27,79, 131 and 183	Visits: 53, 105, 157 and 209 or Last Visit
Urinalysis – dipstick[4]	X[1]				X[3]	X		X	X
Urine pregnancy test[8]	X[1]				X[3]	X		X	X
Mainz Severity Score Index (MSSI)	X[1]							X	X
Short Form Brief Pain Inventory (BPI)	X[1]					X		X	X
Anti-Drug Antibodies (IgG)[4]	X[1]		X[3]		X[3]	X	X[3]	X	X
Electrocardiography (ECG)	X[1]				X[3]	X		X	X
Quality of Life (EQ-5D-5L)	X[1,7]					X		X	X
Cardiac MRI or Echocardiogram (for patients that receive a waiver for the Cardiac MRI)	X[1]							X	X
Cardiac function (Stress test)	X[1]							X	X
Brain MRI	X[1]								X
Plasma Lyso-Gb3[4]	X[1]				X[3]	X	X[3]	X	X

Visit Number / Activity	Screening	Visits: 1 to 209	Visits: 3 and 10	Visits: 20, 33, 46 ,60, 72, 86, 99, 112,124, 137, 150, 163, 176, 189, and 202	Visit: 7	Visits: 14, 40, 66, 92,118, 144, 170 and 196	Visit: 20	Visits: 27,79, 131 and 183	Visits: 53, 105, 157 and 209 or Last Visit
Plasma Gb3 concentration[4]					X[3]	X	X[3]	X	X
Follow-up call[5]				X	X[6]				
Study Drug IV Infusion		X[2]							

Notes:

This flow chart presents the assessments per visit based on the most recent Version 6.0 of the F60 study Protocol. For any previous changes in the assessments, refer to the earlier versions of the study protocol.

The flow chart was built to outline the assessments expected per visit and to cover a treatment period potentially up to 98 months (209 visits). The 98 months is estimated to cover commercial availability in all countries participating in the study (per end of study in protocol section 6.1).

[1]Screening visit will happen at the last visit of the previous study; all information will be copied to protocol PB-102-F60.
[2]The first infusions of patients enrolled from PB-102-F20 will be performed at the site to evaluate the tolerability of the infusions and discontinuation of pre-medications if used.
[3]Only applicable for patients who completed PB-102-F20 study.
[4]Will be performed pre-infusion.
[5]A follow-up call should take place with the patients on the Home Care program.
[6]Phone call at Visit 7 applicable only for patients who completed PB-102-F30 and PB-102-F03 studies.
[7]Patients who complete PB-102-F03 need to perform in addition to the procedures from the last visit at the study (Visit 131 or rollover visit) - Sample for serum creatinine and Cystatin C and Quality of life.
[8]Females of childbearing potential only.

3. Study Objectives

The objective of this study is to evaluate the ongoing safety, tolerability, and efficacy parameters of pegunigalsidase alfa in adult Fabry patients who have completed studies PB-102-F20, PB-102-F30 studies or completed at least 48 months inPB-102-F03 study.

4. Study Variables

4.1 Efficacy Endpoints

The following efficacy endpoints will be evaluated in this study:

- Estimated glomerular filtration rate ($eGFR_{CKD-EPI}$) (2009). For simplicity, for the remainder of this document the subscript of CKD-EPI will be omitted.
- eGFR slope
- Plasma globotriaosylsphingosine (Lyso-Gb3) concentration
- Plasma globotriaosylceramide (Gb3) concentration
- Urine proteine/Creatinine ratio (UPCR) spot urine test
- Short Form Brief Pain Inventory (BPI)
- Mainz Severity Score Index (MSSI)
- Quality of life (EQ-5D-5L)
- Exercise tolerance (Stress Test)
- Cardiac Function
- Frequency of pain medication use
- Occurrence of Fabry-disease clinical events (FCE)

4.2 Safety Endpoints

The following safety variables will be analyzed for this study:

- Treatment-emergent adverse events (TEAEs)
- Infusion-related reactions (IRRs)
- Injection site reactions (ISRs)
- Anti-Pegunigalsidase Alfa Antibodies (ADA)
- Clinical laboratory tests

- Physical examination
- Vital signs
- Infusion pre-medication
- Electrocardiogram (ECG)
- Magnetic resonance imaging (MRI) of the Brain

5. Sample Size

This extension study's sample size depends on the number of patients who completed PB-102-F20 study, PB-102-F30 study or completed at least 48 months in PB-102-F03 and enrolled into this study. In total, ninety-seven (97) patients were enrolled in F60.

6. Analysis Set

The definitions of the populations for analysis are summarized below.

6.1 Safety Population

The Safety Population includes all patients who provided informed consent of F60 study and received any dose (including a partial dose) of the study medication (PRX-102) in this study.

6.2 Intent-to-Treat Population

The Intent-to-Treat Population includes all patients who provided informed consent of F60 study and received any dose (including a partial dose) of the study medication (PRX-102) in this study.

Since the ITT population and the safety population are the same, all analysis will be done on the same population.

7. General Considerations for Statistical Analysis

7.1 Statistical Significance

No formal statistical hypothesis testing is planned. Analyses will be descriptive, with data listings, frequency tabulations, and summary statistics as appropriate.

7.2 Multiplicity

No multiplicity adjustment will be performed.

7.3 Handling of Missing Data

Imputation of missing data associated with AE severity and relatedness is described in Section 10.2.1.

Below are imputation rules related to missing or incomplete dates for Acute Kidney Injury (AKI), medications, and date of birth.

7.3.1 Partial or Missing Dates of Episodes of Acute Kidney Injury

The following rules will be followed in the case of an incomplete start or end date of an AKI event in F60 study only:

- AKI start date
  - If month and year are available and day is missing, then the 1st of the month will be imputed. In case the event is during the month of the first infusion of F60, it will be imputed to the date of 1st infusion in F60.
  - If month is missing and year is available, then if the year is the same as the year of 1st infusion date in F60 then should be the date of 1st infusion in F60. Otherwise, the date should be set to January 1st.
  - If year is missing, then the date should be imputed to date of 1st infusion in F60.
- AKI end date
  - If month and year are available and day is missing, then 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 the date should be 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 samples taken for the study while the AKI AE did not resolve will be excluded from the summary tables and considered to be missing. See Section 9.1 for more details.

7.3.2 Partial or Missing Fabry Disease Diagnosis Dates and Medication Dates

The following imputations will be used in case of incomplete FD diagnosis or medication dates:

- The middle of the month (i.e., 15th) 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 1st of July.
- No imputation will be done in case the year is missing.
- No imputation will be done in case of fully missing date.

For medications:

In some of the analyses, a flag of whether a medication was used at a certain visit is needed (e.g., usage of pain medication at baseline or in the last visit). In these cases, when a partial start date and/or end date exist, imputation will be based on the above rules and determination of the flag will be based on the imputed dates and comparison with the date of the visit of interest.

In case the year is missing from the start date, 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.

7.3.3 Partial Dates of Birth

Under Chiesi Sponsorship, in accordance with the data minimization principle, the day of birth field has been removed from the eCRF. The value "15" will be imputed as the day of birth for all patients with collected month and year in the analysis.

7.4 Interim Analyses

The interim analysis was conducted with a clinical cut-off date of [redacted]

The primary objective of the interim analysis was to present ongoing clinical data on patients exposed to 1 mg/kg PRX-102 every other week in F60 study before a change in sponsorship occurred in February 2023. Selected efficacy and safety analyses were performed. The statistical analysis of this interim data was described in the interim SAP (dated [redacted]).

7.5 Examinations of Subgroups and Subset

7.5.1 Subgroups

The selection of subgroups will be from the following list:

- Study Cohort

Study cohort is defined as following:

  - F03: patients coming from the parent study F03 (at least 4 years and up to 6 years PRX-102 exposure before F60)
  - F30: patients coming from the parent study F30 (1-year PRX-102 exposure before F60)
  - F20 PRX-102: patients coming from the parent study F20 and randomized to the PRX-102 arm in F20 (2 years PRX-102 exposure before F60)
  - F20 agalsidase beta: patients coming from the parent study F20 and randomized to agalsidase-beta arm in F20 (no prior PRX-102 exposure before F60)

- Gender (male or female)
- ADA status at baseline (Negative or Positive). Determination of status is based on Immunoglobulin G (IgG) positive at treatment baseline (see Section 7.7.1. for more information on derivation of baseline).
- 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, angiokeratomas.

Unless otherwise indicated, all analyses will be performed in the overall analysis population and by study cohort (i.e., by length of PRX-102 exposure prior to F60). Other subgroup analyses will be conducted based on baseline characteristics and demographics for selected

efficacy and safety endpoints. Whether an analysis will be conducted for a specific endpoint will be discussed in the analysis section of the specific endpoint. Subgroup analyses within study cohort will not be performed due to the small sample size.

7.5.2 Subsets

7.5.2.1.1 Subset of Treatment Duration

Since patient treatment duration varies, it is of interest to repeat analysis for selected efficacy and safety endpoints based on patient total treatment duration. This analysis is similar to subgroup analysis, but patients may belong to several duration groups, and the determination of the groups is not based on information collected prior to treatment baseline (see Section 7.7.1). The following 3 levels of duration will be considered: Treatment duration ≥ 1 year, ≥ 3 years; and ≥ 5 years, where treatment duration is measured from first PRX-102 infusion.

The subset analysis will only be performed on certain efficacy and safety variables of interest (i.e. eGFR, plasma lyso-Gb3, FCEs, TEAEs, and IRRs). By visit tables, for this subset, will show visits every 12 months even if the procedure is conducted more often.

7.5.2.1.2 Subset of F60

Subset of F60 contains data collected in the F60 study. Given differences in study design between parent studies and F60, selected safety and efficacy endpoints analyses will be performed for subset of F60 only (i.e. plasma lyso-Gb3 and plasma Gb3 for F03, [redacted] for F03, FCE, vital sign, physical exam, Brain MRI), or repeated for subset of F60 (i.e. TEAEs, IRRs, and use of premedication). By visit tables, for this subset, will show the scheduled visits per Table 2. Note that TEAEs which started post first PRX-102 infusion in study F60 but were collected in the parent studies will be considered as in the subset of F60.

7.6 Descriptive Statistics

Descriptive statistics, number of patients (n), number of patients with missing values, mean and its standard error (SE), standard deviation (SD), median, minimum, and maximum for continuous variables. For variables as defined in the shells, the 25th (Q1) and 75th (Q3) percentiles will be presented. Confidence Intervals (CIs) will be described in the relevant sections.

For categorical variables, the number and percentages of patients will be presented.

Unless otherwise specified, summaries by visit will present only scheduled visits based on the protocol-planned visits for each procedure. Procedures that were performed at an unscheduled visit, or at scheduled visits in which the procedure was not planned per protocol, will only be listed.

7.7 Definitions

7.7.1 Baseline and Change from Baseline

The baseline value is defined as the last assessment prior to the first infusion of the study treatment (PRX-102). This baseline value will be created for all safety and efficacy endpoints. For patients from study cohort F03, F30 and F20 PRX-102, the baseline value is defined as the baseline assessment in the parent study, while for patients who were randomized to the

agalsidase beta arm in study F20 and continue to study F60, this consists of the baseline of study F60, prior to the first infusion of PRX-102.

- Cohort F03: baseline in study F01, prior to the first infusion of PRX-102 (regardless of dose)
- Cohort F20 – PRX-102: baseline in study F20, prior to the first infusion of PRX-102 in F20.
- Cohort F20 – agalsidase beta: baseline in study F60 (i.e., last assessment of F20), prior to the first infusion of PRX-102 in F60. In case that the last assessment was recorded more than 3 months prior to the last infusion in the parent study or the last assessment was not applicable (e.g. ADA status), the last assessment from study F60 prior to the first infusion of study F60 will be used.
- Cohort F30: baseline in study F30, prior to the first infusion of PRX-102 in F30.

Change from baseline is defined at each visit as:

Absolute change from baseline = value at visit – baseline value.

7.7.2 Date of First and Last Study Medication Intake

The dates of first/last infusion, collected on the eCRF for each patient, will be considered as the start/stop reference dates (RFSTDTC and RFENDTC), respectively, in the demographics (DM) domain in accordance with the CDISC Study Data Tabulation Model (SDTM).

7.7.3 Study Day

The study day (_ _DY) relative to the first study medication (reference start date – RFSTDTC) will be calculated as per the CDISC SDTM model, as follows:

- Date collected – date of first study medication + 1 (if date collected ≥ date of first study medication)

or

- Date collected– date of first study medication (if date of event < date of first study medication)

7.7.4 Last Observation

For each patient the last observation will be the last non-missing assessment for each respective parameter. If changes from baseline results are indicated per visit, this will also include the last observation.

Furthermore, descriptive statistics on the duration of treatment at the last observation will be presented.

7.8 Data Re-allocation

To reflect the longitudinal efficacy and safety profile, patients' data collected during parent studies and F60 will be integrated and shown in tables and listings. Only patients who

completed PB-102-F20, PB-102-F30 studies or completed at least 48 months in PB-102-F03 study and continued to F60 will be included in the analysis.

Patients' data will be integrated to reflect the longitudinal profile of a patient. Study days will be numbered relative to the first day of PRX-102 administration. All scheduled visits will be mapped to a week/month based on the time window described in Table 3. In case of more than one assessment at the time window, the assessment closest to the nominal time will be used for the summary. In case of two assessments with the same distance to the nominal time (say one is 7 days after and one is seven days before), the later one among the two will be used.

Summary tables of change from baseline of overall study will be presented by visit week/month of visit since 1st exposure per Table 3. All collected data will be listed with the date of collection and re-mapped visit week/month.

Summary tables of visits in the F60 subset will be presented by scheduled visit week/month in F60 per Table 2.

Table 3: Time window for mapping of the visits

Week (Nominal)	Month	Time Window
4	1	Day 28+/- 14 days
12	3	Day 84 +/- 28 days
18*	4.5	Day 126+/- 14 days
26	6	Day 182 +/- 28 days
38	9	Day 266 +/- 28 days
52	12	Day 364 +/- 28 days
66	15	Day 462 +/- 49 days
80	18	Day 560 +/- 49 days
94	21	Day 658 +/- 49 days
106	24	Day 742 +/- 49 days
120	27	Day 840 +/- 49 days
132	30	Day 924 +/- 49 days
146	33	Day 1022 +/- 49 days
158	36	Day 1106 +91/- 49 days
184	42	Day 1288 +/- 91 days
210	48	Day 1470 +/- 91 days

Week (Nominal)	Month	Time Window
236	54	Day 1652 +/- 91 days
262	60	Day 1834 +/- 91 days
286	66	Day 2002 +/- 91 days
312	72	Day 2184 +/- 91 days
338	78	Day 2366 +/- 91 days
364	84	Day 2548 +/- 91 days
390	90	Day 2730 +/- 91 days
416	96	Day 2912 +/- 91 days
442	102	Day 3094 +/- 91 days
468	108	Day 3276 +/- 91 days
490	114	Day 3458 +/- 91 days

**Applicable for patients who completed the PB-102-F20 study in F60 for selected variables (i.e. eGFR and ADA)*

Note: In case two analysis time windows include the same day, the previous window prevails.

7.9 Exclusion of Data from the Statistical Analyses

Serum creatinine measurements, if any, taken during an AKI episode or from the moment either of dialysis initiation or of renal transplantation will be excluded from the eGFR calculation, from summary tables and from any analyses related to eGFR. These measurements will be flagged in the individual data listings.

AKI episodes will be reported by the Investigators as TEAEs. The first occurrence of either the initiation of chronic dialysis or renal transplantation will be reported by the Investigators in association with a TEAE and will be assessed as renal FCE.

In addition, all protocol violations will be assessed at the DRM prior to database lock (DBL) and decisions will be documented.

7.10 Listings

Data will be presented in the listings based on the safety population.

Derived variables will also be presented in the listings.

In listings, patients will be sorted by study cohort. Visits (scheduled and unscheduled) within patients 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.

7.11 Coding

General medical history and AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) 20160601E.

8. Study Population

8.1 Disposition of Patients and Discontinuations

The number and percentage of patients who signed F60 informed consent and the number of patients treated with PRX-102, as well as the number (%) of patients who completed or discontinued the F60 study will be provided. Note that patients who complete the end of study (EOS) form and select either the "Subject completed the trial" or "pegunigalsidase alfa is commercially available" will be considered completers.

The number and percentage of patients who completed at least 24, 36, 48, 60, 72, 84, 96, 108 and 120 months of treatment will be summarized as well. The number and percentage of patients who discontinued the study will also be summarized by reason of discontinuation.

The patient disposition will be presented by study cohort and overall.

The number of patients in the analysis set (ITT / Safety) will be summarized. For each patient, the reason for exclusion from analysis population will be detailed in the corresponding listing.

Only protocol deviations which occurred during the F60 study will be presented. Protocol deviations will be classified as minor, major and critical. A summary table will show the numbers of subjects with at least one major or critical deviations as well as with breakdown by deviation type. All protocol deviations in F60 will be listed.

8.2 Demographic and Baseline Characteristics

8.2.1 Demographic Characteristics

The demographics (age, gender, race, and ethnicity) will be summarized using descriptive statistics by study cohort, gender, and baseline ADA status defined in Section 7.5.1 and overall. This analysis will be done on the ITT set and will be based on data collected at baseline visit as defined in Section 7.7.1. For subjects who were treated with agalsidase beta in F20 and switched to PRX-102 in F60 their ages at Visit 1 of F60 will be reported.

8.2.2 Baseline Characteristics

The following baseline characteristics (based on the baseline definition in Section 7.7.1) will be summarized on the ITT analysis set by descriptive statistics for subgroups of study cohort, gender, and baseline ADA status defined in Section 7.5.1 and overall:

- Weight (Similar rule used as for reporting of Age in Section 8.2.1 will be applied)
- Height
- Region (US, ex-US)
- Age at FD diagnosis (taken from the parent study); derived based on the date of birth and date of FD diagnosis and rounded down to the nearest integer. For rules on incomplete dates refer to Section 7.3.
- Previous ERT prior to PRX-102 (agalsidase alfa, agalsidase beta and none (i.e. naïve

subjects))

- The duration of the last continuous previous ERT (agalsidase alfa and agalsidase beta) treatment (years). Last treatment refers to patients who had several periods of treatment with same ERT in the past. In case of several records with a gap ≤ 14 days between the end date and the start date of the following record they are considered as same treatment. The end-date of previous ERT should be set to the first PRX-102 treatment date. For patients in F30, the duration of ERT includes the 3 months of screening in which patients continued to receive agalsidase-alfa. For patients who were randomized to agalsidase-beta in F20 and switched to PRX-102 in F60, the duration of previous ERT includes the time in F20 in which they received agalsidase-beta.
- The duration of PRX-102 treatment (years) prior to F60. For patients who were previously treated with PRX-102, duration of treatment is calculated from first PRX-102 dose in F01, F20 and F30 to first PRX-102 dose in study F60.
- Baseline eGFR (estimated using CKD-EPI equation and expressed in ml/min/1.73 m^2 - see Section 9.1), both as continuous variable and categorized as (≤ 60; 60 < and ≤ 90; > 90 mL/min/1.73m^2)
- Baseline Plasma Lyso-Gb3
- Treatment with ACEi or ARB (yes/no) at baseline
- Fabry disease (FD) classification (classic / non-classic) (See Section 7.5.1 for definition)

For patients who were randomized to agalsidase-beta in F20 and switched to PRX-102 in F60, FD classification is based on information collected at screening visit of F20.

- UPCR Categories (UPCR ≤ 0.5 gr/gr, overall and split in the 2 subcategories of < 0.15 gr/gr and ≥0.15 gr/gr to ≤0.5 gr/gr; UPCR > 0.5 gr/gr, overall and split in the 2 subcategories of UPCR > 0.5 gr/gr and < 1 gr/gr, and UPCR ≥1 gr/gr)
- Baseline ADA status for PRX-102 (positive /negative).
- Infusion premedication use for ERT infusion prior to 1st PRX-102 infusion (yes / no). This information was not collected in F03 study.

8.3 General Medical History and Fabry Disease Medical History

Medical history collected in parent studies (F01, F30, and F20) was coded using MedDRA v15.0 for F01 and v19.0 for F20 and F30.

All the previous entered Medical History in the main study have been auto displayed in Medical History and imported. Any updates in the main study have not been automatically reflected in F60. 'Update' button was available if there were any updates in main study. If any medical condition was changed during the F60, it has been updated in F60 study.

Medical history will be summarized by System Organ Class (SOC) and Preferred Terms (PT) using frequency counts overall and by study cohort.

In addition, Fabry Disease Medical history data as collected in parent studies will be summarized by body system and conditions, overall and by study cohort.

8.4 Prior and Concomitant Medications

Medication data collected during parent studies and F60 will be shown in tables and listings.

Prior and concomitant medications reported during the study were coded by WHO-DD Version 20160601E. Concomitant medications are defined as those taken at any time while on study

drug treatment, including medications that were started before the first dose of study drug but were ongoing at the time of the first dose, or initiated after the first dose of study drug and within 20 days of the last study drug administration. Medications whose end dates were prior to first study drug intake are considered prior medications and will only be listed.

Concomitant medications will be summarized by the count and percentage of patients with each medication by standardized medication name within medication class. Medication classes will be presented alphabetically, and within each medication class, standardized medication names will be sorted by decreasing order of frequency. This analysis will be performed overall and by study cohort.

Listing of medications will include start and end date together with a flag to mark medications which stopped prior to first study drug intake.

8.5 Procedures

Concomitant Procedures and Therapies (from relevant forms/fields) will be summarized and included in concomitant medication (Section 8.4) through frequency distributions and percentages by SOC and PT.

8.6 Compliance

Treatment compliance will be assessed in percent as the number of infusions (partial or complete administrations) divided by the expected number of infusions for each patient based on the patient treatment duration, multiplied by 100. For patients who terminated the study, 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. Treatment compliance will be summarized using the ITT set for subgroups of study cohort, gender, and baseline ADA status, and the three treatment duration subsets in Section 7.5, and overall. Compliance will be summarized also by the following categories: < 60%; 60% >= and < 80%; ≥80%. Compliance analysis will be presented for F60 subset only.

9. Efficacy Analyses

Efficacy analysis will be presented on the ITT Population, per cohort and overall.

9.1 eGFR

The eGFR is not measured directly but is derived from the value of the serum creatinine and from patient characteristics. eGFR will be calculated based on the value of the serum creatinine values according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (2009)[6]:

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

where:

S_{Cr} (standardized serum creatinine) = mg/dL

$\kappa = 0.7$ (females) or 0.9 (males)

$\alpha = -0.329$ (females) or -0.411 (males)

min = indicates the minimum of SCr/κ or 1

max = indicates the maximum of SCr/κ or 1

age = actual age in years when the subject's serum creatinine is collected.

AKI episodes are reported by the investigators as an AE. An AKI episode is defined between the start and the end date of the AKI AE. Serum creatinine measurements, if any, taken during an AKI episode or from the moment either of dialysis initiation or of renal transplantation will be excluded from the eGFR calculations. The eGFR measurements which are excluded from the analysis will be listed by cohort. eGFR values associated with the AKI events or dialysis or renal transplantation will only be listed (and flagged to identify that they were excluded from tables).

In case that serum creatinine value (and hence eGFR) is missing in a planned visit, but the test was performed up to 17 days after the date of the planned visit, the serum creatinine and eGFR will be mapped to the planned visit and will be included in the summary tables by visit.

For both the analysis of eGFR by visit and the analysis of eGFR slope (see below), serum creatinine values assessed by the local laboratory will be excluded (i.e. the analysis will be based on assessments by the central laboratory only). In case of more than one value for serum creatinine from the central laboratory at the same date in one patient from individual studies, the mean of the values will be taken for analysis. In case there are two assessments at the same date from the central laboratory, but one from the parent study and one from the extension (i.e. last assessment from a parent study was replicated to the extension study), the value from the parent study should be used. In case there are repeated assessments in F60 from biochemical method and Enzymatic measurement, the enzymatic assessment should be taken for analysis.
In the eGFR listing, if in the same visit, there are eGFR assessments based on both local and central laboratory, only the one based on the central laboratory will be presented; if there is an eGFR assessment from the local laboratory at an unscheduled visit without eGFR assessment from the central laboratory at the same date, the eGFR value from the local laboratory will be presented. The listing will contain a column indicating whether the value comes from the central or local laboratory.

The eGFR values at baseline, and at planned follow-up visits as well as the change from baseline to those timepoints will be summarized descriptively, this analysis will include the 25^{th} and 75^{th} percentiles (Q1 and Q3). The summary table will include a 95% Confidence Interval (CI) for the mean based on t-distribution and a non-parametric 95% CI for the median. The analysis will be performed for subgroups of study cohort, gender, baseline ADA status, FD classification, and three treatment duration subsets defined in Section 7.5.1, and overall.

The plots of mean eGFR ± SE and mean eGFR change from baseline over time ± SE will be performed. Boxplots of eGFR values at baseline, months 12, 24, 36, 48, 60, 72, 84, 96, 108, and 120 will be plotted. All figures will be generated for subgroups of study cohort, gender, baseline ADA status, FD classification, and three treatment duration subsets defined in Section 7.5. and overall.

9.2 eGFR Slope

Individual eGFR slopes will be derived for each patient using the following linear regression model and using all eGFR assessments:

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

The slope β (mL/min/1.73 m^2 / year) will be an estimate of the individual slope. The [time in year]" in the formula denotes time measured in years, from baseline (defined as date of 1st infusion) to the respective visit and will be estimated by (date of the visit – date of Baseline)/365.25. All data points (scheduled and unscheduled) for a patient will be used to estimate the slope. The linear model will be fit for all patients with at least 4 eGFR measurements (after exclusion of eGFR during AKI or after dialysis initiation or renal transplantation). For patients with fewer than 4 measurements, the slope will be missing. Considering most patients had at least one year follow up since first PRX-102 infusion, it is expected that the number of patients with missing slopes will be very low. The individual slopes will be summarized descriptively for subgroups of study cohort, gender, baseline ADA status, FD classification, and three treatment duration subsets defined in Section 7.5. and overall. Descriptive statistics will include the 25th and 75th percentiles (Q1 and Q3).

The summary will include a 95% CI for the mean slope based on a t-distribution and a non-parametric 95% CI for the median.

eGFR slope listing will include the number of eGFR assessments used for the slope calculation and the time span between the 1st and last assessment.

A boxplot of eGFR slopes will be generated overall and for subgroups of study cohort, gender, baseline ADA status, FD classification, and treatment duration subsets defined in Section 7.5.

9.3 Plasma Lyso-Gb3 Concentrations

Plasma Lyso-Gb3 was assessed in different laboratories in F03 compared to the other studies (F20, F30 and F60). The analysis described below will be performed separately for patients originating from F03 in the visits of F60 study (F60 subset), and pooled sample of patients from F30 and F20 unless otherwise stated.

For study cohorts F30, F20 PRX-102 and F20 agalsidase beta, descriptive statistics of plasma Lyso-Gb3 concentration (nM) will be summarized at each visit by study cohort, gender, baseline ADA status, FD classification, three treatment duration subsets and overall. The change from baseline will be summarized as well. Descriptive statistics will include the 25th and 75th percentiles (Q1 and Q3).

In case of more than one value for plasma Lyso-Gb3 at the same date in one patient, the mean of the values will be taken for analysis.

Mean plasma Lyso-Gb3± SE and mean plasma-Lyso-Gb3 (absolute) change from baseline ± SE at treatment baseline, months 12, 24, 36, 48, 60, 72, 84, 96, 108, and 120 will also be plotted by gender. In addition, plasma Lyso-Gb3 values for the above time points will be presented graphically in boxplots by gender.

For F03 study cohort, change from baseline will not be evaluated. Descriptive statistics of plasma Lyso-Gb3 concentration (nM) will be summarized at each scheduled visit in F60 per Table 2 by gender, baseline ADA status, FD classification, and overall.

9.4 Plasma Gb3 Concentrations

Plasma Gb3 was assessed in a different unit (ug/mL) in F03 compared to study F60 (nM) which cannot be converted (the different isoforms have different masses). The analysis described below will be performed separately for patients originating from F03 in F60 subset, and pooled sample of patients from F30 and F20 unless otherwise stated.

For study cohorts F30, F20 PRX-102 and F20 agalsidase beta, descriptive statistics of plasma Gb3 concentration (nM) will be summarized at each visit by study cohort, gender, baseline ADA status, FD classification, and overall. The change from baseline will be summarized as well. These analyses will include the 25th and 75th percentiles (Q1 and Q3).

In case of more than one value for plasma Gb3 at the same date in one patient, the mean of the values will be taken for analysis.

For F03 study cohort, change from baseline will not be evaluated, due to the fact that plasma Gb3 was assessed in a different unit (ug/ml) compared to study F60 (nM). The results cannot be converted as the different isoforms have different masses, consequently, the results for study cohort F03 will also not be included in the overall results. Descriptive statistics of plasma concentration (nM) will be summarized at each scheduled visit in F60 per Table 2 by gender, baseline ADA status, FD classification, and overall.

9.5 Urine Protein/Creatinine Ratio

Urine protein/creatinine ratio (UPCR), by a spot urine test, will be summarized at each visit using the following categories:

- UPCR ≤ 0.5 gr/gr, overall and split in the 2 subcategories of < 0.15 gr/gr and 0.15 gr/gr – 0.5 gr/gr
- UPCR > 0.5 gr/gr, overall and split in the 2 subcategories of UPCR > 0.5 gr/gr and < 1 gr/gr, and UPCR ≥1 gr/gr

The laboratory limit of detection for urine protein is 4 mg/dL, and for a large number of the measurements, the protein is undetectable ('< 4 mg/dL'), resulting in a UPCR of '< x gr/gr' (where x is calculated by 4 divided by the measured level of creatine and the '<'comes from the protein value). Any such observation will be classified in one of the above categories, ignoring the '<' sign in the observation. This is considered a conservative assignment to categories.

The analysis will be performed by subgroups of study cohort, gender, baseline ADA status, FD classification and overall.

Shift tables to show changes from baseline to Month 12, 24, 36,48, 60, 72, 84, 96, 108, 120 and to the end of the study (where appropriate), will be presented for the overall results.

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

9.6 Short Form Brief Pain Inventory (BPI)

Descriptive statistics of the quantitative assessments and change from baseline regarding pain severity (worst pain in the last 24 hours, least pain in the last 24 hours, right now, pain in the average, and relief pain treatment provided) and pain interference will be summarized at each

visit. Change from baseline will be presented. This analysis will be performed by study cohort and overall.

The descriptive analysis of average pain over the last 24 hours will also be performed by subgroups of gender and baseline ADA status as well.

9.7 [redacted] ([redacted])

Descriptive statistics of the total scores and change from baseline of each of the domains (general, neurological, cardiovascular, renal dysfunction, and overall score (sum of these four scores)) will be summarized at each visit the [redacted] is evaluated. This analysis will be performed by subgroups of study cohort, gender, baseline ADA status and FD classification and overall.

A total [redacted] score < 20 is considered as mild; a score 20 ≤ and ≤ 40 is considered moderate and > 40 is considered severe (Beck, 2006)[1]. A shift table from baseline to month 12, 24, 36, 48, 60, 72, 84, 96, 108, 120 and to the end of the study (where appropriate), between the three categories will be presented for overall. For patients who terminated early, the table will show their shift to their last assessment prior to discontinuation.

9.8 [redacted]

[redacted] was not assessed in in study F03. The analysis described below will be performed separately for patients originating from F03 in the visits of F60 study (F60 subset), and pooled sample of patients from F30 and F20 unless otherwise stated.

Frequency counts of the qualitative assessments regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression will be summarized at each visit (every 6 months). The number and proportion of patients with no change or improvement compared to baseline (difference from baseline is ≥ 0) and the number and proportion of patients with a worsening compared to baseline (difference from baseline is < 0) will be summarized by visit.

The overall health score (Visual Analog Score (VAS), from 0 to 100) will be summarized using descriptive statistics at each visit together with the change from baseline.

The analysis will be performed by subgroups of study cohort, gender, and baseline ADA status and overall.

For F03 study cohort, change from baseline will not be evaluated. Descriptive statistics will be summarized at each scheduled visit in F60 per Table 2.

9.9 Stress Test

Qualitative evaluation (yes/no) of symptoms (chest pain, shortness of breath, dizziness, palpitations, and other), the overall impression: normal stress test (yes/no), and ST change (yes/no) and target heart rate achieved (yes/no) will be summarized by count and percentage at each visit. The analysis will be performed by subgroups of study cohort, gender, and baseline ADA status and overall.

In addition, a shift from baseline will be presented: normal stress test (yes / no) to show changes from baseline to Month 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, and to the end of the study (where appropriate), and it will be presented overall. For patients who terminated early, the table will show their shift to their last assessment prior to discontinuation.

9.10 Cardiac Function

9.10.1 Cardiac MRI

Left ventricular mass (LVM), left ventricular mass index (LVMI, indexed to patient's body surface area (g/m^2)), left ventricular cardiac fibrosis, left ventricular ejection fraction (%EF), number of left ventricular segments with fibrosis, and percentage of cardiac fibrosis will be summarized using descriptive statistics for each 12-month visit that has cardiac MRI performed. The change from baseline will be summarized.

The LVM and LVMI analysis will be done separately for patients who have hypertrophy at baseline, patients who don't have this abnormality, and patients whose hypertrophy at baseline is missing. Hypertrophy is defined as LVMI > 91 g/m^2 for males and LVMI > 77 g/m^2 for females (Kawel-Boehm, 2015)[5].

The analysis will be performed by gender and overall.

The cardiac function listing will include all MRI parameters, including number and location of left ventricular segments with fibrosis, percentage, and mass of cardiac fibrosis, LVM, LVMI, and %EF.

9.10.2 Echocardiogram

The echocardiogram evaluations by nature include substantial variation and therefore only a data listing will be provided. LVMI (units: g/m^2) will be calculated and listed, using the following formula:

$$LVMI = LVM / BSA.$$

with LVM (Left Ventricular Mass in g) collected as part of the echocardiogram and BSA (Body Surface Area) calculated using the equation in Du Bois and Du Bois (1916)[2]:

$$BSA = 0.007184 \times W^{0.425} \times H^{0.725},$$

where H is the height (cm) measured at screening and W is the weight (kg) measured at the same visit of the ECHO. In case that weight at the visit is missing, the last available weight prior to the visit will be used.

9.11 Use of Pain Medications

Categorization and summary of the use of pain medication will be done as described in Section 8.4. for general medication use. All pain medication taken will be identified based on the classification assigned by the investigator in the eCRF ("Pain Medication").

In addition, the number of patients who used pain medication at any time during the study will be summarized presenting count and percentage of patients by the number of medications they used (0, 1, 2, up to the maximum, where medications with identical standard names are counted once and 0 represents patients who did not take any pain medication during the studies).

The change from baseline to Month 12, 24, 36,48, 60, 72, 84, 96, 108, 120 and to the end of the study (where appropriate) in the number of different pain medications used will be examined by shift tables with the following categories for the number of pain medications used: 0, 1, and 2+. For patients 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.

Section 7.3.3 provides information on handling partial or complete missing dates of pain medications.

All pain medication analysis will be performed by gender and overall.

9.12 Occurrence of Fabry Clinical Events

Fabry Clinical Events (FCEs) are classified into four categories: renal events, cardiac events, cerebrovascular events, and non-cardiac-related deaths (Hopkin, 2016)[4].

The adjudication criteria used in F60 study is not the same as the ones used in parent studies. Thus, the FCE analysis will be created for F60 subset only. The adjudicated decisions will be made by the adjudication committee, based on reported adverse events and clinical information included in the database. The adjudication process is further described in the FCE adjudication charter (Appendix 1).

The number and percentage of patients with at least one FCE overall and for each of its components will be presented together with the number of events and the rate per 100 person-years exposed (calculated as number of events x 100 /exposure to PRX-102 within F60 (in years). For the number of patients with at least one FCE, patients who had more than one type will be counted only once.

The analysis will be performed for subgroup of study cohort and treatment duration subsets defined in Section 7.5. and overall.

Time to the 1st FCE in F60 will be presented graphically by Kaplan-Meier per study cohort in case there are at least 5 events overall. The time (months) will be measured from date of first PRX-102 infusion in F60 and patients with no FCE will be censored at the date of last F60 infusion. The number of days will be converted to months by multiplying by 12/365.25.

The FCE listing will show the categories by Hopkin (2016)[4] as well as by SOC and PT and the time to the event from first infusion in F60 (months).

10. Safety Analyses

The safety variables will be analyzed in the Safety Population.

10.1 Exposure

Two measurements of exposure to study drug (months) will be calculated for each subject: exposure to PRX-102 and exposure to PRX-102 within F60.

Exposure to PRX-102:

(date of last infusion– date of first PRX-102 infusion+ 1)*12/365.25.

Exposure to PRX-102 within F60:

(date of last infusion– date of first PRX-102 infusion in F60+ 1)*12/365.25.

Two durations of exposure (months) will be summarized by study cohort and overall. The cumulative exposure in person-months will be provided.

In addition, the number of subjects and percentage of the exposure to PRX-102 for the following categories: 12 months < exposure ≤ 24 months; 24 months < exposure ≤ 36 months and so on in 12 months intervals up to exposure > 120 months will be presented.

The number of partial or complete infusions that a patient received will be summarized overall and by location of administration (home/site), both by study cohort and overall. In addition, the cumulative number of partial or complete infusions will be provided by study cohort, location of administration (home/site) and overall.

Note: regarding location of administration: all infusions during studies F01 and F02 and early part of F03 were on site. Home infusions were allowed only from some point during F03, and the location of administration was collected only from that time onwards and hence the field in the database is blank for the earlier infusions and in these cases the infusion should be considered as administered on site.

Summary of infusion duration (hours) will be presented by study cohort, baseline ADA status, location of administration, and overall, in 6 months interval.

For F60 subset, the summary of infusion duration both as continuous variable and categorized (<=1 hour, 1 < and ≤ 1.5 hours, 1.5 < and ≤ 2 hours, and >2 hours) will be presented for all scheduled visits per Table 2 by study cohort, baseline ADA status, location of administration, and overall.

For F60 subset, in case four consecutive, complete infusions have been given within the same duration category (<=1 hour, 1 < and ≤ 1.5 hours, 1.5 < and ≤ 2 hours, and >2 hours), the infusion duration is considered tolerated by the patient. Per patient the shortest tolerated infusion duration (based on complete infusions only) will be defined.

Frequency counts on the number of patients with the shortest tolerated infusion duration (<=1 hour, 1 < and ≤ 1.5 hours, 1.5 < and ≤ 2 hours, and >2 hours) will be presented by study cohort, body weight category (<70 kg, 70-100, >100 kg) and overall.

For F20 patients who enrolled in F60 study, the duration of infusion can be reduced from 3 hours to 1 hour as a minimum in a standardized fashion which is outlined in Appendix 6 of the study protocol. A stepwise approach is taken. Per visit frequency counts on the infusion duration (<= 1 hour, 1 < and ≤ 1.5 hours, 1.5 < and ≤ 2 hours, 2 < and ≤ 2.5 hours, 2.5 < and ≤ 3 hours, and >3 hours) will be presented for each of the four infusion transition groups as identified in this appendix.

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

10.2 Adverse Events

AEs will be coded using the MedDRA version 19.0.

Pre-treatment AEs include all AEs occurred prior to the first study drug infusion, regardless of the clinical study. Pre-treatment AEs will only be presented in a dedicated listing.

10.2.1 Treatment Emergent Adverse Events (TEAEs)

All adverse events starting on or after the time of first study drug initiation will be classified as TEAEs. If the date of onset is completely unknown, an AE will be classified as TEAE. If the date of onset is partially known, an AE will be considered as treatment emergent unless there is clear evidence otherwise. TEAEs will include TEAEs from the parent studies for study cohort F03, F20 PRX-102 and F30, and TEAEs occurring on or after first PRX-102 infusion in F60 for patients who were randomized to the agalsidase beta arm in study F20 and continue to study F60.

AEs which started post first PRX-102 infusion in study F60 are considered on-study TEAEs. In case the date is partially known, it will be classified as on-study TEAE unless there is evidence, from the partial info (e.g. month of AE onset is earlier than the month of first infusion), that the AE was prior to first PRX-102 treatment in study F60.

The TEAE summaries will be performed for all patients and will be presented separately for patients originating from F20 and F30 (Switchers) since first PRX-102 infusion as well. The analysis for the switchers will be performed overall and by study cohort.

The TEAE summary table for all patients will be generated for subgroups of study cohort, gender, baseline ADA, and treatment duration subsets defined in Section 7.5 and overall. TEAE summary tables for all patients will be repeated for all on-study TEAEs since first infusion in F60, except the summary by treatment duration subsets.

This summary table will include for each category the number (%) of patients with at least one AE, the number of AE in the category and the rate per 100 person-years exposed (calculated as number of events x 100 / total exposure to PRX-102 (in years)).

The number and percentage of patients with at least one TEAE and the number of TEAEs will be reported for the following parameters:

- Any TEAE
- Related (showing “Reasonable possibility of a relatedness”) TEAE (adverse drug reaction; ADR)
- Severe TEAE
- Related Severe TEAE
- Serious TEAE (TESAE)
- Non- Serious TEAE
- Related SAE (serious adverse drug reaction, SADR)
- TEAE leading to withdrawal
- TEAE leading to death

In the analysis of severity, patients with events collected as “Severe” and “Very Severe” on the eCRF will be presented in the category “Severe” for analysis.

The overall analysis by study cohort and overall will be repeated for injection site reactions. Injection site reactions will be identified by their SOC and PT, as defined in Table 4 and their start time that should occur within 24 hours from the infusion, following the algorithm described in Section 10.2.2. These events are related to the procedure and not to the product.

Table 4: Injection Site Reaction (ISRs)a SOC and PT

MedDRA SOC	MedDRA PT
General disorders and administration site conditions	Catheter site hypoaesthesia
	Catheter site pain
	Infusion site bruising
	Infusion site discomfort
	Injection site discomfort

	Infusion site pain
	Injection site pain
	Infusion site bruising
	Infusion site hematoma
	Injection site hematoma
	Injection site extravasation
	Infusion site extravasation
	Infusion site oedema
	Vessel puncture site pain
Injury poisoning and procedural complications	Contusion
	Procedural site reaction
	Procedural pain
	Vascular access complication
	Vascular access site pseudoaneurysm
	Vascular pseudoaneurysm
	Vessel puncture site pain
Vascular disorders	Poor venous access
	Vascular fragility
	Vein rupture

TEAE summary tables by MedDRA SOC and PT will present the number and percentage of patients with at least one TEAE and the number of TEAEs for subgroups of study cohort, gender, baseline ADA, defined in Section 7.5.1 and overall. The tables will show the number (%) of patients with at least one TEAE, the number of TEAEs and the rate per 100 person-years.

In summary tables by SOC and PT, SOCs will be sorted alphabetically, and within each SOC, PTs will be sorted in a decreasing order of frequency.

The TEAE summary tables by SOC and PT will be repeated for related TEAEs by study cohort, and overall.

The TEAE summary tables by SOC and PT will also be repeated for serious TEAEs, related serious TEAEs, severe TEAEs, and TEAEs leading to withdrawal by study cohort and overall.

In the summaries of severity and relationship to study drug, for those patients who experience the same TEAE (per PT) on more than one occasion, the most extreme value (highest severity and closest relationship to study drug, respectively) will be used.

Missing values associated with TEAEs will be treated as missing except for causality, severity, and outcome of a TEAE, at which occurrence a “worst case” approach will be taken in the analysis. Thus:

- If causality is missing, the TEAE will be regarded as related to study drug
- If the severity is missing, the severity of the TEAE 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, and if still missing, the AE will be assumed to be "serious"

All TEAEs will be listed (information about start and end date/time, seriousness, severity, relationship to study drug, action taken, outcome and the TEAE day in study relative to first infusion).

Serious TEAEs, related TEAEs and TEAEs leading to withdrawal or death will be listed separately.

10.2.2 Infusion-Related Reactions (IRRs)

An IRR is a reaction to the infusion of pharmacological or biological substances. Symptoms may appear within minutes to 2 hours following the end of the infusion and may include pruritus, flushing, swelling, dyspnea, bronchospasm, and hypotension.

Injection site reactions with SOC and PT listed in Table 4 are not considered IRRs and should not be considered for the IRR analysis.

[redacted] an additional analysis on adverse drug reactions (ADRs) up to 24 hours from the end of the infusion will be done. Therefore, two timeframes will be considered for the IRR analysis: during the infusions or within 2 hours after its completion (IRR-2H) or within 24 hours after its completion (IRR-24H). Classification rules for assignment of TEAEs to occur within the time frame are provided below in Section 10.2.2.1.

Different studies used a slightly different IRR-2H algorithm for the classification of the timing of the events with regards to time of a prior infusion. In addition, the SOC and PT included in Table 4 have changed over the time. All IRR tables will be done on IRR-2H and repeated for IRR-24H.

The number and percentage of patients with at least one IRR and the number of IRRs with the rate per 100 infusions (defined as number of IRR X 100 / Number of Infusions) will be reported in an overview table with the following parameters: Any IRR; Severe IRR; Serious IRR; IRR leading to withdrawal; IRR leading to death. The number of IRR will be shown together with the rate per 100 infusions defined as number of IRR X 100 / Number of Infusions as well.

This IRRs summary table will be presented for all patients, and separately for patients originating from F20 and F30 (Switchers) as well.

The analysis for all patients will be performed overall and by study cohort, gender, baseline ADA, FD classification, and treatment duration subsets defined in Section 7.5 and location of administration (Home or Site). The analysis for the switchers will be performed overall and by study cohort.

All IRR summary tables but the summary by treatment duration subsets will be repeated for those IRRs occurred since first infusion in F60. In addition, the IRR frequency summary table will be presented separately by the shortest tolerated infusion duration groups (1 <=1 hour, 1 < and ≤ 1.5 hours, 1.5 < and ≤ 2 hours, and >2 hours) defined in Section 10.1 for F60 subset.

IRR summary tables by SOC and PT will present the number and percentage of patients with at least one IRR and the number of IRRs with the rate per 100 infusions. This analysis will be

performed for subgroups of study cohort, gender, baseline ADA, and overall and repeated by severity and seriousness.

In summary tables by SOC and PT, SOC will be sorted alphabetically. Within SOC, PT will be sorted in a decreasing order of overall frequency.

All IRRs will be listed together with an indication for the time frame, i.e., IRR-2H or IRR-24H

A graphical display showing for each patient the timeframe in which an IRR (for both time categories) was experienced in relationship to ADA status (see Section 10.3 for more information on derivation of ADA status) will be generated.

10.2.2.1 Time Frame Categories of IRR

10.2.2.1.1 TEAE Occurring During the Infusion Or within 2 Hours After the Infusion

In order to classify a TEAE timeframe (during the infusion or within 2 hours after the infusion completed/more than 2 hours after the infusion completed), information collected in two eCRF pages will be considered: AE form (fields of onset date and time) and Drug Administration Form.

Due to a slight difference between the Drug Administration Form in Studies F01, F02 and F03 versus studies F20, F30, and F60, a different algorithm will be used, based on the study.

F01, F02 and F03 Classification Algorithm

The Drug Administration form includes the following fields: administration date; start and end times; question "Did the patient experience an AE during or 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 the question above;
- The answer to the question above is Yes and the AE is linked to the drug administration form and the date/time of the infusion or the TEAE is not complete (note that the question in the CRF does not limit the timeframe of the TEAE to be during the infusion or within two hours. Hence, in case that the date/time of the TEAE onset and infusion are complete and the TEAE is not within the timeframe, the event will not be considered even if the answer is Yes).

All other events will not be classified into the 2H time category.

F20, F30 and F60 Classification Algorithm

The Drug Administration form includes the following fields: 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, the options selected are either 1a or 1b, and the AE is linked to the drug administration form.

All other events will not be classified into the 2H time category.

10.2.2.1.2 TEAE Occurring During the Infusion or Within 24 Hours After the Infusion

F01, F02 and F03 Classification Algorithm

The algorithm is similar to above with the following slight modification to the 1st conditions:

- Date and time for both TEAE and infusion are complete, and the onset of the TEAE is during the infusion or up to 24 hours from its completion (stop time), regardless of the answer to the question above.

All other events will not be classified into the 24H time category.

F20, F30, and F60 Classification Algorithm

The algorithm is similar to above with a slight modification to the two conditions, as below:

- Date and time for both TEAE and infusion are complete, and the onset of the TEAE is during the infusion or up to 24 hours from its completion (stop time), regardless of the answer to question 1 above;
- The answer to question 1 above is Yes (regardless of selection of 1a, 1b or 1c) and the AE is linked to the drug administration form.

All other events will not be classified into the 24H time category.

10.3 Anti-Drug Antibodies (ADA) to PRX-102

A summary table for IgG ADA antibodies to PRX-102 and neutralizing antibodies will present the number and percentage of patients who are positive or negative by visit. In case that IgG was tested more than once on the same visit (for example, due to hypersensitivity) based on a conservative approach, a positive result will be taken over a negative one.

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 Positive”, 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”

The derivation of baseline ADA status will follow the definition as outlined in Section 7.7.1.

The table will also show for IgG and neutralizing antibodies the number and percentage of patients with their overall (i.e., throughout the study) post-treatment status where post-treatment positive is defined as positive in at least one (scheduled or unscheduled) visit post baseline (Visit 1), or negative if negative at all (scheduled or unscheduled) post-baseline visits, regardless of status at baseline.

IgE is tested in case of hypersensitivity. The table will show the number and percentage of IgE positive and negative at baseline and the IgE post-treatment status, defined as above. No IgE tests were done in F03.

Patients will be defined as treatment-emergent ADA positive if they satisfy one of the following conditions:

1. Titer boosted: Patients who were IgG positive at baseline and had a titer increase of at least 4-fold from baseline post-treatment (See Shankar et al. 2014 and FDA Guidance for Industry, January 2019)[7,3].
2. Treatment Induced: Patients who were IgG negative at baseline, or their IgG at baseline was missing, and are positive at least one time point post first infusion.

The number and percentage of patients who do or do not have treatment-emergent ADA (yes/no) will be presented by study cohort and overall; and for those who do have it, the table will indicate whether the ADA is titer boosted or treatment induced. Treatment-emergent status will be missing if a patient is missing all the post-baseline assessments.

A shift table from ADA status at baseline (positive / negative / missing) to overall status during the study (positive if positive at least one visit post-baseline; negative if negative at all post-baseline visits; missing if missing at all post-baseline assessments) will be presented by study cohort, gender, FD classification, and overall. In addition, a shift table from baseline to Month 12, 24, 36,48, 60, 72, 84, 96, 108, 120 and to the end of the study (where appropriate) will be presented.

All ADA analysis will be performed by study cohort, gender, and overall.

Note that only patients who have tested positive for IgG ADA will be tested for ADA characterization (i.e., neutralizing antibodies, anti-BCL (before cross-linking) antibodies, anti-PEG antibodies, and anti-plant glycan antibodies), and will be listed accordingly.

10.4 Clinical Laboratory Tests

The following laboratory test results will be summarized at each visit by study cohort and overall. Continuous measures will include the change from baseline:

- Hematology: total white blood cell count, hemoglobin, and platelets assessed by local laboratory(ies).
- Biochemistry: sodium, potassium, glucose, blood urea nitrogen, calcium, phosphate (inorganic), uric acid, total protein, albumin, bilirubin (total), alkaline phosphatase, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, creatine Phosphokinase (CPK).
- Serum Enzymatic Creatinine and Cystatin C. In case a patient reaches an end-stage renal disease condition, the Principal Investigator and the Sponsor's Medical Expert will discuss whether or not to continue collecting the Enzymatic Creatinine and Cystatin C.
- Urinalysis: dipstick for the presence of blood, glucose, nitrite, leukocyte, and protein. Note that dipstick was assessed by local laboratory(ies).

In case a blood sample is taken twice at the same visit, only the results of the first sample (based on the time it was taken) will be used in the analyses, but both will be listed.

All collected laboratory results will be listed (as well as parameters that are not tabulated).

Descriptive statistics for parameters for which there are test results below the level of detection and reported as '<' will not include the change from baseline analysis. For these parameters, 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.

10.5 Physical Examination

Physical examination data from F60 subset will be listed.

10.6 Vital Signs

Vital signs from F60 subset will be listed.

10.7 12-lead Electrocardiogram (ECG)

Descriptive statistics for the quantitative and qualitative ECG parameters will be summarized at each visit by study cohort and overall. For quantitative parameters, the change from baseline will be summarized by study cohort and overall. All parameters will be listed.

10.8 Brain MRI

Brain MRI will be listed for overall. A summary table of % of normal results will be presented for F60 subset.

10.9 Use of Premedication to Manage Infusion-Related Reactions

Patients undergoing ERT treatment may need to take medication prior to, during, or following infusion for the prevention and treatment of infusion-related reactions; thus, the requirement for such medications is an indicator of treatment tolerability. Use of infusion premedication will be monitored throughout the study.

Information on infusion premedication is collected on two different CRF forms in studies F20, F30, and F60: in the concomitant medication eCRF form where the identification of medications used for that purpose is done by the classification provided by investigator. In addition, the drug administration form, collects information whether premedication was used or not in relation to each infusion (and if yes, the timing – before, during or before and during infusion).

Since this data was not collected for studies F01 – F03, the analysis described below will be performed separately for patients in the F60 subset, and pooled sample of patients from study cohorts of F30, F20-PRX-102, and F20- agalsidase beta unless otherwise stated.

10.9.1 Infusion Premedication Usage

Infusion premedication will be tabulated by medication class and standardized medication name. Medication classes will be presented alphabetically; and within each medication class, standardized names will be sorted by decreasing order of the frequency. This analysis will be performed by study cohort and overall.

For study cohorts F30, F20 PRX-102 and F20 agalsidase beta, the number (%) of patients who received or did not receive at least one infusion premedication will be summarized for the following timeframes: first PRX-102 infusion, 2nd infusion until infusion month 6; infusions between months 6 and 12; infusions between month 12 and 18 and so on in categories of 6 month up to 120 months (for the categories with high duration, if n in a category is less than 5 then consecutive categories should be merged). This analysis will be performed by subgroups of study cohort, gender and baseline ADA status.

A shift table to identify how many patients changed the number of infusion premedication from baseline to Month 12, 24, 36, 48, 60, 72, 84, 96, 108, and 120 will be presented. The shift table will include the following categories: 0, 1, 2, and 3+.

The above analysis will be repeated for F60 subset. Note that all infusion premedications taken in study F60 including those that were started before and were ongoing at the first infusion in study F60 will be considered as premedications in F60 subset.

In addition, the summary table will be presented separately by the shortest tolerated infusion duration category (1 <=1 hour, 1 < and ≤ 1.5 hours, 1.5 < and ≤ 2 hours, and >2 hours) defined in Section 10.1 for F60 subset.

A dedicated listing will be provided for infusion premedications.

10.9.2 Infusion Premedication and IRRs

The analysis in this section will be performed for both IRR-2H and IRR-24H.

Each infusion will be classified based on whether infusion premedication was used for that infusion (Yes/No) and whether infusion premedication was used at first infusion (Yes/No) to create 4 categories. This classifies infusions and not patients, so that different infusions for the same subjects can be classified differently for the first question above.

The following will be summarized for each category: the number of post baseline infusions and the number of patients. The number of post baseline IRR, the number (%) of post baseline infusions with at least one IRR, and the number (%) of patients with at least one IRR. This summary will be for all IRR-2H/24-H and for severe IRR-2H/24-H. The analysis will be repeated for ≤ 6 months, ≤ 1 year, >1-2 years, >2-3 years, >3-4 years, > 4-5 years and >5 years of exposure and beyond.

For study cohorts F30, F20 PRX-102 and F20 agalsidase beta, the summary table will be generated from the treatment baseline.

Since there is no baseline premedication for F03 patients, this summary table will be repeated for F60 subset by study cohort and overall starting from the 1st infusions of F60.

11. Changes in the Planned Analyses

11.1 Changes from Study Protocol to SAP Version 2.0

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-F60 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. Baseline value was defined as the last assessment in the parent study (i.e., PB-102-F03, PB-102-F20, or PB-102-F30) in the protocol. During the Interim Analysis Report review, it was suggested that baseline value should be changed to last assessment prior to the first infusion of the study treatment (PRX-102) to show the long-term efficacy and safety effect in the final analysis.
2. The SAP clarified that eGFR slope was considered as an efficacy variable in addition to $eGFR_{CKD\text{-}EPI}$ changes from baseline.
3. The following endpoints were added: Infusion Related Reactions (IRRs) and Fabry Clinical Events.
4. The statistical section of the protocol stated that hypersensitivity will be analyzed as an AE of special interest. Since IRR is a wider analysis which was added, the analysis of hypersensitivity will be part of the IRR evaluation.
5. Analysis on the duration of infusion have been added.
6. This is an extension study, all patients who provided informed consent will be included in the analysis. Per Protocol Population has been removed from the study population.
7. The OLE_FCE Adjudication Charter_Final_29May2024 is added as Appendix 1.

11.2 Changes from SAP Version 2.0 to Version 3.0

Changes are made during the review of Dry Run outputs. The main changes in the SAP V3.0 compared to V2.0 are as following:

1. After checking the visit numbers in parent studies SDTM data, we noticed nominal visit numbers between study protocols were different. The decision is made to use visit time windows in Table 3 to map the analysis visits relative to the first day of PRX-102 administration instead of the visit number mapping. And in order to map all scheduled study visits and avoid missing any assessments, the time windows in Table 3 are modified.
2. Baseline eGFR slopes were not available for F03 cohort patients and F20 patients who were treated with agalsidase beta. Since there will be no analysis based on baseline eGFR slope, the decision is made to remove it from the baseline summary table in Section 8.2.2.
3. The percent change from baseline is removed from plasma Gb3 summary in Section 9.4.
4. EQ-5D-5L was not assessed in study PB-102-F03. The analysis described in Section 9.8 will be performed separately for patients originating from F03 in the visits of F60 study (F60 subset), and pooled sample of patients from F30 and F20 studies.
5. The ADA shift table and the IRRs summary by FD classification are added in Section 10.3 and Section 10.2.2.
6. The definition of concomitant medications is added in Section 8.4.
7. Table 4 (ISR) is updated based on the final data review.
8. Clarification on multiple creatinine assessments is added in Section 9.1.
9. It is clarified that serum creatinine measurements from the moment either of dialysis initiation or of a renal transplantation will be excluded from the eGFR calculations in Section 7.9 and Section 9.1.
10. Clarification is made in the Section 7.5.2.1.2 that adverse events which started post first infusion in study F60 but were collected in parent studies should be included in the F60 subset.
11. Clarification on analysis of TEAE for switchers is added in Section 10.2.1.
12. Clarification on infusion premedication in F60 subset is added in Section 10.9.1.
13. It is clarified that all IRR tables will be done for both IRR-2H and IRR-24H in Section 10.2.2.

14. Clarification is made for IgE summary table in Section 10.3.

12. Output

12.1 Software

SAS version 9.4 or later will be used to perform all the statistical analyses.

12.2 Reporting Conventions

12.2.1 Treatment and Visit

As all patients will receive the same treatment of PRX-102.

Unless otherwise indicated, on the summary tables and listings, the treatment will be identified by PRX-102 1.0 mg/kg E2W since all subjects enrolled in this study received this dose.

Note: 9 out of 10 patients from F03 initially received 0.2 or 2.0 mg/kg E2W in F01/F02 studies.

All assessments except for event type data (e.g., AEs, concomitant treatments, etc.) are labelled according to the nominal Visit identifier. Unscheduled visits are not included in summary analyses, and any data collected will only be listed. A documented unscheduled visit will be labelled as “Unscheduled Visit”. In case of more than one unscheduled visit, the label will be adapted to “Unscheduled Visit x”, where x is a sequential number.

12.2.2 Decimal Places

Quantitative variables will be listed with the same number of decimal places as in the actual data.

The following rules on decimal places will be considered in the listings for the derived variables (in the analyses datasets rounding will not be performed):

- Any duration (expressed as year in 2 decimal places, month in one decimal place, and day as whole numbers)
- Scores and other indexes like EQ-5D-5L index: 2 decimal places
- Absolute change from baseline/pre-dose: same as the variable considered.

The following rules on decimal places will be considered for the results of the analyses (if the analyses are performed on derived variables, the level of precision of the actual data is derived from the previous list):

- Min, max: same as actual data
- Mean, median, first and third quartiles: actual data + 1 decimal place; Standard Deviation (SD), Standard Error (SE): actual data + 2 decimal places.
- Percentage and rates: 1 decimal place

All p-values will be presented to 3 decimal places. If a p-value is less than 0.001, it will be presented as <0.001.

Missing descriptive statistics or p-values that cannot be estimated will be reported as “-”.

12.2.3 Other Reporting Conventions

Study Cohorts will be presented in the tables in the following order: F03, F30, F20 PRX-102, F20 agalsidase beta, and overall.

Unless otherwise stated, listings will be sorted by study Cohort, patient ID, and visit number or collection day/date/time, where applicable. Visits (scheduled and unscheduled) within patient will be shown in chronological order on the date of the visit.

For numeric variables, units will be included as appropriate.

For presenting the categorical parameters in a summary table, if the categories of a parameter are ordered, then all categories between the maximum and minimum category will be presented in the table. If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least one patient represented in one or more groups will be included. Unknown or Missing categories are added to each parameter for which information is not available for one or more patient.

Where a category with a subheading (such as SOC) must be split over more than one page, the subheading will be followed by "(cont.)" at the top of each subsequent page. The overall summary statistics for the subheading should only appear on the first relevant page.

Listings should include all collected data and derived data used for analysis. The derived data must be clearly identified.

In a listing, if a patient's record continues to the next page, an appropriate identification (e.g., the subject ID number) must be repeated at the beginning of that page.

In general, dates will be presented in listings in the format ddmmmyyyy (SAS format date9.) and time in the format hh:mm (SAS format time5.). In case of partial dates or times, missing information will be replaced by dashes. Time will only be reported if it was measured as part of the study.

12.3 Format

In the top of each output, a number followed by the title of the output will be presented. The analysis set will be added. After the title line, an optional subtitle can be presented. Horizontal lines will appear before and after the column heading of the table/listing. Footnotes will be placed under the main body of text at the bottom of the page.

Each TLF must include the following information:

- Chiesi Farmaceutici S.p.A.
- Protocol code CLI-06657AA1-04 (Previously PB-102-F60)

The sponsor's name and the protocol number will appear on the top left corner of each output. 'Confidential' and the status of the table/listing (i.e., draft or final) will appear on the top right corner. The extraction date and SAS program name will appear on the bottom left, and the page number (as page x of y) will appear on the right corner of each output. The source listing number and the date and time of creation of the output will appear in the bottom left, below the footnotes. Listings will include the source data as a footnote.

Tables and listings will be produced in Rich Text Format (i.e., they will be tabular in format).

Landscape orientation will be used for all outputs.

All tables, listings, and figures will be collated into three Microsoft Word documents (including title page and table of contents). If the listings are too large to be included in one file, they will be separated into files of manageable size. The Microsoft Word documents will be subsequently converted to PDF format.

13. References

1. Beck M. The Mainz Severity Score Index (MSSI): Development and validation of a system for scoring the signs and symptoms of Fabry disease. Acta Paediatrica. 2006; 95:43-6.
2. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Archives of Internal Medicine (1916): 17 (6): 863-71.
3. FDA Guidance for Industry, February 2019: Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/immunogenicity-testing-therapeutic-protein-products-developing-and-validating-assays-anti-drug).
4. Hopkin RJ, Cabrera G, Charrow J, et al. Risk factors for severe clinical events in male and female patients with Fabry disease treated with agalsidase beta enzyme replacement therapy: Data from the Fabry Registry. Mol Genet Metab. 2016; 119(1-2):151-9
5. Kawel-Boehm N, et al. Normal values for cardiovascular magnetic resonance in adults and children. Journal of cardiovascular magnetic resonance. 2015: 17-29.
6. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604-612.
7. Shankar G, et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. AAPS Journal, 2014 Jul;16(4):658-73.

14. List of Tables, Listings and Figures

The list of proposed TLFs is provided in the shell document.

15. Appendix

Appendix 1: OLE FCE Adjudication Charter