CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761161Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

CDTL/Division Director/Office Summary Memo

Date	May 8, 2023
From	DRDMG/ORPURM
Subject	CDTL/Division Director/Office Summary Memo
NDA/BLA # and Supplement#	761161
Applicant	Chiesi Farmaceutici
Date of Submission	November 9, 2022
PDUFA Goal Date	May 9, 2023
Proprietary Name	Elfabrio
Established or Proper Name	Pegunigalsidase alfa
Dosage Form(s)	Injection: solution in a single-dose vial
Applicant Proposed Indication(s)/Population(s)	Fabry disease, adults
Applicant Proposed Dosing Regimen(s)	1 mg/kg (actual body weight) intravenously every 2 weeks, (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adults with Fabry disease
Recommended Dosing Regimen(s) (if applicable)	1 mg/kg (actual body weight) intravenously every 2 weeks

Overview

Chiesi (Applicant) submitted this Class 2 resubmission biologics license application (BLA) 761161 for pegunigalsidase alfa (PRX102) (tradename Elfabrio), seeking approval of this product as an enzyme replacement therapy (ERT) for Fabry disease.

Fabry disease is a rare and serious inborn error of glycosphingolipid metabolism characterized by deficiency of a single lysosomal enzyme, alpha-galactosidase A (alpha-Gal A). As a result of the missing enzyme, patients with Fabry disease have a progressive accumulation of the upstream metabolite (substrate) globotriaosylceramide (Gb3) due to the enzymatic block in the pathway of its degradation. The major clinical manifestations, which are chronically progressive, severely debilitating, and sometimes life-threatening, include chronic renal impairment leading to renal failure; myocardial infarction, arrhythmias leading to sudden death, strokes, and chronic neuropathic pain and gastrointestinal dysmotility. Currently, there are two FDA-approved therapies for Fabry disease, Fabrazyme (an ERT, traditional approval) and Galafold (a protein chaperone, accelerated approval for a subset of FD patients).

The Applicant submitted the original BLA on May 27, 2020, seeking accelerated approval. The BLA received a complete response on April 27, 2021, based on CMC manufacturing major deficiencies and the use of the accelerated approval (AA) pathway when there is available therapy. The OPQ team concluded that the data submitted in the original application were not sufficient to support a conclusion that the manufacture of PRX102 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf life. Records inspection of the drug product manufacturing site in (b) (4) led to a withhold recommendation on the facility, and the inspection of the drug substance site had not yet occurred due to COVID related travel issues. During this initial review cycle for PRX102, the BLA for Fabrazyme (agalsidase beta), an ERT, was converted from accelerated to traditional approval, making Fabrazyme an available therapy relevant to considering the use of AA for other drugs intended to treat Fabry disease. As such, PRX102 no longer qualified for AA because of insufficient evidence to determine whether PRX102 provided meaningful therapeutic benefit to patients over the available treatment (Fabrazyme). In this resubmission, the Applicant submitted the results of Study PB-102-F20 (F20), a randomized, double-blind, active-controlled study seeking traditional approval for PRX102.

Substantial evidence of effectiveness for PRX102 in Fabry patients was established in this Complete Response resubmission with one adequate and well-controlled study with confirmatory evidence. The adequate and well-controlled Study PB-102-F01/02 (F01/02) demonstrated a large and statistically significant reduction from baseline in the surrogate endpoint of renal Gb3 inclusions in the peritubular capillaries (PTC) assessed via the BLISS methodology renal Gb3 inclusion score. While there was no concurrent control group in this study, the literature supports the conclusions that Gb3 deposition is the cause of the disease manifestations, the disease is progressive, and that Gb3 PTC inclusions do not spontaneously regress. Therefore, there is strong biological rationale that a reduction in Gb3 accumulation would be expected to modify the pathophysiology of FD beneficially. Thus, we determined the baseline-control design is appropriate to allow inference about the effectiveness of PRX102 and concluded Study F01/02 to be adequate and well-controlled. Robust confirmatory evidence included:

- Results from Study F20, a multicenter, randomized, blinded, active-control study demonstrating a comparable annualized eGFR slope between ERT-experienced patients randomized to PRX102 or to agalsidase beta, an approved ERT with the same mechanism of action, after two years of investigational product exposure.
- The pharmacologic effect of PRX102 on a disease specific biomarker (reduction of plasma Lyso-Gb3 levels in ERT-naïve patients).
- Strong mechanistic support:
    - The well-established etiology of the disease as a monogenic inborn error of glycosphingolipid metabolism from a single enzymatic deficiency.
    - The targeted mechanism of action of PRX102 as an exogenous enzyme replacement for the deficient/absent endogenous enzyme.

The safety profile for PRX102 is generally consistent with the known safety profile for other enzyme replacement therapies and is acceptable for its intended use. The main safety concerns are the risk of hypersensitivity reactions, including anaphylaxis and infusion-associated reactions. These known risks can be adequately mitigated via product labeling. Risk mitigation will include a boxed warning for hypersensitivity reactions including anaphylaxis, and Warnings/Precautions describing the risk of hypersensitivity (including anaphylaxis) and infusion-associated reactions as well as treatments to manage such events should they occur. Additionally, membranoproliferative glomerulonephritis (MPGN) was diagnosed in a subject treated with PRX102 during the clinical study and it was determined to be related to the treatment. Both Fabry disease and MPGN cause renal function decline, and distinguishing these causes is important because management differs significantly. The product labeling will include a Warning/Precaution to alert prescribers to the possibility of MPGN in PRX102-treated patients with declining renal function where the proper management is to discontinue PRX102.

Important uncertainties not precluding approval will be addressed with PMRs or PMCs. A total of 11 PMR/PMCs will be issued, including a PREA deferred pediatric study, a long-term maternal-fetal descriptive study, a nonclinical pre and post development study, a nonclinical efficacy study, new or improved immunogenicity assays, evaluation of neutralizing antibodies, and CMC-related PMCs.

In summary, the review team determines Study F01/02 clearly demonstrates PRX102 has a large treatment effect on renal Gb3 inclusion reduction in adult Fabry subjects. Although there are currently limited data to evaluate that a drug effect on renal Gb3 inclusions will reliably predict clinical benefit with respect to kidney function in Fabry disease, the data from Study F20 suggesting a comparable effect on eGFR slope to an approved ERT gives us adequate confidence, within the context of this development program, the effect of PRX102 on renal Gb3 inclusions confers clinical benefit. Therefore, the review team concludes PRX102's benefits outweigh its risks when PRX102 is used as recommended in the approved labeling. Despite some residual uncertainties identified in discipline reviews, each scientific discipline and the clinical teams support a recommendation for traditional approval of PRX102 for the treatment of Fabry disease in adult patients. The CDTL, Division Director, and Office signatory authority concur with the recommendation for traditional approval.

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
Fabry disease (FD) is a rare and serious inborn error of glycosphingolipid metabolism characterized by deficiency of a single lysosomal enzyme, alpha-galactosidase A (Alpha-Gal A). This single enzyme defect leads to progressive accumulation of the upstream metabolite (substrate) globotriaosylceramide (Gb3) due to the enzymatic block in the pathway of its degradation. The major clinical manifestations, which are slowly progressive, severely debilitating, and sometimes life-threatening, include chronic renal impairment leading to renal failure; myocardial infarction; and arrhythmias leading to sudden death, strokes; and chronic neuropathic pain and gastrointestinal dysmotility. Although Fabry is an X-linked disease, both males and females are affected. The disease course and severity can vary as a function of the phenotype (Classic versus non-Classic). FD can be particularly variable in females, depending on the degree of X inactivation in diseased tissues. Current available treatments for Fabry in the U.S. include Fabrazyme (agalsidase beta), an ERT that received accelerated approval in 2003 followed by traditional approved in 2021 for the treatment of adult and pediatric patients 2 years and older with confirmed FD and is administered by bi-weekly IV infusions over a few hours. Fabrazyme may not be tolerated by all patients because of hypersensitivity reactions, infusion associated reactions, the development of anti-drug antibodies that may impact efficacy and/or safety, among other reasons. Galafold is an alpha-Gal A pharmacological chaperone, administered orally every other day that received accelerated approval in 2018 for the treatment of adult FD patients. Its use is limited only to patients with certain amenable *GLA* variants, and its clinical benefits have yet to be confirmed.

PRX102 is a pegylated, covalently cross-linked recombinant human protein α-galactosidase enzyme that replaces the deficient enzyme in FD. Published literature have characterized the central causal role of Gb3 inclusions in the disease manifestations of FD. The evidence showed Gb3 accumulation to be toxic to tissue, that Gb3 accumulates in tissues where FD causes structural damage and functional loss, and that Gb3 accumulation correlates with tissue damage. Substantial evidence of effectiveness for PRX102 in Fabry adult patients was established with one adequate and well-controlled study (Study F01/02) with several lines of confirmatory evidence. In the pivotal Study F01/02, PRX102 administered to ERT-naïve (naïve to or off-ERT for at least 6 months with no evidence of ADA) FD adult subjects significantly reduced from baseline Gb3 inclusions in the peritubular capillaries in the kidney (assessed by the BLISS methodology). After 6 months of treatment with PRX102, among the 14 FD subjects with evaluable data, the observed median percent reduction compared to baseline in number of Gb3 inclusions per PTC was -78% (95% CI: -86%, -53%); the median absolute reduction compared to baseline was -2.5 (95% CI: -5.3, -0.7); and 11 subjects (79%) had at least a 50% reduction from baseline in renal Gb3 inclusions (ranged from -53% to -95%). The consistent and large magnitude of clearance of renal Gb3 inclusions observed are highly unlikely to occur spontaneously based on the known natural history of renal Gb3 inclusions in FD. Therefore, the results from F01/02 contribute compelling evidence of PRX102's efficacy. Renal Gb3 inclusions do not directly measure clinical benefit (e.g., renal function decline) and, to date, there are insufficient clinical data in this rare disease to conclude that a drug effect on renal Gb3 inclusions would always predict clinical benefit for FD. However, within the context of PRX102's development program, Study F20 suggests a comparable eGFR slope between PRX102 and the active comparator (agalsidase beta), providing confidence that the effect of PRX102 on renal Gb3 inclusions confers a positive effect on clinical renal outcomes and represents a clinical benefit. In addition to Study F20's findings on eGFR slope, other confirmatory evidence includes the reduction in plasma lyso-Gb3 demonstrated in ERT-naïve adult FD subjects in Study F01/02 and strong mechanistic support (well-understood disease pathophysiology (single enzyme deficiency), and the targeted mechanism of action of PRX102 as ERT).

The overall safety findings of PRX102 are consistent with the known safety profile of an enzyme replacement therapy. Important risks are adequately mitigated through drug labeling. The drug label will include a boxed warning for hypersensitivity reactions/anaphylaxis, consistent with ERT class labeling, and Warnings/Precautions provide guidance on the signs and symptoms of hypersensitivity and infusion-associated reactions seen in the clinical studies as well as treatments to manage such events should they occur. A Warnings/Precautions for MPGN will alert prescribers to the possibility of MPGN and guide appropriate patient management. In Study F20 where ERT-treated FD patients were randomized to switch to PRX102 or to continue with agalsidase beta for two years, there were no notable differences in safety findings between the two treatment groups.

In the context of Fabry Disease as a rare, serious disease with limited therapeutic options that may not be suitable to all individual patients, the review team has determined the benefit-risk of PRX102 to be favorable for the treatment of adults with confirmed Fabry disease.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Fabry disease (FD) is a rare, X-linked, slowly progressive, monogenic disease caused by deficiency of the lysosomal enzyme galactosidase A (alpha-Gal A), which metabolizes glycosphingolipid globotriaosylceramide (Gb3) in lysosomes. • Progressive intra-lysosomal accumulation of Gb3 and its metabolite globotriaosylsphingosine (lyso-Gb3) in the vascular, endothelial, epithelial, smooth muscle, and ganglion cells of the kidneys, cardiovascular system, cerebrovascular system, gastrointestinal (GI) tract, peripheral nerves, and skin lead to the manifestations of the disease. • Published literature collectively show that: a) accumulation of Gb3 is toxic to tissues, b) Gb3 accumulates in tissues/organs which exhibit structural damage and functional impairment due to Fabry disease, and c) Gb3 accumulation in affected tissues correlates with tissue and end-organ damage and functional impairment. • Both males and females are affected. FD spans a spectrum of disease progression and severity ranging from early-onset, severe disease (classic FD) to later-onset, milder disease (late-onset FD) in males. Affected females can be asymptomatic to symptomatic with a wide range of manifestations and severity (depending on the extent of X-inactivation in the corresponding cells/tissues). • The major clinical manifestations, which are chronically progressive, severely debilitating, and sometimes life-threatening, include chronic renal impairment leading to renal failure; myocardial infarction; and arrhythmias leading to sudden death, strokes; and chronic neuropathic pain and gastrointestinal dysmotility.	FD is a serious and rare disease with chronic, life-threatening complications. Gb3 and lyso-Gb3 are the tissue-toxic intermediates and play a central role in the pathological clinical manifestations of FD. Intra-lysosomal accumulation of Gb3 and its related product (lyso-Gb3) in affected tissues can cause tissue damage and organ dysfunction with progressive and life-threatening complications, including chronic renal failure, cardiac arrhythmias, myocardial infarction, sudden death, and stroke. Reduction of accumulated Gb-3 in affected tissues is expected to ameliorate and/or prevent the clinical effects from the cellular and tissue damage and organ dysfunction caused by this single enzyme deficiency.
Current Treatment Options	There are currently two FDA-approved products for Fabry Disease: • Fabrazyme (agalsidase beta), an enzyme replacement therapy, originally received accelerated approval in April 2003 based on the histological clearance of Gb3 in the PTCs of the kidney (as well as cardiac and skin) and subsequently received traditional approval in March 2021 based on evidence showing that the reduction in Gb3 inclusions are expected to result in clinical benefit (slowing the rate of decline in renal function as measured by eGFR slope, trends for improvement in Fabry's clinical events), specifically in the context of the Fabrazyme clinical development program. Fabrazyme is administered intravenously every other week and is approved for treatment of patients 2 years of age and older with confirmed FD. • Galafold (migalastat), an oral chaperone therapy, was approved in Aug 2018 under accelerated approval for adults with FD who have specific gene variants that are "amenable" to treatment with the drug based on results of an in-vitro assay (human embryonic kidney, HEK, assay). Approximately 30% of FD patients carry these qualifying variants. Efficacy was based on findings of proportion of patients with ≥ 50% reduction from baseline in the average number of Gb3 inclusions per kidney interstitial capillary in renal biopsy samples.	There are limited therapeutic options for FD patients. Only one product, Fabrazyme, an enzyme replacement therapy, has received traditional approval. Galafold is currently approved under accelerated approval for only a subset of patients "amenable" to therapy and its clinical benefit is still unverified.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	PRX102, an enzyme replacement therapy, is proposed for the treatment of adults with confirmed Fabry Disease. • The primary support for efficacy was Study F01/02, the only study in the PRX102 clinical development program that enrolled ERT-naïve or off-ERT FD patients. This was an open-label, single-arm study in 18 adult FD subjects, 14 of whom were evaluable, who have never received or were off ERT for at least 6 months without evidence of ADA development. After 6 months of PRX102, the observed median percent reduction compared to baseline in number of renal Gb3 inclusions per PTC was -78%; the mean absolute reduction compared to baseline was -3.1 (95% CI: -4.8, -1.4). Additional analyses performed at the patient level showed that 11 of 14 subjects who had data available had at least a 50% reduction compared to baseline in the number of renal Gb3 inclusions (ranged from -53% to -95%). Based on what is known about renal Gb3 inclusions in FD, regression of these inclusions, especially with such consistency and magnitude observed in Study F01/02, is highly unlikely absent treatment effect. • A body of confirmatory evidence to confirm the treatment benefit demonstrated in study F01/02 includes the following: o Study F20: a multicenter, randomized, double-blind, active-controlled (agalsidase beta) study of 24-month duration in 77 ERT-treated adult FD subjects randomized 2:1 to PRX-102 (1 mg/kg) or continue with agalsidase beta (1 mg/kg) every other week. The primary efficacy analysis was the comparison of the mean annualized change (slope) in estimated glomerular filtration (eGFR) rate between treatment groups. The annualized eGFR slope was comparable between PRX102 and the active comparator, an approved ERT, after 2 years of treatment. Based on the Applicant's primary analysis, the estimated mean eGFR slopes were -2.4 and -2.3 mL/min/1.73 m2/year in the PRX102 and agalsidase beta arms, respectively, and the treatment difference was -0.1 (95% CI: -2.3, 2.1) mL/min/1.73 m2/year. o Reduction in plasma lyso-Gb3 was seen in ERT-naïve FD adults subjects in F01/02 All patients had reduction in plasma Lyso-Gb3 (a metabolite of Gb3) concentrations from baseline following treatment with PRX102 for 12 month and/or 24 months. The individual percentage change from baseline ranged from -5% to -79% at Month 12 across all patients. The reduction of plasma Lyso-Gb3 also showed statistical correlation with the reduction of renal Gb3 inclusions from baseline providing additional supportive evidence. o A well-understood underlying disease pathophysiology (caused by a single enzyme deficiency) and a clear, targeted mechanism of action of PRX-102 (enzyme replacement therapy).	In principle, enzyme replacement therapy for FD provides an exogenous source of the deficient enzyme that works to break down the accumulated Gb3 in lysosomes and prevents further accumulation in affected tissues. Study F01/02 serves as a single adequate and well-controlled study even though it was a single-arm study design. Evidence from untreated FD patients shows spontaneous clearance of Gb3 deposition in the kidney does not occur, so baseline control is an acceptable comparator to elucidate treatment effect. The consistent and large magnitude of reduction from baseline in renal Gb3 inclusions with PRX102 provides compelling evidence of drug efficacy. Based on the available published literature on the central causal role of Gb3 in FD disease manifestations, the magnitude of PRX102 effect on clearing renal Gb3 inclusions, and the confirmatory evidence of PRX102 on eGFR slope in study F20, substantial evidence exists that PRX102 confers a positive effect on clinical renal outcomes. Additional confirmatory evidence includes pharmacodynamic effect on a disease-specific biomarker for FD (plasma lyso-Gb3 reduction) and strong mechanistic support. Regarding the imbalance in FCEs not favoring the PRX102 arm in Study F20, considerable uncertainties regarding the small number of events, confounding by prior ERT treatment, or disease progression preclude reliable conclusions on this finding.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	In Study F20, a higher proportion of subjects on PRX102 experienced a Fabry Clinical Event (FCE) compared to those on agalsidase beta. However, the number of events were small, criteria for adjudicating potential FCE events were not particularly robust, and FD subjects were treated, often for several years, with agalsidase beta prior to study enrollment making it challenging to ascribe these events to drug (agalsidase or PRX102) or disease progression (without a placebo arm), or a chance finding.	
Risk and Risk Management	The safety profile of PRX102 is generally consistent with that of other enzyme replacement therapies. The F20 study is the only study from which randomized, controlled safety data are available from the PRX102 program. There were no deaths attributable to PRX102 in any study. There were 5 SAEs of infusion associated reactions attributed to PRX102; 4 of these 5 cases met criteria for anaphylaxis and all 4 events occurred during or shortly after the first infusion. A case of membranoproliferative glomerulonephritis (MPGN), considered related to PRX102, was seen in Study F50. The most frequently reported TEAEs seen in the studies were hypersensitivity reactions, infusion-associated reactions, nasopharyngitis, fatigue, headache, back pain, cough, diarrhea, pain in extremity, nausea, upper respiratory infection, vomiting, arthralgia, pyrexia, abdominal pain, sinusitis, oropharyngeal pain, dizziness, and rash. There were no notable differences in TEAEs in Study F20 between the PRX102 and agalsidase beta arms.	The safety profile and tolerability of PRX102 is acceptable for its intended use. The size of the safety database is adequate for the proposed indication given the rarity of the disease. Important risks are adequately managed with drug labeling, including: ○ A boxed warning for severe hypersensitivity reactions/anaphylaxis, consistent with the ERT drug class ○ A Warning/Precaution which includes guidance on the signs and symptoms of hypersensitivity and infusion-associated reactions seen in the clinical studies as well as treatments to manage such events should they occur. ○ A Warning/Precaution alerting prescribers to the possibility of MPGN developing in Fabry patients on treatment and provide guidance on management should this occur. Uncertainties not precluding approval will be addressed with PMR's/PMCs. These include: a pediatric study deferred under PREA, a pre- and post-natal development study in rats, a 13-week repeat-dose pharmacokinetic and pharmacodynamic (PK/PD) study in α-galactosidase deficient (αGAL KO) mice to evaluate changes in the GL3 biomarker in the kidney, skin, heart, brain, spleen, and liver in relation to treatment with pegunigalsidase alfa, as well as several assay validation studies.

2. Background

Fabry disease is a rare and serious inborn error of glycosphingolipid metabolism characterized by deficiency of a single lysosomal enzyme, alpha-galactosidase. As a result of the missing enzyme, patients with Fabry disease have an accumulation of the upstream metabolite (substrate) globotriaosylceramide (Gb3) due to the enzymatic block in the pathway of its degradation. The first clinical manifestations in the classic form of the disease in males typically appear in childhood starting around age 5 years with development of diarrhea or abdominal pain, neuropathic pain crises, angiokeratomas and hypo/anhidrosis Typically, chronic renal insufficiency (initially manifesting as proteinuria, on average appearing in the 20s in classic FD males) slowly progresses to renal failure and end-stage renal disease. Gradual decline in renal function and the development of azotemia typically occur in the third to fifth decades and are managed with hemodialysis and renal transplantation. Males with classic FD with untreated end-stage renal disease (ESRD) typically die in their early 40s. Major causes of mortality in FD include life-threatening cardiovascular (sudden cardiac death, arrhythmias, myocardial infarction) and cerebrovascular complications (stroke). The cardiovascular manifestations can include hypertension, left ventricular hypertrophy, and ischemic heart disease, which can progress to heart failure, myocardial infarction, or arrhythmias. Cardiac disease is progressive and is typically present in most males with classic FD by middle age. Certain cardiac phenotypes can develop hypertrophic cardiomyopathy that may lead to cardiovascular events. Cardiac manifestations tend to occur earlier in affected males than in females.

Currently, there are two approved therapies for Fabry disease in the U.S, Fabrazyme (accelerated approval converted to traditional approval) and Galafold (accelerated approval). Fabrazyme was initially approved under accelerated approval in 2003. The basis of that approval was a reduction in Gb3 inclusions seen in renal biopsies in treated subjects compared to placebo. In 2021, Fabrazyme was granted traditional approval based on additional evidence that the reduction in renal Gb3 inclusions were expected to confer clinical benefit, especially with respect to renal function decline, within the context of the Fabrazyme development program. Galafold was approved under accelerated approval in 2018 based on a reduction in renal Gb3 inclusions compared to placebo. Limitations to the current options include having only one FDA-approved ERT and the use of Galafold is limited to only to patients that have specific genes amenable to treatment.

An original BLA (761161) was submitted on May 27, 2020, seeking accelerated approval (AA) based on the findings of Study F01/02. The primary evidence of efficacy was findings of reduction of Gb3 inclusions from baseline (demonstrated by PTC renal histology) in PRX102 treated ERT-naïve patients in Study F01/02 (single arm, open-label). A complete response letter (CRL) was

issued on April 27, 2021. The main deficiencies cited in the CRL were Manufacturing site issues. The conversion of Fabrazyme's approval to traditional approval, qualifying Fabrazyme as "available therapy," occurred in March 2021, prior to the PRX102 BLA's action date in April 2021. As such, PRX102 was no longer eligible for AA unless the Applicant could demonstrate that PRX102 provides a meaningful advantage over available therapies (Fabrazyme). The Applicant submitted a Complete Response in November 2022 seeking traditional approval of PRX102 based primarily on the findings of Study F20. Study F20 was a multicenter, randomized, double-blind, active controlled (agalsidase beta) study in 77 adult FD subjects randomized 2:1 to PRX102 or to continue with agalsidase beta with a primary efficacy endpoint of change in annualized eGFR slope followed for 2 years.

PRX-102 is a PEGylated, covalently cross-linked plant cell-expressed recombinant human α-galactosidase-A protein, developed as an enzyme replacement therapy. The Applicant is seeking approval (b) (4) 1.0 mg/kg, intravenously (IV), every (q) 2 weeks (b) (4) The indication being sought is for adults with confirmed Fabry disease.

3. Product Quality

Please refer to the quality executive summaries and reviews dated April 26, 2021, and May 8, 2023, for details.

Pegunigalsidase alfa-iwxj, a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme, is a PEGylated, crosslinked, chemically modified, recombinant human alpha-galactosidase A (alpha-Gal A) enzyme produced by genetically modified Bright Yellow 2 (Nicotiana tabacum) plant cells. Pegunigalsidase alfa-iwxj is a homodimeric glycoprotein covalently crosslinked with an average of nine 2.3 kD PEG per dimer. The total molecular weight of the cross-linked dimer is approximately 116 kDa. Pegunigalsidase alfa-iwxj has specific activity of approximately 35 to 62 U/mg (one enzyme unit is defined as the amount of enzyme which catalyzes the hydrolysis of one micromole of synthetic substrate, p-nitrophenyl-α-D-galactopyranoside per minute at 37°C). Pegunigalsidase alfa-iwxj injection is a sterile, preservative-free, 20 mg/10 mL (2 mg/mL) solution in a single-dose vial for intravenous infusion. Each mL contains 2 mg of pegunigalsidase alfa-iwxj, and anhydrous citric acid (0.2 mg), sodium chloride (7.06 mg), sodium citrate (6.73 mg), and Water for Injection, USP. The pH is approximately 5.9 to 6.4.

The overall ELFABRIO control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for ELFABRIO are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The BLA is recommended for approval from product quality, facility, microbiology, and sterility assurance perspectives.

Assessment of method validation concluded that the peptide map purity method required additional consideration of oxidized product-related substances to establish quantitative correlations between the levels of the peaks and the levels of the impurities. PMC number 11 will address this analytical method issue and confirm that the method is suitable for its intended purpose.

The potential impact of the shipping and handling process on product quality has not been directly evaluated. Evaluating the shipping impact is important because pegunigalsidase alfa drug product is shipped in liquid form. The sponsor plans to perform a real-time shipping validation study using the first three commercial drug product batches. The confirmatory shipping study in PMC number 10 includes tests to compare critical quality attributes before and after shipping.

Four PMRs, numbers 3 through 6, relate to immunogenicity assay development and improvement. These PMRs were developed collaboratively with Clinical Pharmacology Reviewers Dr. Jack (Jie) Wang and Dr. Michelle (Xiaohui) Li. The neutralizing antibody assay will be used to assess banked clinical samples from studies PB-102-F01/02, PB-102-F03, and PB-102-F20, which will be recommended as separate PMR study number 7.

The Office of Pharmaceutical Manufacturing Assessment will request a post approval inspection of the drug product manufacturing facility, Chiesi Farmaceutici, to be conducted by the Office of Regulatory Affairs in order to verify adequate completion of corrective actions from the Form 483 Observations.

Comment: *According to the OPQ memo dated May 8, 2023*: "*The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761161 for ELFABRIO manufactured by Chiesi Farmaceutici S.p.A. The data submitted in this application are adequate to support the conclusion that the manufacture of ELFABRIO is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert." We concur with this recommendation.*

4. Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical section of the Integrated Review dated April 27, 2021, and the nonclinical review dated May 8, 2023, for details.

The nonclinical pharmacology/toxicology team provided a review in the original integrated review and at that time, concluded that there were no approvability issues from a nonclinical safety perspective. The application did not include a pre- and postnatal development (PPND) study; therefore, the team required this study be conducted as a post marketing requirement (PMR) should the

BLA be approved. Because the original review was focused on evaluating the data for accelerated approval of PRX102, the nonclinical team was not asked to evaluate the nonclinical confirmatory evidence in the original review.

With this CR resubmission, the nonclinical team evaluated whether the nonclinical data could serve as a line of confirmatory evidence of PRX102's efficacy. The Nonclinical team concluded the strength of the nonclinical confirmatory evidence is weak. They concluded that the nonclinical data submitted to BLA 761161 provide limited support for the proposed mechanism of action, including uptake into cultured cells, transport to the lysosome, and in vitro biochemical data showing similar activity to agalsidase alpha. However, the Nonclinical team noted significant limitations in correlating activity against the clinical biomarker (Gb3) and a clinically meaningful endpoint in the animal models. The data collected on the clinical biomarker in their Fabry mouse model were not generated using a validated bioanalytical method and the method employed (thin layer chromatography with primuline staining) was nonspecific and nonquantitative. As a result, although there was evidence that PRX102 in Fabry mice reduced accumulated lipids in multiple tissues, the evidence could not demonstrate a reduction in Gb3, specifically, in animals, as the method was not capable of differentiating Gb3 from other molecular species present in the tissue homogenate. In addition, the animal model the Applicant utilized did not recapitulate the clinical course of disease, so it was not possible to evaluate a change in the biomarker in relation to a clinically meaningful endpoint in an animal model**.**

As a condition of approval, there will be a PMR for the previously agreed-upon PPND study in rats with pegunigalsidase alfa. A post-marketing commitment (PMC) will be requested for the Applicant to provide additional data to support the mechanism of action (as described in Section 12.1 of the label). This PMC will consist of a 13-week repeat-dose pharmacokinetic and pharmacodynamic (PK/PD) study in α-galactosidase deficient (αGAL KO) mice, and to use a validated bioanalytical method to evaluate changes in the Gb3 biomarker in plasma and in the kidney, skin, heart, brain, spleen, and liver in relation to treatment with pegunigalsidase alfa. The study will correlate reductions in Gb3 with pharmacokinetic exposures to pegunigalsidase alfa using methods that have been cross validated to the clinical methods, to facilitate interpretation of these data in relation to data obtained in the clinical studies. Because pegunigalsidase alfa is a biotechnology-derived product and given the lack of an identified clinical or nonclinical signal for carcinogenicity, genetic toxicity and carcinogenicity studies were not considered necessary to support an approval for this product.

Comment: *According to the nonclinical pharmacology/toxicology review dated May/8/2023: "The nonclinical team has no objections to the approval of pegunigalsidase alfa for the treatment of adult patients with Fabry disease." We concur with this recommendation.*

5. Clinical Pharmacology

See the Clinical Pharmacology review in DARRTS dated May 8, 2023, for a more detailed review.

PRX102 is 100 % bioavailable as it is administered IV. The metabolic pathway of PRX102 has not been characterized. The excretion pathways of PRX102 have not been characterized. As a lysosomal neutral glycosphingolipid-specific enzyme, PRX102 is expected to be metabolized into small peptides by catabolic pathways. At the proposed dose of 1 mg/kg Q2W, the mean terminal elimination half-life ($t_{1/2}$) of PRX102 was 79 hours on Day 1 and increased to 121 hours after 12 months treatment in ERT-naïve patients with Fabry disease, and 83 to 97 hours after up to 24 months treatment in ERT-experienced patients. Based on population PK analysis, age or sex did not significantly affect the PK of PRX102.

No formal study was conducted to evaluate the effect of renal impairment on the PK of PRX102. Intact pegunigalsidase alfa (molecular weight of approximately 116 kDa) is unlikely to be filtered by kidney or excreted in urine. No formal study was conducted to evaluate the effect of hepatic impairment on the PK of pegunigalsidase alfa. Metabolism by CYP enzymes or secretion into bile is generally not a significant contributor to the elimination of therapeutic proteins such as pegunigalsidase alfa. Drug-drug interactions (DDI) are not required for ERTs because ERTs are large proteins that are catabolized by proteolytic enzymes into peptides and amino acids, and they do not involve metabolizing enzymes and/or transporters.

Thorough QT study or other QT assessment are in general not required for ERTs as enzyme products are too big to block the hERG channel to impact the electric activity of the heart.

The to-be-marketed product of PRX102 was used in clinical studies; therefore, there is no need to bridge between the to-be-marketed formulation to the clinical study formulation.

Treatment with PRX102 reduced Gb3 inclusions in kidney peritubular capillary cells in Study F01/F02. In addition, Fabry patients randomized to PRX102 treatment suggested a comparable annualized eGFR slope change as patients who continued with agalsidase beta treatment in Study F20. All patients in this study were previously treated with agalsidase beta prior to randomization.
The pharmacodynamic (PD) effect on plasma Lyso-Gb3 reduction in ERT-naïve patients demonstrated a pharmacologic effect of PRX102 in humans and provided confirmatory evidence of drug effectiveness. Treatment with PRX102 (1 mg/kg Q2W) reduced the plasma Lyso-Gb3 levels in ERT-naïve patients in Study F01/02/03. However, the PD effect on plasma Lyso-Gb3 was variable in ERT-experienced patients. In patients who were previously treated with Replagal (Study PB-102-F30), plasma Lyso-Gb3 levels in male patients were significantly reduced after switching to PRX102 treatment for 12 months. In patients who were previously treated with agalsidase beta (Study F20), the median plasma Lyso-Gb3 levels were slightly elevated (by 18%) after switching to PRX102 treatment at 1 mg/kg Q2W for 24 months in male patients who were previously treated with agalsidase beta, while plasma Lyso-Gb3 levels were reduced (by 18%) in male patients who continued with the previous agalsidase beta treatment in Study F20. Compared to

male patients, female patients had lower baseline Lyso-Gb3 levels and maintained the low levels after the PRX102 treatment in both ERT-naïve and ERT-experienced patients.

The Applicant tested the 2 mg/kg Q4W dosing regimen in Study PB-102-F50 which was a single-arm open-label study in patients who had previously been treated with either agalsidase beta or agalsidase alfa. (b) (4) Refer to Clinical Pharmacology review dated May 8, 2023, Section 3.2.2 for more details.

Comment: *From a clinical perspective, the clinical implications of the trends in the change from baseline in plasma lyso-Gb3 seen with PRX102 after FD subjects switch from either agalsidase beta or agalsidase alpha are unknown. The baseline values are not true untreated values; rather, they reflect the values already reduced by prior ERT. At plasma levels already significantly reduced by prior ERT treatment, variations could be due to biological variations or some other reasons. The drug effect of PRX102 can most reliably be assessed in ERT-naïve patients as seen in studies in F01/02/03.*

The clinical pharmacology team recommends 5 PMRs for development and validation of assays for detection of cellular uptake neutralizing antibodies and anti-PEG IgE; improve the current anti-pegunigalsidase alfa IgG antibody assay or develop a new assay, revise and re-validate the anti-pegunigalsidase alfa IgM assay with anti-pegunigalsidase alfa IgM antibodies as positive controls, and to evaluate neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa in clinical samples from studies F01/02/03 and F20 using the assay developed and validated under PMR 3972-3 and assess the impact of cellular uptake neutralizing antibodies on the pharmacokinetics, pharmacodynamics, efficacy, and safety of pegunigalsidase alfa-iwxj.

Comment: *The Clinical Pharmacology review dated May/8/2023 states: "from a clinical pharmacology standpoint, the BLA resubmission is acceptable to support approval of pegunigalsidase alfa for the treatment of adults with Fabry disease." We concur with this recommendation.*

6. Clinical Microbiology

N/A

7. Clinical/Statistical - Efficacy

This section focuses on two clinical studies, F01/02 and F20, with a summary of confirmatory evidence other than Study F20, that in total, constitutes substantial evidence of effectiveness for PRX102. The Applicant submitted Study F01/02 in the original May 2020 BLA submission for accelerated approval and Study F20 in the current Complete Response submission seeking traditional approval. Refer to the Clinical Review (Mehul Desai, May/8/2023) and Statistical Review (Yared Gurmu, May/8/2023) for further details.

Adequate and well-controlled study:

Study F01/02: This was a single arm, open-label, dose-ranging study in adult FD subjects considered ERT-naïve (either never exposed to ERT or off ERT for at least 6 months without evidence of ADA) enrolled into one of three PRX-102 treatment groups (0.2, 1.0 or 2.0 mg/kg) and received IV infusions every 2 weeks for 12 weeks. Upon completion of the 12-week treatment period in Study F01, subjects had the option to enroll in an open-label extension study (F02) for an additional 9-month treatment period. Subjects continued to receive the same dose of pegunigalsidase alfa that they received in Study F01. An interim analysis was planned to evaluate a subset of pre-defined exploratory efficacy parameters in patients with a total of 6 months of treatment. Biopsy for Gb3 inclusions in the kidney peritubular capillaries was performed at baseline of Study F01 and 6 months post-treatment (Month 3 of Study F02). Two subjects had biopsy slides that were not usable and thus 14 subjects had complete biopsy data at baseline and Month 6 for efficacy assessment.

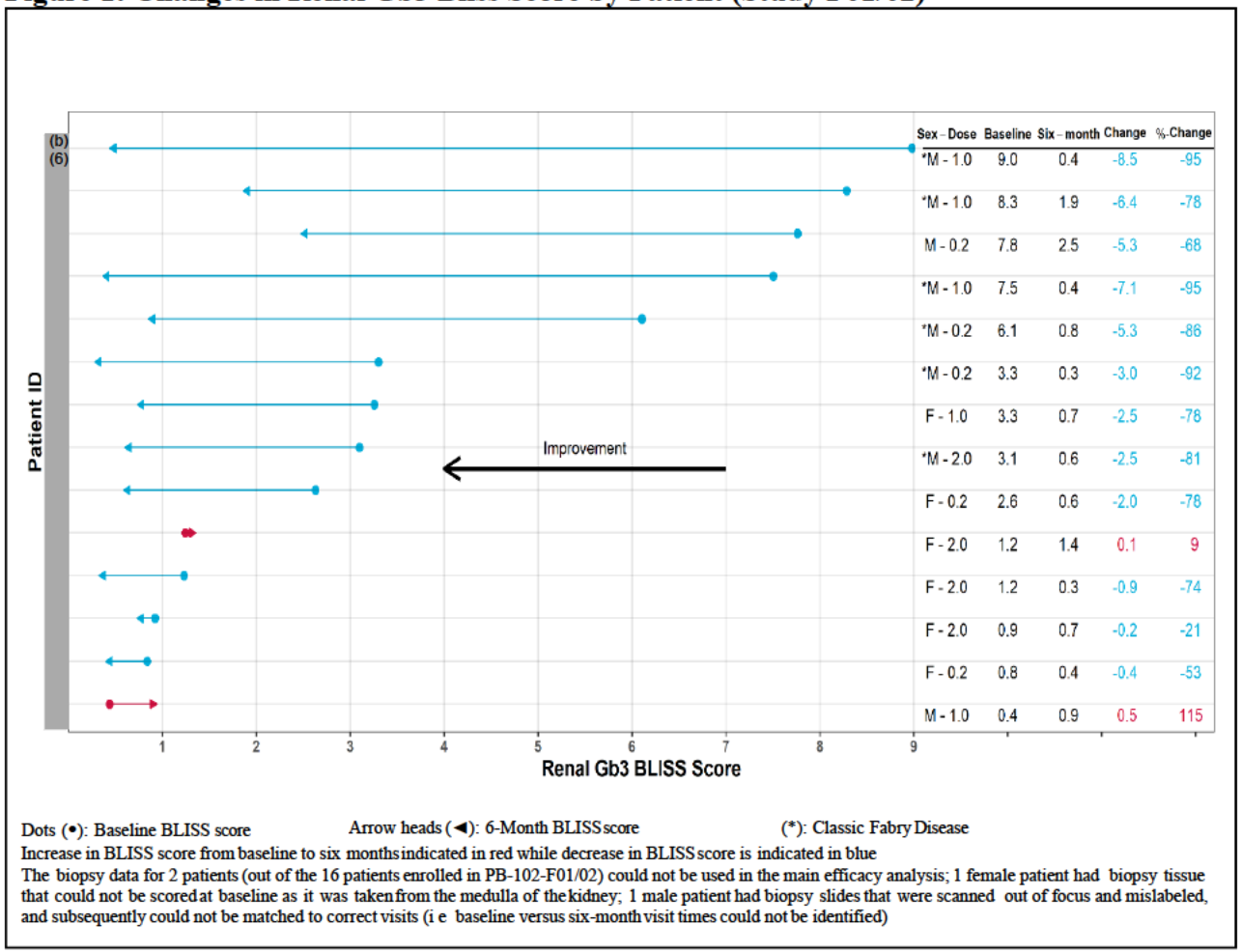
Approximately 300 kidney peritubular capillaries were scored in each biopsy specimen. Two scoring systems, a quantitative Barisoni Lipid Inclusion Scoring System (BLISS) and a semi-quantitative modified Fabrazyme Scoring System (mFSS), were used for the assessment of Gb3 inclusions in kidney peritubular capillary (PTC) biopsy samples. These two scoring systems were implemented by 3 blinded pathologists. The BLISS counts the number of Gb3 inclusions in each PTC. The final score of each biopsy was the average number of Gb3 inclusions across all PTCs. A higher score is indicative of more severe disease on the histologic level. The BLISS was previously used in a clinical study of migalastat (Galafold) for Fabry disease (Barisoni, et al., 2012). Subgroup analysis results using the mFSS approach were comparable to those using the BLISS scoring system. Overall, there was a high correlation between mFSS and BLISS methodologies.

Comment*: The renal biopsy Gb3 inclusion scoring method for Fabry disease has evolved since the 2003 approval of Fabrazyme. For the Fabrazyme program, the Fabrazyme scoring (FSS) system was used. This was a semi-quantitative scoring system which evaluated 50 PTCs as opposed to 300 PTCs in the BLISS. The BLISS is quantitative and considered more sensitive than the FSS. The modified FSS (mFSS) which was used in the PRX program (along with the BLISS) correlates well with the BLISS especially in those patients with high baseline Gb3 levels. The FSS is essentially the same as the mFSS for patients with high baseline Gb3 (scores of 2 and 3).*

Therefore, we believe that the FSS correlates reasonably with the BLISS for patients with high baseline GB3. Refer to the statistics team review in DARRTS for more detail.

A total of 14 patients who had Gb3 inclusions assessed at both baseline and 6 months were included in the main efficacy analysis of Gb3 inclusions. The median absolute reduction in the renal Gb3 BLISS score was -2.5 (95% CI: -5.3, -0.7; p = 0.001), and the median percent reduction was -78%. The mean absolute reduction in the number of Gb3 inclusions was -3.1 (95% CI: -4.8, -1.4; nominal p < 0.001), and the mean percent reduction was -55% (95% CI: -88%, -22%; p = 0.01). For the nine patients who had a baseline renal Gb3 BLISS score above 2, the minimum percent reduction in Gb3 inclusions at 6 months was 68%. Analysis of change in renal Gb3 BLISS score at the patient level showed that 11/14 (79%) patients had a nominally significant reduction (p<0.001) at 6 months. These 11 patients had at least 50% reduction in Gb3 from baseline (ranged from -53% to -95%). Of the remaining three patients, two patients (baseline scores: 0.4 and 1.2) had a minimal increase (change score at six months: 0.5, 0.1) and one patient had a minimal decrease (baseline score: 0.9, change score at six months: -0.2). **See Figure 1.**

Figure 1: Changes in Renal Gb3 Bliss Score by Patient (Study F01/02)



Dots (•): Baseline BLISS score Arrow heads (◄): 6-Month BLISS score (*): Classic Fabry Disease

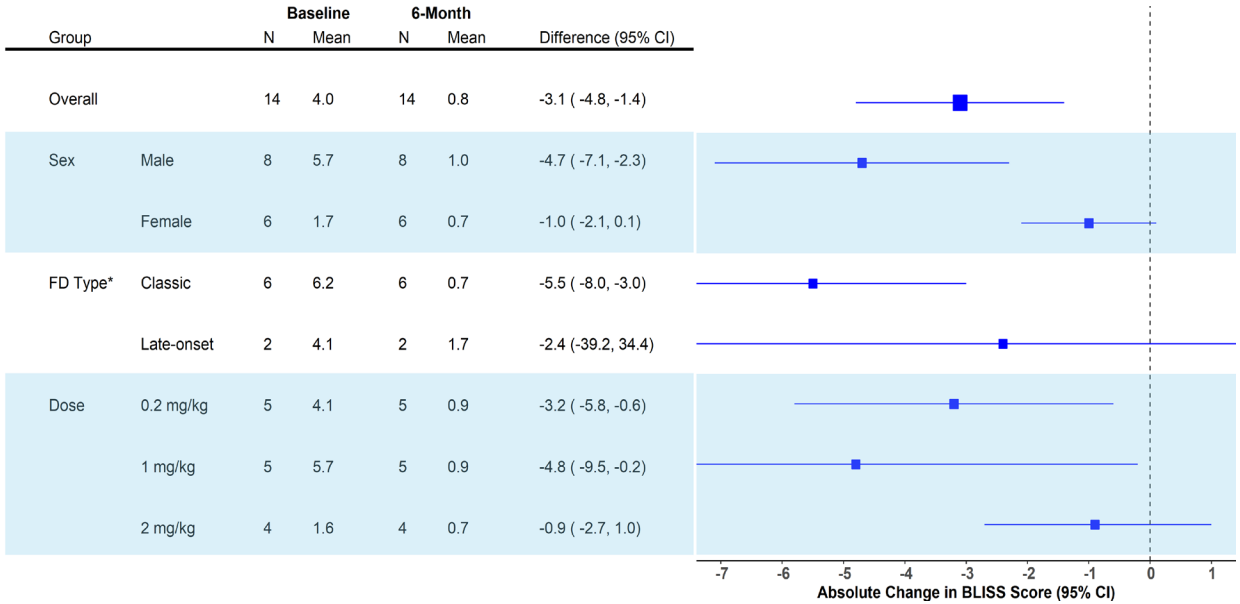
Increase in BLISS score from baseline to six months indicated in red while decrease in BLISS score is indicated in blue

The biopsy data for 2 patients (out of the 16 patients enrolled in PB-102-F01/02) could not be used in the main efficacy analysis; 1 female patient had biopsy tissue that could not be scored at baseline as it was taken from the medulla of the kidney; 1 male patient had biopsy slides that were scanned out of focus and mislabeled, and subsequently could not be matched to correct visits (i e baseline versus six-month visit times could not be identified)

Source: FDA's analysis using analysis datasets submitted to BLA761161 (eCTD 0025)) on November 11, 2020

Figure 2 shows PRX treatment over 6 months reduced renal Gb3 inclusions from baseline regardless of sex, FD type, and dose.

Figure 2: Absolute Change in Renal Gb3 BLISS Score from Baseline to 6 months By Sex, Dose, and FD phenotype



Source: FDA's analysis using the analysis datasets submitted to BLA761161 (eCTD 0025) on November 11, 2020

To understand the significance of the results of F01/02, it is important to understand what is known about the central role of Gb3 in the pathophysiology and resultant clinical manifestations of Fabry disease. Several published studies have established the central pathophysiological role of tissue Gb3, and its accumulation, in FD that has progressive, detrimental effects on tissue structure and organ function in FD. In vitro data show that Gb3 increases inflammatory biomarkers such as cyclooxygenase-2 and decreases anti-inflammatory biomarkers such as homeostatic nitric oxide synthase in cardiac epithelial cells (Namdar et al. 2012). A proinflammatory cytokine profile was found to be expressed in the peripheral blood mononuclear cells in Fabry disease patients compared to normal controls. Gb-3 was also found to induce the same inflammatory profile in normal cells. (De Francesco et al. 2013) Gb-3 accumulation in podocytes led to an increase in autophagy and a decrease of mTOR and AKT signaling which led to podocyte damage (Liebau et al. 2013). Autopsy data from Fabry patients suggested that Gb3 accumulates in cardiac muscle fibers, vascular smooth muscle, endothelium, mitral valve connective tissue, and the dorsal root ganglia (Ferrans et al. 1969; Gadoth and Sandbank 1983) all tissues known to be affected in Fabry patients. Gb3 accumulation was found in podocytes and distal tubules in renal biopsies from 9 adolescent patients with Fabry disease (mean age 13.5 years) (Tondel et al. 2008). Arteriopathy which may indicate potentially progressive vascular disease was found in 5 of 9 patients. A cross-sectional study assessing renal biopsies in 35 males and 24 females found vacuolization of podocytes with males having greater vacuolization and Gb3 inclusions than females (consistent with the general principle that males are more affected in Fabry disease). Proximal tubule, peritubular capillary, and vascular intimal inclusions

and arteriolar hyalinosis was also seen (Fogo et al. 2010). Histopathological examination of Gb3 within the central and peripheral nervous system found Gb3 accumulation in the dorsal root ganglion, substantia nigra and anterior horn cells with degeneration of nerve fibers in the dorsal root entry zone and substantia gelatinosa of the spinal cord (Politei et al. 2016). Renal biopsies that were obtained in 14 untreated Fabry disease patients with median age of 12 years were compared to 9 normal living kidney donor controls. Fabry disease biopsies showed Gb3 inclusions in all glomerular cell types. The volume fraction of Gb3 inclusions in the podocyte increased with age, as did podocyte foot process width. Segmental foot process effacement was present in all glomeruli. The volume fraction and foot process width correlated directly with proteinuria (Najafian et al. 2011). Proteinuria has been found to be a risk factor for worsening renal disease (January 2013). Given the central role of Gb3 inclusion in the progression of FD clinical manifestations, spontaneous clearance of these inclusions is not reasonably expected. Also, the published data from the placebo-arm of two randomized, controlled studies reported no spontaneous regression of renal Gb3 inclusion over the study duration (Thurberg et al. 2002) (Weidemann et al. 2022), corroborating this expected natural history.

Renal Gb3 inclusions do not directly measure clinical benefit. To date, evidence in this rare disease is insufficient to establish that reduction in renal Gb3 inclusions, in and of itself, could reliably predict clinical benefit in FD. The relationship between change in BLISS score and eGFR slope was explored in Study F01/F02/F03. The eGFR slope was calculated based on data obtained over a period ranging from 12 months up to 60+ months. Overall, a larger decline from baseline in renal Gb3 inclusions at Month 6 appeared to be associated with better outcome in eGFR slope. Overall, given knowledge from published literature, the consistent and robust efficacy findings from Study F01/02, indicating PRX102 removed Gb3 from the Fabry target tissue, together with confirmatory evidence of PRX102's treatment effect on eGFR slope seen in Study F20 (discussed below) within the context of this development program, provide assurance PRX102's effect on renal Gb3 inclusions confers clinical benefit.

Confirmatory Evidence:

Study F20: This was a multicenter, randomized, active-controlled, parallel-group study in 77 ERT-experienced adult FD subjects. The primary objective as stated in the protocol was to "evaluate the efficacy of PRX-102 compared to agalsidase beta in Fabry disease patients with impaired renal function." Enrolled subjects were all on agalsidase beta at baseline and randomized 2:1 to either switch to PRX102 or continue treatment with agalsidase beta. Randomization was stratified according to whether the urine protein-to-creatinine ratio (UPCR), a measure of kidney function, was > or < 1 gr/gr, in a binary fashion. Both study products were administered as an intravenous infusion every 2 weeks, at a dosage of 1 mg/kg, for up to 24 months. The primary efficacy endpoint was the annualized rate of change of eGFR (eGFR slope). Of note, eGFR does not directly measure how a patient feels, functions, or survives. However, FDA accepts the demonstration of a sustained treatment effect on the rate of loss of renal function (e.g., as measured by annualized change in estimated eGFR) as the basis for traditional drug approval for FD. The secondary endpoints included change from baseline to all time points in the following measures: plasma globotriaosylsphingosine (Lyso-Gb3), left ventricular mass index (LVMI), plasma

globotriaosylceramide (Gb3), urine Lyso-Gb3, protein/creatinine ratio spot urine test, frequency of pain medication use exercise tolerance (Stress Test), Short Form Brief Pain Inventory (BPI), Mainz Severity Score Index (MSSI) and Quality of life (EQ-5D-5L).

***Comments**: The Applicant originally planned Study F20 as a superiority study of PRX102 compared to agalsidase beta. In April 2021, the Applicant conducted an unblinded interim analysis of study at Month 12, as prespecified in the protocol and intended to support a Marketing Authorization Application (MAA) submission to the European Medicines Agency (EMA). In September 2021, FDA held a Type A End-of-Review meeting with the Applicant to discuss the resubmission of the BLA in response to the CR letter. In the meeting package, the Applicant proposed to change the primary evaluation of Study F20 from superiority to non-inferiority (NI) of PRX-102 compared to agalsidase beta after 24 months of treatment. The Applicant's proposed non-inferiority margin of -3 mL/min/1.73 m2/year was the same as the one used for the interim analysis at Month 12. The Agency stated that this may be a reasonable approach provided there was adequate justification and strong evidence to support this statistical approach. In December 2021, in response to the Applicant's request for concurrence on the proposed NI margin and new primary analysis for Study F20, the Agency indicated non- agreement with the NI margin because of inadequate support on its face but stated this would ultimately be a review issue once the BLA is resubmitted.*

In the CR resubmission, the Applicant relied on the results of the randomized active-controlled Study F20 to establish efficacy of PRX102 for traditional approval. The review team concluded that the Applicant's proposed "non-inferiority" margin (specified in the protocol) was inadequate because the margin was based on the absolute change of eGFR in certain clinical experiences the Applicant posited as clinically meaningful instead of preserving a minimum effect of the comparator compared to placebo. In addition, there were also concerns around constancy assumption (i.e., differences in patient population relative to historic Fabrazyme studies). The randomized, controlled study of agalsidase beta (Fabrazyme) was conducted in a treatment naïve population and primarily in subjects with Classic FD whereas Study F20 was done in treatment experienced patients with just under 50% of enrolled subjects having non-Classic FD. Further, the randomized, controlled study of Fabrazyme evaluated a population with more severe renal impairment relative to Study F20. Because of these important differences in the study populations, the magnitude of drug effect of agalsidase beta in a study population similar to that of Study F20 cannot be sufficiently quantified to determine an NI margin. The review team determined that, while Study F20 could not be used as the one adequate and well controlled study to establish efficacy based on demonstration of non-inferiority to an approved product because of the lack of a definable NI margin, the study results are acceptable as confirmatory evidence to support a single adequate and well-controlled study.

Multiple supportive analyses were conducted by the statistical review team of the Study F20 eGFR slope data. All analyses yielded comparable results between the two treatment arms (Refer to Statistical Review for details). Based on the Applicant's original primary analysis, the estimated mean eGFR slopes were -2.4 and -2.3 mL/min/1.73 m^2/year in the PRX102 and agalsidase beta arms, respectively, and the treatment difference was -0.1 (95% CI: -2.2, 2.1) mL/min/1.73 m^2/year. Based on the ANCOVA adjusted for

continuous baseline proteinuria, the estimated mean eGFR slopes were -2.0 and -3.1 mL/min/1.73 m^2/year in the PRX-102 and agalsidase beta arms, respectively, and the treatment difference was 1.1 (95% CI: -0.8, 3.1) mL/min/1.73 m^2/year. The rationale for performing an analysis adjusting for proteinuria as a continuous covariate is as follows: first, UPCR is known to be a strong predictor of eGFR decline; second, although the binary proteinuria variable appeared balanced between the two treatment arms, there was a noted imbalance in the continuous proteinuria variable and; lastly, baseline proteinuria had the strongest correlation with eGFR slope over 2 years ($r = 0.57$; $p<0.0001$) and was the strongest predictor of Fabry clinical events (HR associated with 1 unit increase was 3.1 (95% CI: 1.6, 5.9; $p<0.001$).

The results of the analyses on eGFR slopes were supported by the analysis of change from baseline in the average eGFR at the last two visits (100 and 104 weeks). The estimated mean changes were -3.0 and -3.8 mL/min/1.73 m^2 in the PRX102 and agalsidase beta arms, respectively. The difference in mean change (PRX102 – agalsidase beta) was 0.8 (95% CI: -3.0, 4.6) mL/min/1.73 m^2 or annualized change of 0.4 (95% CI: -1.5, 2.3) mL/min/1.73 m^2/year.

To interpret the comparable results of the eGFR slope between the two treatment arms, the team considered assay sensitivity. Evidence supporting the expected treatment effect of agalsidase beta in the population studied in Study F20 follows:

- In an observational study, Weideman et al. (2014)[9] showed significant worsening in eGFR and albumin-to-creatinine ratio when in patients who switched to half the normal dose of ERT treatment compared to those who continued the regular dose.
- A long-term observational study showed that Fabrazyme-treated patients had a slower rate of decline in eGFR compared to the untreated patients, as described in the Fabrazyme label. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103979s5309lbl.pdf).
- Study F20: The agalsidase beta arm had point estimates of the mean eGFR slopes ranging from -3.1 to -2.6 mL/min/1.73 m^2/year depending on the analysis used. These estimated slopes were favorable compared to those previously reported for the untreated or placebo-treated patients. This observation was supported by considering the baseline median eGFR values in the placebo and untreated patients relative to those in Study F20. Compared to the patients in Study F20 who had a median baseline eGFR of 73 mL/min/1.73 m^2, overall, the placebo-treated patients in the Fabrazyme phase 4 study had more advanced disease with a median baseline eGFR of 52 mL/min/1.73 m^2 whereas the untreated patients in the observational study had less advanced disease with median baseline eGFR of 93 mL/min/1.73 m^2. Thus, it is reasonable to expect that if a placebo arm were enrolled with patients that had a similar baseline eGFR as those in Study F20, its mean eGFR slope would likely fall between -4.1 and -3.2 mL/min/1.73 m^2/year. There are notable limitations to this comparison including that it relies on non-randomized data from different studies and that the untreated and placebo-treated patients were treatment naïve whereas the patients enrolled in Study F20 were treatment-experienced. Nonetheless, this information helps to contextualize the results in Study F20.

Fabry Clinical Events: The Applicant conducted an analysis of Fabry Clinical Events (FCE = cardiac, cerebrovascular, renal, and non-cardiac death) (one of the secondary endpoints), and the findings were unfavorable for PRX102 compared to agalsidase beta. The Applicant's medical monitor determined whether reported adverse events constituted a Fabry Clinical Event. While the medical monitor was blinded to treatment, there was no adjudication by relevant specialists to ensure robust qualification of these clinical events. This analysis relied on adverse event terms reported during the study that did not provide a granular determination of the FCE for the individual cases. This analysis is especially problematic because all subjects who experienced an FCE were on prior ERT for durations ranging from 4 years to well over a decade and on PRX102 for a relatively short duration when the FCE occurred. The FCEs can take years to develop and may be influenced by many factors (e.g., age and disease severity at first exposure to treatment, history of previous FCEs). Additionally, without a concurrent placebo arm, the role of disease progression leading to these events could not be characterized. Due to these significant uncertainties, it was not possible to reliably conclude whether the imbalance in the FCEs unfavorable to PRX102 could have been attributed to PRX102, prior agalsidase beta treatment, disease progression, chance findings, or some other reasons.

Other lines of confirmatory evidence include the following:

- Plasma lyso-Gb3 reduction in ERT-naïve FD subjects: Plasma globotriaosylsphingosine (lyso-Gb3, a metabolite of Gb3) concentrations are elevated in patients with Fabry disease. Treatment with PRX102 resulted in reductions of plasma lyso-Gb3 concentrations by Week 52 compared to baseline in ERT-naïve patients (studies PB-102-F01/02 and PB-102-03). The individual percentage change from baseline ranged from -5% to -79% at Month 12 across all patients. The PD effect on reductions of plasma lyso-Gb3 demonstrated pharmacological activity of pegunigalsidase alfa in humans. Furthermore, lyso-Gb3 reductions showed statistical correlation with the renal Gb3 inclusion changes from baseline.
- Strong mechanistic support: well-understood pathophysiology of FD (Fabry disease is caused by deficiency of the lysosomal enzyme alpha-galactosidase A) and targeted mechanism of action of therapy (PRX102 provides an exogenous source of alpha-galactosidase A).

Efficacy Conclusion:
Substantial evidence of effectiveness for PRX102 in adult Fabry patients was established with one adequate and well-controlled study with confirmatory evidence. The adequate and well-controlled Study F01/02 demonstrated a large and statistically significant reduction in renal Gb3 inclusions in the peritubular capillaries (PTC) assessed via the BLISS methodology renal Gb3 inclusion score. While there was no placebo control group in this study, knowledge of natural history supports the conclusions that both Gb3

deposition is the cause of the disease manifestations and that Gb3 PTC inclusions do not spontaneously improve. The findings in F01/02 contribute compelling results of the efficacy of PRX102. Confirmatory evidence providing strong support includes the results of Study F20 demonstrating that the annualized eGFR slope in PRX102 group was comparable to that of the comparator (an approved ERT). Additional confirmatory evidence is the reduction of plasma Lyso-Gb3 levels in ERT-naïve patients demonstrating a pharmacologic effect of PRX102 and the clear mechanistic support (well-established pathophysiology of the disease, the targeted mechanism of action of PRX102 as ERT).

Comments:

- *According to the Statistical review dated May 8, 2023: "From a statistical perspective, the team recommends traditional approval of PRX102." We concur with this recommendation.*
- *According to the Clinical review dated May 8, 2023: "In summary, in the context of Fabry Disease as a rare, serious disease with limited therapeutic options that may not be suitable to all individual patients, the review team concludes PRX-102's benefit outweighs its risks when used as recommended in the approved labeling and traditional approval is recommended for the treatment of adults with confirmed Fabry disease". We concur with this recommendation.*

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8. Safety

An integrated assessment of safety (ISS) pooled data across multiple studies included a total of 142 unique FD subjects. The studies that contributed to this integrated safety dataset were: PB-102-F01/02/03, PB-102-F20, PB-102-F30, PB-102-F50/51, PB-102-F60. Refer to the clinical review for more details (Mehul Desai, May 8, 2023).

This integrated safety dataset contains 4875 subject-months of exposure. The mean exposure time was 34.3 months with a maximum exposure duration of 91 months (approximately 7.5 years). The review team considered this safety database adequate, especially in the context of a rare disease. The mean age of subjects in the integrated safety dataset was 42.5 years (range 17 to 60 years). Two-thirds of subjects were male. 133 (94%) of the subjects were white.

There were 4 deaths in the PRX102 program. None of the deaths are considered related to the drug.

The most frequently reported adverse events in the ISS data set are nasopharyngitis (25%), fatigue (21%), headache(20%), back pain (19%), cough (18%), diarrhea (18%), pain in extremity (16%), nausea (16%), upper respiratory tract infection (15%), vomiting (15%), arthralgia (13%), pyrexia (13%), abdominal pain (12%), sinusitis (11%), dizziness (11%), oropharyngeal pain (11%) and rash (11%).

Hypersensitivity reactions are associated with ERTs. As such the clinical reviewer conducted an analysis using both broad and narrow hypersensitivity FMQs. Most adverse events in subjects who experienced a hypersensitivity were considered non-serious and were classified as mild to moderate in severity. See the Table below for details:

Table 1 Summary of Hypersensitivity FMQ, Infusion Reactions and other related FMQ's (Integrated dataset)[1]

FDA Medical Query	Scope	PRX-102 (N = 142)
Hypersensitivity	Broad	54 (38%)
Local Administration Reaction	Broad	23 (16.2%)
Bronchospasm	Broad	17 (12%)
Dyspnea	Broad	11 (7.7%)
Anaphylactic Reaction	Broad	9 (6.3%)
Pruritus	Broad	8 (5.6%)
Erythema	Broad	7 (4.9%)
Angioedema	Broad	6 (4.2%)
Local Administration Reaction	Narrow	23 (16.2%)
Dyspnea	Narrow	11 (7.7%)
Hypersensitivity	Narrow	10 (7%)
Pruritus	Narrow	8 (5.6%)
Erythema	Narrow	7 (4.9%)
Bronchospasm	Narrow	5 (3.5%)

1 Source: Medical Officer Review

A total of 43 subjects experienced at least 1 SAE while on treatment with PRX102. Five subjects experienced a serious adverse reaction related to PRX102, all of which were associated with drug infusion. Four of the five subjects met Sampson's criteria for anaphylaxis. All four cases of anaphylaxis occurred with the first infusion of PRX102 (3 were ERT-experienced (Fabrazyme, Replagal) and one was ERT-naïve). Anaphylaxis is a known risk with enzyme replacement therapies. The labeling will include a boxed warning for the risk of hypersensitivity reactions including anaphylaxis and will also provide guidance for health care providers

[1] Source: Medical Officer Review

on risk mitigation and patient management. The 5th subject developed rigors within minutes after infusion completed and was hospitalized for observation.

***Comments**: Observed cases of severe anaphylaxis adverse drug reactions in the small safety database of PRX102 confirm the existence of this serious risk with PRX102. Consistent with the Division's current labeling practices the ERT drug class, labeling for PRX will include a boxed warning for severe anaphylaxis in the label.*

Additionally, there was a subject who developed a severe TEAE considered treatment related. In Study F20, a subject developed membranoproliferative glomerulonephritis while on PRX102. A kidney biopsy obtained as part of the work-up for the subject's persistent proteinuria, confirmed immune complex mediated membranoproliferative glomerulonephritis (MPGN) with subendothelial IgG deposits as well as lambda and kappa immunoglobulin deposits. Immune complexes found in capillary and endothelial cells tested positive for alpha galactosidase. This severe TEAE led to interruption of treatment but not to study discontinuation. Its onset was on Day 647 of the study, and its status was "Recovering/Resolving" at the end of follow-up. This patient experienced 14 other AEs, including a moderate event of proteinuria on Day 550. The drug label will include a Warning/Precaution for MPGN to inform clinicians to consider MPGN in cases of acute deterioration in renal function.

Study F20:

There were no significant differences between the two arms in terms of hypersensitivity reactions or infusion-associated reactions. The terms that occurred with an incidence of greater than 10% on PRX-102 include infusion associated reaction, nasopharyngitis, headache, cough, dizziness, nausea, diarrhea, sinusitis, abdominal pain, fatigue, proteinuria, pyrexia, bronchitis, upper respiratory tract infection, rash, muscle spasm and urinary tract infection. Given the small sample size and the nature of some of these adverse events, drug causality is uncertain for some of these events. It should be noted that it is challenging to reliably compare the safety between PRX102 and agalsidase beta because all enrolled subjects in the study were agalsidase beta-treated at baseline for years,

Immunogenicity

Baseline. Pre-existing anti-pegunigalsidase alfa IgG antibodies (IgG ADA) were detected at baseline in patients with Fabry disease, with higher incidence in patients previously treated with Fabrazyme than previously treated with Replagal or ERT-naive patients, 34.6%, 9.1% and 11.1%, respectively. Cross-reactivity of antibodies to anti-Fabrazyme, anti-Replagal, and anti-pegunigalsidase alfa were indicated. In the ERT-experienced patients who were tested at baseline for anti-Fabrazyme or anti-Replagal antibodies in

addition to anti-pegunigalsidase alfa antibodies, it was found that the patients who had pre-existing anti-pegunigalsidase alfa IgG antibodies also had anti-Fabrazyme or anti-Replagal antibodies before switching to pegunigalsidase alfa treatment.

Post-baseline. The percentage of patients having post-baseline IgG ADA following 1 mg/kg Q2W administration was similar cross the 3 patient populations (ERT-Fabrazyme experienced patients, ERT-Replagal experienced patients, and ERT-naïve patients), 38.5%, 35%, and 31.3%, respectively. Among those patients who had positive anti-pegunigalsidase alfa IgG antibodies, antibody specificity was predominantly (80% to 100%) directed against the non-PEGylated enzyme moiety (anti-BCL) of pegunigalsidase alfa across the patient population, and neutralizing antibodies (NAb) inhibiting enzyme activity was detected in 75%, 28.6% and 60% of the 3 patient populations, respectively. In addition, anti-pegunigalsidase alfa IgG antibodies were developed more in male patients than in female patients at baseline and post-baseline.

Immunogenicity effect on PK. The development of ADA significantly decreased pegunigalsidase alfa exposures (e.g., AUC and Cmax), which is associated with high ADA IgG titer.

Immunogenicity effect on efficacy and PD biomarker. Plasma Lyso-Gb3 levels at baseline and post-treatment were higher in ADA positive patients compared to ADA negative patients, especially in male patients. However, it appears that ADA responses had no apparent effect on efficacy (kidney Gb3 inclusions and eGFR slope) after pegunigalsidase alfa treatment.

Immunogenicity effect on safety. In ERT-naïve and ERT-experienced patients (studies F01/02 and F20, respectively), patients who experienced serious hypersensitivity reactions during the first infusion were positive for IgE ADA. Other IARs occurred more frequently in IgG ADA positive patients compared to IgG ADA negative patients. However, there were no apparent unique safety issues associated with pegunigalsidase alfa immunogenicity.

Safety Conclusion

The safety and immunogenicity profile of PRX102 are in line with what is expected of an ERT. The safety data from both the integrated safety analysis and from Study F20 demonstrate that hypersensitivity reactions including anaphylaxis are a risk when taking this product. One subject experienced membranoproliferative glomerulonephritis determined to be related to PRX102. The important risks of PRX102 can be adequately mitigated with labeling.

9. Advisory Committee Meeting

An advisory committee meeting was not deemed necessary for this BLA resubmission as expert advice was not needed to finalize the regulatory decision.

10. Pediatrics

N/A.

11. Other Relevant Regulatory Issues

Pediatric Study under the Pediatric Research Equity Act (PREA): The PRX102 application triggered PREA. Because this application is ready for approval in adults, a pediatric study with PRX102 in pediatric patients 2 to <18 years old will be deferred (see PMR 1). FDA has granted a waiver for pediatric patients younger than 2 years old because children in this age group are typically asymptomatic and studies in them will likely be infeasible.

12 Labeling

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes incorporated into the finalized PI (see Table 2). The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 2. Key Labeling Changes and Considerations

Full Prescribing Information Sections[1]	**Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)[2]**
All Sections	Approximately 28% of the active control arm treated patients in Trial 1 were treated with non-US-approved agalsidase beta at non-US sites. The statistical team analyzed the eGFR data both with and without the non-US subjects and determined the results of the eGFR analysis comparison between ELFABRIO and the US-approved/non-US-approved agalsidase beta arm did not substantially differ in the two analyses. This review issue was discussed with OND Policy, and they advised that in light of these factors and the review team's consideration of other specific issues presented by this application (i.e.., the role of the F20 study results in support of the application) that there was not an established policy that would otherwise require requesting additional bridging data in this situation. Therefore, the review team determined that reference to the partial use of non-US approved agalsidase beta product in the Prescribing Information is not necessary for the safe and effective use of the product by healthcare providers.
BOXED WARNING	Like other ERTs, the safety data from both the pooled analysis and from trial F20 demonstrate that hypersensitivity reactions including anaphylaxis are a risk when taking this drug product. The Division has required all newly approved ERTs to have a Boxed Warning (BW) for hypersensitivity reactions including anaphylaxis. Therefore, a BW for Elfabrio is consistent with our current risk mitigation approach for this serious adverse reaction.
1 INDICATIONS AND USAGE	Accepted applicant's proposed indication that ELFABRIO is indicated for the treatment of adults with confirmed Fabry disease.
2 DOSAGE AND ADMINISTRATION	2.1 Recommendations Prior to Elfabrio Treatment • Created sub-section to include pre-treatment information specific to ERT-experienced and naïve patients per the *Guidance for Industry-Dosage & Administration Section of Labeling for Human*

	Prescription Drug and Biological Products-Content and Format. 2.2 Recommended Dosage and Administration (b) (4) [redacted] • Added instructions for healthcare providers to follow should the bi-weekly dose of Elfabrio be missed. 2.3 Dosage and Administration Modifications Due to HSR's and IAR's. • Re-worded instructions in the event of a mild to moderate hypersensitivity reaction or a mild to moderate IAR to ensure clarity. • Included additional dosage modification instructions to mitigate the risk of IAR's. 2.4 Preparation Instructions • Re-organized information and text for clarity on preparation instructions for Elfabrio. 2.5 Storage of the Diluted Solution • Edits made to streamline the presentation of the storage information for Elfabrio. • Included recommendations pertaining to use after removal from the refrigerator (e.g., within how many hours must it be infused) and discard instructions if not used. • Included statement "Do not freeze or shake" as no data were submitted to support freezing or shaking of the drug product in the infusion bag. 2.6 Administration Instructions • Revised Table 1 to reflect the initial infusion rate for ERT-experienced patients and created Table 2 to reflect the initial infusion rate for ERT-naïve patients as the duration of infusion rates for the initial and maintenance phase in the clinical trials was longer for the ERT-naïve patients.
4 CONTRAINDICATIONS	• No contraindications were proposed for ELFABRIO PI.
5 WARNINGS AND PRECAUTIONS	5.1 Hypersensitivity Reactions Including Anaphylaxis • Included steps for re-administering ELFABRIO following severe HSR's.

	• Removed [redacted] (b) (4) 5.3 Membranoproliferative Glomerulonephritis • Include glomerulonephritis as a Warning and Precaution as it was determined that this risk is serious and clinically significant and could have implications for prescribing decisions or patient management. Risk mitigation steps included appropriate monitoring for this adverse reaction.
6 ADVERSE REACTIONS	6.1 Clinical Trials Experience • The review team based the safety evaluation on data from Trial 2 which included 52 patients with Fabry disease treated with ELFABRIO. • Re-organized subsection 6.1 to align with the *Guidance for Industry-Adverse Reactions Section of Labeling for Human Prescription Drug & Biological Products-Content and Format*. • Re-focused sub-section 6.1 on the adverse reaction profile for Trial 2 given that this was the randomized controlled study that included the to be recommended dosage. • Included text on the study design and exposure for Trial 2 and revised Table 3 to only include common adverse reaction data from Trial 2. Cross-referenced the Clinical Studies section for the baseline demographics and important baseline disease characteristics. • Included in the title for Table 2, a description of data sources to indicate the type of study from which the information in the table was derived. • Included group term information under Table 2 for hypersensitivity and infusion-associated reactions as well as component term information in the common adverse reaction table. • Added glomerulonephritis membranoproliferative as a separate heading as a basis exists to believe there is a causal relationship between the drug and the adverse event. • Included an immunogenicity heading for anti-drug antibody-associated adverse reactions.
7 DRUG INTERACTIONS	• N/A
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.1 Pregnancy • Revised Applicant proposed language to align with Pregnancy and Lactation Labeling Rule and ensure consistency with other recently approved ERT's. 8.2 Lactation • Revised Applicant proposed language to align with Pregnancy and Lactation Labeling Rule and ensure consistency with other recently approved ERT's. 8.4 Pediatric Use

	• Re-numbered sub-section to 8.4 instead of 8.3 as applicant proposed. The Pediatric Use sub-section is represented by 8.4. 8.5 Geriatric Use • Revised Applicant proposed language to align with the *Guidance for Industry-Content and Format for Geriatric Labeling*. 8.6 Patients with Prior Enzyme Replacement Therapy • Created sub-section 8.6 as the effect of pre-existing ADA due to prior ERT treatment on PK/PD was determined to be clinically meaningful and pertinent to informing relevant clinical management strategies for patients with prior ERT.
9 DRUG ABUSE AND DEPENDENCE	N/A
10 OVERDOSAGE	N/A
12 CLINICAL PHARMACOLOGY	12.2 Pharmacodynamics • Modified this sub-section to report PD data separately for male and female patients because the PD responses were different between male and female patients in Trial 2. • Added a statement about unknown exposure-response relationship. 21 CFR 201.57(c)(13)(i)(B) requires that 'Exposure-response relationships (e.g., concentration-response, dose-response) must be included if known.' If the information is unknown, this subsection must contain a statement about the lack of information. 12.3 Pharmacokinetics. • Reported PK parameters from Trial 1 as the PK data in treatment-naïve patients better describes the PK properties of pegunigalsidase alfa. Reported the exposure (Cmax and AUC) information from Trial 2 to facilitate the interpretation of the efficacy and safety results. • Added a metabolism heading to provide relevant information about metabolic degradation. 12.6 Immunogenicity • Created subsection as recommended in Guidance for Industry-*Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling* to contain immunogenicity information • Updated the immunogenicity information based upon data from Trial 1 and 2 and to align with the *Guidance for Industry Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling-Content and Format*
13 NONCLINICAL TOXICOLOGY	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility • Revised Applicant proposed language to ensure consistency with other recently approved

	ERT's.
14 CLINICAL STUDIES	• Started this section with a description of Trial 2 (i.e., F01/02) followed by a description of Trial 1 (i.e., F20). • Added additional details such as dose, dosing frequency, and route of administration for agalsidase beta • Added baseline disease characteristics including who discontinued from the studies and the reasons for discontinuation. More specifically, focused the reporting of baseline disease characteristics and demographics from those patients on the recommended dosing regimen. • Included baseline renal disease characteristics so healthcare providers can improve interpretation of results as the primary endpoint is a measure of renal function. • Included baseline mean (SD) eGFR values when describing the results of the clinical studies. • Included additional information about the meaning of the efficacy endpoint of mean annualized eGFR change from baseline after 24 months as healthcare providers who treat these patients may not be familiar with this endpoint. • To minimize confusion, removed [redacted] (b) (4) • Added percentage of patients in each racial group per *Guidance for Industry Collection of Race and Ethnicity Data in Clinical Trials (October 2016)*. Ethnicity data were not available to include in the Prescribing Information.
17 PATIENT COUNSELING INFORMATION	Revised for consistency with the revisions to the Full Prescribing Information focusing on major risks of the drug (e.g., W&P), and when appropriate, how the patient may mitigate or manage these risks.

Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	3 Dosage Forms and Strengths Revised presentation of information for this sub-section. 11 Description • Revised inactive ingredient list by using established names for drugs (i.e., drug products and ingredients) which required recalculation of quantitative amount based on USP monograph definition. 16 How Supplied/Storage and Handling • Added full expression of strength as this product is in solution. • Moved storage of diluted solution to under Section 2 Dosage & Administration

[1] The product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved. The finalized PI was compared to the Applicant's draft PI.

12. Post marketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No REMS are required for PRX102.

Post marketing Requirements (PMRs) and Commitments (PMCs)

PMR 3972-1: Clinical trial to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamic effects of pegunigalsidase alfa-iwxj in pediatric patients aged 2 to <18 years with confirmed Fabry disease. The trial will evaluate patients over at least 1 year from the time of enrollment and will include assessments of immunogenicity and correlative analyses between antibody formation (and titers if appropriate) and safety, efficacy, pharmacokinetics, and pharmacodynamics in treated patients.

PMR 3972-2: Conduct a worldwide descriptive study that collects prospective and retrospective data in women and their offspring exposed to ELFABRIO (pegunigalsidase alfa-iwxj) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

PMR 3972-3: Develop and validate an assay for detection of neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa-iwxj.

PMR 3972-4: Develop and validate an anti-PEG IgE antibody assay.

PMR 3972-5: Improve the current anti-pegunigalsidase alfa-iwxj IgG antibody assay or develop a new assay to improve the drug tolerance. Validate the assay.

PMR 3972-6: Revise and re-validate the anti-pegunigalsidase alfa-iwxj IgM antibody assay with anti-pegunigalsidase alfa-iwxj IgM antibodies to be used as positive controls.

PMR 3972-7: Evaluate neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa-iwxj in clinical samples from studies PB-102-F01/02, PB-102-F03, and PB-102-F20 using the assay developed and validated under PMR 3972-3. Assess the impact of cellular uptake neutralizing antibodies on the pharmacokinetics, pharmacodynamics, efficacy, and safety of pegunigalsidase alfa-iwxj.

PMR 3972-8: A pre- and postnatal development study in rats treated with pegunigalsidase alfa-iwxj.

PMC 3972-9: Conduct a 13-week repeat-dose pharmacokinetic and pharmacodynamic (PK/PD) study in α-galactosidase deficient (αGAL KO) mice to evaluate changes in the GL3 biomarker in plasma and in the kidney, skin, heart, brain, spleen, and liver in relation to treatment with pegunigalsidase alfa. Correlate reductions in GL3 with pharmacokinetic exposures to pegunigalsidase alfa in this study.

PMC 3972-10: Conduct a drug product (DP) shipping validation study using the first three commercial shipments of final finished DP vials from Chiesi Farmaceutici (Parma, Italy) to Chiesi USA (Cary, NC, USA). Include at minimum the following testing on DP samples at release and post-shipping: appearance by visual inspection, particulate matter, non-denatured and denatured SE-HPLC, peptide map purity assay, enzyme kinetics assay, protein content and container closure integrity.

PMC 3972-11: Improve and revalidate the peptide mapping purity method for the drug substance and drug product to quantify the relative concentrations of product-related substances. Characterize oxidized product-related substances and identify those that may be

critical quality attributes or stability-indicating; update the drug substance and drug product specifications accordingly with quantitative acceptance criteria for the relevant substances.

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13. Recommended Comments to the Applicant

N/A

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 761161 (Class 2 Re-submission)
Supplement #:	NA
Drug Name:	ELFABRIO (Pegunigalsidase alfa, PRX-102)
Indication(s):	Fabry disease
Applicant:	Chiesi
Date(s):	Submitted: 11/09/2022 Review Completion Goal Date: 04/01/2022 PDUFA Goal date: 05/09/2023
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Yared Gurmu, Ph.D.
Concurring Reviewers:	Yan Wang, Ph.D., Team Leader
Medical Division:	Division of Rare Diseases and Medical Genetics
Clinical Team:	Mehul Desai, MD Sheila Farrell, MD, Team Leader
Project Manager:	Diego Diaz

Keywords: Fabry disease, active-controlled trial

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1 EXECUTIVE SUMMARY

This resubmission to a previous Complete Response of Biologic License Application (BLA) 761161 seeks approval of PRX-102 (pegunigalsidase alpha), an enzyme replacement therapy, for the treatment of Fabry disease. Fabry disease (FD) is an X-linked, slowly progressive, lysosomal disease affecting both males and females which has progressive, detrimental effects on tissue structure and organ function.

The Agency's statistical evaluation of efficacy for the PRX-102 program relied primarily on two trials, PB-102-F20 and PB-102-F01/F02. PB-102-F01/02 consisted of a dose-ranging portion (F01) of three doses of PRX-102, followed by a single-arm, open-label extension (F02). PB-102-F01/02 provided safety data and efficacy data on histological decrease in accumulated globotriaosylsphingosine (Gb3) substrate in kidney peritubular capillaries (PTC) at 6 months. PB-102-F20 was a two-year, phase 3, double-blind, active-controlled trial providing data on kidney function as measured by the estimated glomerular filtration rate (eGFR) slope and other efficacy outcomes, as well as additional safety data.

In trial PB-102-F01/F02, 19 patients were initially enrolled into one of three PRX-102 treatment groups (0.2, 1.0 or 2.0 mg/kg) and received IV infusions every 2 weeks for 12 weeks. Study F02 (extension study of F01) enrolled 16 patients that were treated with 1.0 mg/kg dose of PRX-102 every 2 weeks for 9 months. After 6 months of treatment with PRX-102, among the 14 patients who had evaluable data on Gb3 inclusions, the observed median percent reduction compared to baseline in the average number of Gb3 inclusions per PTC was -78% (95% CI: -86%, -53%); the mean absolute reduction compared to baseline was -3.1 (95% CI: -4.8, -1.4). Additionally, eleven out of 14 patients had at least 50% reduction in Gb3 from baseline (ranged from -53% to -95%). Notable limitations of this trial are the small sample size, the lack of a control arm, and reliance on a biomarker as a surrogate outcome. However, given the historical data showing the absence of spontaneous reduction in Gb3 inclusions for untreated patients with Fabry disease and the significant reductions in the plasma lyso-Gb3 over a 2-year period for all patients in Study PB-102-F01/F02/F03, the observed mean reduction in the Gb3 inclusions was unlikely due to chance and thus provides compelling evidence of a true drug effect on this outcome. The renal Gb3 endpoint is not a clinical endpoint and there is limited clinical data to empirically evaluate that an effect on this endpoint will reliably predict an effect on the clinical outcomes of interest (i.e., decline in kidney function) due to the rarity of the disease. However, the compelling drug effect on this endpoint is clinically relevant given the following published literature on the central pathophysiologic role of Gb3 accumulation in Fabry disease: (1) when it accumulates, the Gb3 substrate is toxic to tissues and causes damage to organ systems, (2) Gb3 accumulates in tissues/organs which exhibit structural damage and functional impairment due to Fabry disease, and (3) the degree of accumulation of the substrate appears to correlate with the degree of damage in renal tissue. Therefore, in the context of the supporting efficacy results from Trial PB-102-F20, we consider this trial to be adequate and well-controlled and contribute to substantial evidence of effectiveness for PRX102.

Trial PB-102-F20 was a randomized, double-blind, active-controlled trial in N = 77 Fabry patients randomized (2:1) to PRX-102 or Fabrazyme and followed for two years for eGFR slope. Though eGFR is also not a direct measure of how a patient feels, functions, or survives, it has previously been determined and described in published guidance on drug development in Fabry disease that Sponsors can use the demonstration of a sustained treatment effect on the rate of loss of renal function (e.g., as measured by annualized change in estimated eGFR) as the basis for traditional drug approval. Based on the Applicant's primary analysis adjusted for the binary baseline proteinuria (< 1 vs ≥ 1 gr/gr), the estimated mean eGFR slope between the two arms were comparable (-2.4 for PRX-102 and -2.3 for agalsidase beta), and the estimated treatment difference was -0.1 (95% CI: -2.3, 2.1) mL/min/1.73 m^2/year. These comparable results were supported by the review team's post-hoc analysis adjusted for the continuous baseline proteinuria. This analysis yielded the estimated mean eGFR slopes of -2.0 and -3.1 mL/min/1.73 m^2/year in the PRX-102 and agalsidase beta arms, respectively, and the treatment difference of 1.1 (95% CI: -0.8, 3.1) mL/min/1.73 m^2/year. Despite these comparable results, this trial cannot support a non-inferiority claim due to the lack of data to support a non-inferiority margin for agalsidase beta. However, based on evaluating the assay sensitivity issue using external data, the review team considers the comparable rates of decline in eGFR between the treatment arms to be informative and supportive of efficacy of PRX-102.

The complete safety evaluation was conducted by the clinical reviewer, Dr. Mehul Desai. Based on the information collected, the safety profile of PRX-102 was generally consistent with the known safety profile of other ERTs. The main safety concerns identified were the risks of severe hypersensitivity reactions which will be adequately mitigated through product labeling with a boxed warning for severe hypersensitivity reactions, and further evaluated through routine pharmacovigilance. Although there was a numerically higher proportion of Fabry Clinical Events (FCE) in the PRX-102 arm compared to the agalsidase beta arm, there was considerable uncertainty around the estimates due to the small number of subjects experiencing an event and the process of identifying and evaluating potential FCE events was not robust.

FDA generally requires evidence of effectiveness from at least two adequate and well-controlled trials to support new drug approval. However, there are circumstances where substantial evidence of effectiveness may be established based on one adequate and well-controlled clinical investigation and confirmatory evidence[1]. Furthermore, when the disease is rare, the small population calls for appropriate flexibility and presents additional considerations, including the feasibility of trial design, sample size, and endpoints, using methods and thresholds for demonstrating substantial evidence that are appropriate to these settings. In the context of this rare disease submission, the evaluation of substantial evidence of effectiveness is based on one adequate and well-controlled trial (PB-102-F01/F02) with long-term follow up, and confirmatory evidence from a randomized, double-blind, active-controlled trial (PB-102-F20). Additional confirmatory evidence comes from the well-established etiology of the disease, and the mechanism of action of PRX-102 as discussed in the clinical review. Considering the trials together and incorporating information from other disciplines, the statistical team concluded that

[1] Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, Guidance for Industry https://www.fda.gov/media/133660/download

this BLA provided substantial evidence of effectiveness for PRX102. From a statistical perspective, the team recommends traditional approval of PRX102.

2 INTRODUCTION

2.1 Overview

2.1.1 Background

Fabry disease (FD) is an X-linked, slowly progressive, lysosomal disease affecting both males and females. With an estimated incidence of 1:40,000-1:117,000,[2] it is the second most common lysosomal storage disorder after Gaucher disease. FD is caused by biallelic variants in the *GLA* gene, which encodes the lysosomal enzyme alpha-galactosidase A (alpha-Gal A) that breaks down the glycosphingolipid globotriaosylceramide (Gb3) in lysosomes. Pathogenic *GLA* variants result in complete or partial deficiency of alpha-Gal A, which in turn causes progressive intralysosomal accumulation of the substrate glycosphingolipids globotriaosylceramide (Gb3) and its metabolite globotriaosylsphingosine (lyso-Gb3) in vascular, endothelial, epithelial, smooth muscle, and ganglion cells[1,3] of the kidneys, cardiovascular system, cerebrovascular system, gastrointestinal (GI) tract, peripheral nerves, and skin. Major causes of mortality in FD include life-threatening cardiovascular (sudden cardiac death, arrhythmias, myocardial infarction) and cerebrovascular complications (stroke). The cardiovascular manifestations can include hypertension, left ventricular hypertrophy, and ischemic heart disease, which can progress to heart failure, myocardial infarction, or arrhythmias.[4]

Currently, one enzyme replacement therapy, Fabrazyme, is approved for the treatment of Fabry disease. Fabrazyme received initial approval (accelerated approval) in 2003 and received full approval in March 2021 under an efficacy supplemental BLA (BLA 103979/S-5309) based on evidence establishing that the reductions in Gb3 predict clinical benefit in the context of the Fabrazyme drug development program. The full approval was supported by a phase 3 trial, a phase 4 trial, and a long-term observational study (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103979s5309lbl.pdf) as well as other clinical studies and published literature.

[2] Germain, DP, 2010, Fabry disease, Orphanet J Rare Dis, 5:30, doi: 10.1186/1750-1172-5-30.

[3] Spada, M, S Pagliardini, M Yasuda, T Tukel, G Thiagarajan, H Sakuraba, A Ponzone, and RJ Desnick, 2006, High incidence of later-onset fabry disease revealed by newborn screening, Am J Hum Genet, 79(1):31-40

[4] Patel, MR, F Cecchi, M Cizmarik, I Kantola, A Linhart, K Nicholls, J Strotmann, J Tallaj, TC Tran, ML West, D Beitner-Johnson, and A Abiose, 2011, Cardiovascular events in patients with fabry disease natural history data from the fabry registry, J Am Coll Cardiol, 57(9):1093-1099.

PRX-102 (pegunigalsidase alpha) is being developed as an enzyme replacement therapy for treatment of Fabry Disease. It is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme. It is a PEGylated, recombinant human alpha-Gal-A enzyme that is expressed in plant (Nicotiana tabacum Bright Yellow 2, BY2) cells.

The proposed indication the sponsor is seeking is "ELFABRIO is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme indicated for the treatment of adults with confirmed Fabry disease."

2.1.2 History of Drug Development

PRX-102 was developed under IND 110161. Table **1** below summarizes key regulatory interactions between FDA and the Applicant prior to the original BLA submission.

Table 1: Key Pre-Submission Regulatory Activity

Date	Interaction	Topic
July 15, 2012	IND safety review	Placed on clinical hold because of insufficient nonclinical information
August 9, 2012	IND allowed to proceed	Clinical hold was removed after the Division accepted follow up information by the Applicant
November 3, 2015	End of Phase 2 meeting	The proposed phase 3 study would be adequate to support a BLA
January 23, 2016	Special protocol assessment (SPA) was requested for trial F20	No-agreement letter was issued on March 11, 2016, including the following comments: "We understand that at one year, tests for non-inferiority will be performed for purposes of submitting a marketing application to the European Medicines Agency. However, as stated in the November 3, 2015, End-of-Phase-2 meeting minutes, the current labeling for Fabrazyme does not include a claim of clinical benefit based on eGFR. Therefore, demonstrating noninferiority to Fabrazyme will not provide sufficient evidence of clinical benefit in the US because you are not studying PRX-102 against a comparator that has demonstrated a clear clinical benefit. Specifically, for a non-inferiority study to be interpretable, one would need to know that Fabrazyme was effective in slowing the loss of renal function and have a reliable estimate of the size of the treatment effect. Instead, a study design to demonstrate superiority to Fabrazyme could be acceptable to support regular approval." Note: The effect of Fabrazyme on slowing the decline of eGFR was shown in a long-term observational study which was included in the Fabrazyme's labeling in 2021 when Fabrazyme received traditional approval.

September 5, 2017	Response to FDA requested for information	Final protocol for trial F20 was included in this submission.
January 29, 2018	Fast Track Designation	Applicant was granted Fast Track Designation
February 27, 2019	Type C meeting	The Agency agreed that the Applicant can use the Accelerated Approval Pathway based on histological reduction of Gb3 in kidney peritubular capillaries in treated patients from trials PB-102-F01/F01. The proposed confirmatory trial would be the ongoing F20 trial which would assess superiority of PRX-102 to Fabrazyme on the mean eGFR slope over 24 months
October 15, 2019	Pre-BLA meeting	The Agency asked the Applicant to provide individual graphical patient profiles on the Gb3 scores over time and more details in the immunogenicity section of the BLA. Note: This submission included a draft SAP (dated Sept. 5, 2019) for superiority trial F20. For the primary endpoint of eGFR slope, the SAP stated that the primary analysis would be based on a linear mixed-effect model and a 2-stage analysis (i.e., at the first stage, the eGFR slope for each subject was derived and at the second stage, the treatment comparison in the mean slopes would be conducted using an ANCOVA) would be used as supportive analysis. The Agency recommended the 2-stage analysis as the primary analysis and the Sponsor's proposed primary analysis based on the linear mixed-effect model as a supportive analysis because the former relied on fewer assumptions.
January 29, 2020	Pediatric Study Plan	Agreed iPSP was accepted

On May 27, 2020, the Applicant submitted the original BLA 761161 for an accelerated approval of PRX-102 (pegunigalsidase alfa) for treatment of Fabry disease. In the original submission, the Agency's efficacy evaluation of PRX-102 was primarily based on data from the single-arm, open-label trial PB-102-F01/F02. On April 27, 2021, the Agency issued a Complete Response (CR) Letter outlining deficiencies pertaining to 1) issues with the manufacturing facility and 2) PRX-102's eligibility for accelerated approval following the traditional approval of an available alternative therapy (Fabrazyme) for Fabry disease and the inability of the Agency to determine if PRX-102 provided a therapeutic advantage over the available therapy.

In April 2021, the Sponsor conducted an unblinded interim analysis of trial F20 based on 12-month data (see page 111 of the meeting package at \\CDSESUB1\evsprod\BLA761161\0053). This interim analysis was specified in the protocol and intended to support a Marketing Authorization Application (MAA) submission to the European Medicines Agency (EMA).

On July 26, 2021, the Applicant requested a Type A End-of-Review meeting to discuss the resubmission of the BLA in response to the CR letter. This meeting was held on September 9, 2021. In their meeting package, the Applicant proposed to change the primary evaluation of trial

F20 from superiority to non-inferiority (NI) of PRX-102 compared to Fabrazyme after 24 months of treatment. The proposed NI margin of -3 mL/min/1.73 m^2/year was the same as the one used for the interim analysis based on the 12-month data. The following is the Agency's response to the proposed NI comparison:

> *Yes, your plan to evaluate for PRX-102 non-inferiority to Fabrazyme on eGFR slope at 2 years may be a reasonable approach provided that adequate justification and strong evidence support such a statistical approach. We agree that a meeting prior to data lock will be important in order to discuss and come to agreement on the criteria to demonstrate non-inferiority and associated statistical considerations. We remind you that if substantial evidence of efficacy will be based on a single adequate and well-controlled trial, additional confirmatory evidence must also be provided to support substantial evidence of effectiveness.*

On December 2, 2021, the Applicant submitted a Type C meeting package to seek Agency's agreement on the adequacy of their proposed NI margin and new primary analysis for trial F20 (\\CDSESUB1\evsprod\BLA761161\0053; this submission included the draft SAP dated Nov. 28, 2021). The Agency did not agree with the NI margin because it was not adequately supported by the submitted literature. Nonetheless, the Agency indicated that NI comparison of PRX-102 to Fabrazyme would be a review issue in the BLA resubmission. In addition, for the primary efficacy evaluation, the Applicant proposed to change the primary endpoint from the mean eGFR slope to the median eGFR slope. The Applicant proposed a quantile regression analysis (adjusted for the randomization stratification variable of baseline proteinuria) to analyze the median eGFR slope. To support their proposed analysis, the Applicant cited the paper by Oritz[5] et al. (2021) that used a quantile regression analysis to estimate the treatment effect of agalsidase beta in slowing glomerular filtration rate loss in treatment-naïve patients with classic Fabry disease. The Agency recommended the unadjusted regression analysis as the primary analysis for the median slope due to concerns about a potential non-collapsibility issue.

The sponsor re-submitted the BLA in November 2022 seeking full approval of PRX-102 based on additional efficacy the data from PB-102-F20 study.

2.1.3 Studies Reviewed

The statistical evaluation of efficacy for the PRX-102 program relied primarily on two trials:

[5] Ortiz A, et al. Agalsidase beta treatment slows estimated glomerular filtration rate loss in classic Fabry disease patients: results from an individual patient data meta-analysis. Clin Kidney J. 2020 May 22;14(4):1136-1146. doi: 10.1093/ckj/sfaa065.

1. **Trial PB-102-F01/F02/F03:** A single-arm trial providing efficacy data on histological decrease in accumulated Gb3 substrate in kidney peritubular capillaries (PTC). Study PB-102-F01 was a safety, tolerability, and dose-ranging study (0.2, 1, and 2 mg/kg) with a duration of 3 months. Study PB-102-F02 was an extension of study PB-102-F01 with an additional duration of 9 months where patients continued to receive the same dose as in study PB-102-F01. Study PB-102-F03 was an extension study of PB-102-F02 with a duration of up to 60 months.

2. **Trial PB-102-F20:** A randomized, double-blind, parallel-group, active-controlled, multicenter trial providing efficacy data on eGFR slope. Eligible patients were treated with agalsidase beta for at least 1 year prior to study entry. Patients were randomized 2:1 to receive PRX-102 (1 mg/kg infusion) or agalsidase beta (1 mg/kg infusion) product every 2 weeks for 104 weeks.

The Applicant had conducted additional studies to evaluate the efficacy PRX-102. A high-level summary of the efficacy results of these additional studies is provided in Appendix 5. Given the lack of concurrent control arm in these studies and lack of data on the expected trajectory of eGFR in the absence of treatment, the interpretation of the efficacy findings from these studies was limited.

2.2 Data Sources

BLA761161 was originally submitted on May 27, 2020, and the data and clinical study reports are located at: \\CDSESUB1\evsprod\BLA761161\0001.

The final Gb3 efficacy data for Trial PB-102-F01/F02 were submitted on November 4, 2020 and are located in: \\CDSESUB1\evsprod\BLA761161\0025.

The data and clinical study report for PB-102-F20 were submitted to the Agency on August 23, 2022 and are located at: \\CDSESUB1\evsprod\BLA761161\0057.

BLA 761161 was resubmitted on November 9, 2022 and the data and clinical study reports are located at: \\CDSESUB1\evsprod\BLA761161\0058.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The efficacy data for Trial PB-102-F01/F02 were originally submitted to the Agency on May 27, 2020. The Office of Scientific Investigations (OSI) at FDA cross-checked these efficacy data (on Gb3 and Plasma Lyso-Gb3 endpoints) against certified copies of original source documents. While no discrepancies were identified for the plasma Lyso-Gb3 data, OSI reviewer noted several

discrepancies between source documents and the submitted data for the Gb3 endpoint. In addition, the OSI reviewer noted there was wide variability between reader scores for 2 subjects. The OSI reviewer recommended that the sponsor verify all BLISS scores for all subjects at all sites and to submit revised datasets to this BLA. On November 4, 2020, the Applicant submitted a revised efficacy data (which triggered a major amendment). Based on the results of these inspections, the OSI reviewer concluded the studies appear to have been conducted adequately, and the data generated appear acceptable in support of the respective indication. The review of the revised efficacy data was completed by April 27, 2021, and the results of the efficacy analyses are presented in Section 3.2.

Overall, the submitted data were of good quality with definitions provided for each variable. The reviewer was able to reproduce the Applicant's primary efficacy analyses. The statistical reviewer's analyses were primarily based on the analysis datasets. The final statistical analysis plans (SAPs) for all relevant studies were submitted.

3.2 Evaluation of Efficacy in Trial PB-102-F01/F02/F03

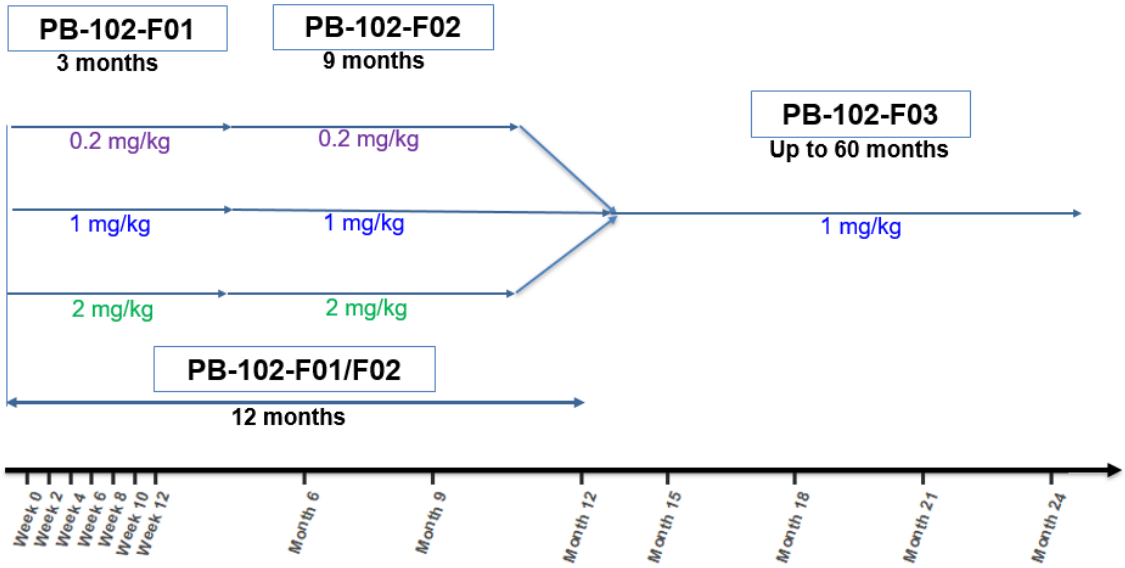
In the original BLA submission, the efficacy evaluation of PRX-102 was primarily based on data from a single-arm, open-label trial consisting of three studies: study PB-102-F01 (F01) and its two extension studies PB-102-F02 (F02) and PB-102-F03 (F03). The design schematic of these three studies is shown in Figure 1. Since the primary objective of Trial PB-102-F01/F02/F03 was to evaluate safety, tolerability, pharmacokinetics, and immunogenicity of PRX-102, all efficacy analyses were considered exploratory per protocol. However, for the Agency's efficacy evaluation, kidney Gb3 inclusion endpoint is considered the main efficacy endpoint because this endpoint was previously used to grant accelerated approval for Fabrazyme and Galafold.

The Agency's efficacy evaluation focused on the following endpoints:

1. **Main efficacy endpoints:** absolute and percent change from baseline to month 6 in the average number of Gb3 inclusions per kidney peritubular capillaries (PTC). Note, the main efficacy endpoint, Gb3 inclusion per kidney PTC, is assessed at baseline and at 6 months in Study PB-102-F01/F02.
2. **Supportive efficacy endpoints:** absolute and percent change in plasma lyso-Gb3

Nominal p-values for comparing baseline and post-baseline values were presented for efficacy endpoints as descriptive statistics.

Figure 1: PB-102-F01, PB-102-F02, and PB-102-F03 Trial Design



The main efficacy endpoint, Gb3 inclusion per kidney PTC, is assessed at baseline and at 6 months in Study PB-102-F01/F02. The supportive efficacy endpoint, change in Plasma Lyso-Gb3 is assessed at all time points shown in the figure. Study drug is administered intravenously every 2 weeks.

3.2.1 Study Design and Endpoints (Trial PB-102-F01/F02/F03)

Study PB-102-F01

PB-102-F01 was an open-label, dose-ranging study that evaluated three different doses of PRX-102. Patients were enrolled into one of three PRX-102 treatment groups (0.2, 1.0 or 2.0 mg/kg) and received IV infusions every 2 weeks for 12 weeks (total of 7 infusions). The first patient was given the lowest dose of 0.2 mg/kg for at least four infusions and, only if the dose was well-tolerated, the second patient was given 0.2 mg/kg. After six patients tolerated all seven infusions of 0.2 mg/kg, the six patients in next group would receive 1 mg/kg and followed the same stepwise progression. Four patients were given 2.0 mg/kg dose after all six patients tolerated the seven doses of 1.0 mg/kg. Patient enrollment into the 2.0 mg/kg dose was then stopped. Regarding early stopping of patient enrollment into the 2.0 mg/kg group, the Applicant's study report provided the following rationale (page 4):

"At the time of enrollment of the 4thpatient into the 2.0 mg/kg treatment group, the Applicant opted to stop enrollment to the 2.0 mg/kg treatment group and made the decision to use 1.0 mg/kg doses for the pivotal studies. This decision was based on the data obtained thus far from the non-clinical studies, but particularly from the preliminary PK/PD and safety data as an optimal dose between pharmacokinetics, potential efficacy, immunogenicity, and infusion-related reactions for the Phase 3 program."

Key Inclusion Criteria:

- Symptomatic adult Fabry patients (≥ 18 years, males and females)
- Males: plasma and/or leukocyte α galactosidase activity less than lower limit of normal in plasma (3.2 nmol/hr/mL) and/or leukocytes (32 nmol/hr/mg/protein)
- Females: historical genetic test results consistent with Fabry mutations
- Gb3 concentration in urine >1.5 times upper limit of normal
- Patients who have never received ERT in the past, or patients who have not received ERT in the past 6 months and have a negative anti-PRX-102 antibody test
- eGFR ≥60 mL/min/1.73m^2

Study PB-102-F02 (extension study of Study PB-102-F01)

Upon completion of the 12-week treatment period in trial PB-102-F01, patients had the option to enroll in an open-label extension study (study -F02) for an additional 9-month treatment period. Patients continued to receive the same dose of PRX-102 that they received in PB-102-F01, as an IV infusion every 2 weeks for 38 weeks. An interim analysis was planned to evaluate a subset of pre-defined exploratory efficacy parameters in patients with a total of 6 months of treatment.

Key Endpoints

1. Safety, tolerability, PK, PD, immunogenicity
2. Efficacy:
   - Change from baseline (measured in Study PB-102-F01) to 6 months in the average number of Gb3 inclusions per kidney PTC assessed by the BLISS. The terms *renal Gb3 BLISS score* or *BLISS score* may be used to refer to the average number of Gb3 inclusions per kidney PTC.
   - Plasma Gb3 concentration (mg/mL) and plasma Lyso-Gb3 concentration (ng/mL).
   - Change in eGFR and proteinuria levels.
   - Cardiac function by echocardiography and stress test.
   - Cardiac MRI (left ventricular mass, left ventricular mass index, ejection fraction and myocardial fibrosis)
   - Short Form Brief Pain Inventory (BPI): Pain severity and pain interference
   - Brain MRI: Qualitative assessments for evidence of stroke
   - Gastrointestinal Symptoms Questionnaire.
   - Mainz Severity Score Index (MSSI): Qualitative assessments regarding signs/symptoms in general, neurological, cardiovascular, renal dysfunction.

Assessment of renal Gb3 inclusions (for details, see Appendix 2)

Kidney biopsy was performed at baseline of Study PB-102-F01 and 6 months post-treatment with PRX-102 (at the Month 3 visit of Study PB-102-F02) for study patients. Approximately 300

kidney peritubular capillaries were scored in each specimen. Two scoring systems, a quantitative Barisoni Lipid Inclusion Scoring System (BLISS) and a semi-quantitative modified Fabrazyme Scoring System (mFSS), were used for the assessment of Gb3 inclusions in kidney peritubular capillary (PTC) biopsy samples. These two scoring systems were implemented by three blinded pathologists.

The BLISS counts the number of Gb3 inclusions in each PTC. The final score of each biopsy was the average number of Gb3 inclusions across PTCs. A higher score is indicative of more severe disease on the histologic level. The BLISS was previously used in a clinical trial of migalastat (Galafold) for Fabry Disease (Barisoni, et al., 2012).

The mFSS assigns a score based on presence/absence of Gb3 inclusions/granules/aggregates and ranges from 0 (no inclusions) to 3 (bulging aggregates) in each PTC. In the original FSS as used in Fabrazyme's clinical trial (Eng et al., 2001; Thurnberg, et al., 2002), the final score for each biopsy slide was the score assigned to the majority of PTCs. In the modified FSS (mFSS) used in Study PB-102-F01/F02, for each severity score (0, 0.5, 1, 2, or 3), the proportion of capillaries receiving the given score was calculated.

A comparative summary of the three scoring systems is provided in Table 2 and Table 3 The BLISS can detect a small amount of Gb3 inclusions and thus it is more sensitive compared to the FSS and mFSS (Barisoni et al. 2012, and Applicant's Histology Report, pages 10 - 11).

Table 2: Comparative Histological Methodologies of BLISS, FSS, and mFSS

	Comparative Histological Methodology		
	Fabrazyme Score System [a]	**Modified- Fabrazyme Score System [b]**	**BLISS Methodology [c]**
Overall scoring approach	Semi-quantitative	Semi-quantitative	Quantitative
Visualization methodology	Conventional light microscopy (glass slides @ 100x)	Digital pathology (whole slide images scanned @100x)	Digital pathology (whole slide images scanned 100x)
PTC Annotation	No	Yes	Yes
Number of Interstitial capillaries scored	≥50	~300	~300
Metric for each PTC score	Semiquantitative (0-1-2-3)	Semiquantitative (0-0.5-1-2-3)	Quantitative: Number of Gb3 inclusions
Scoring protocol	3 scoring pathologists	1 annotator/adjudicator 2 scoring pathologists	1 annotator/adjudicator 2 scoring pathologists
Score per biopsy per pathologist	Given by the majority of PTC with any given score	N/A	Average of inclusion per PTC

Overall impression per biopsy per pathologist	Pathologist's perception of severity (Gestalt)	N/A	N/A
Final biopsy score	Given by the majority of PTC with any given score. In case of discrepancies on PTC score the three pathologists were supposed to reconvene and give an agreed final score	N/A [d]	The score of the biopsy is the average of the scores given by the two pathologists
Definition of "Score 0"	≥ 50% of PTCs have no GL-3 inclusions AND < 5% of PTCs have a score of ≥ 1 (more that 2 or 3 inclusions) [e]	N/A	Zero GL-3 inclusions in any interstitial capillary

a Barisoni 2012
b Eng 2001
c Barisoni 2015, Barisoni Poster
d The final calculation was not done initially but has since been completed following the Agency guidance
e Galafold Approval Package NDA 208623

Source: Table 1 of the Applicant's responses to the Agency's information request, submitted to BLA761161 (eCTD 0046) on April 6, 2021

Table 3: Comparative Information for the Scoring System Among FSS, mFSS, and BLISS

	Score per PTC						Score per Biopsy				
	0	0.5	1	2	3	4,5,…20	0	1	2	3	4,5,….20
FSS	0-2 inclusions	N/A[a]	>3 inclusions – no aggregates	> 1 Non bulging aggregates	Bulging aggregates	N/A[b]	The majority of PTC have a score of 0	The majority of PTC have a score of 1	The majority of PTC have a score of 2	The majority of PTC have a score of 3	N/A[b]
mFSS	0 inclusion	1 inclusion	>2 inclusions – no aggregates	> 1 Non bulging aggregates	Bulging aggregates	N/A	Individual biopsy scores not generated for mFSS	Individual biopsy scores not generated for mFSS	Individual biopsy scores not generated for mFSS	Individual biopsy scores not generated for mFSS	N/A
BLISS	0 inclusion	N/A[a]	1 inclusion counted	2 inclusions counted	3 inclusions counted	4,5,,….20 inclusions counted	When no inclusions are detected in any of the 300 PTC scored	When an average of 1 inclusion per PTC is calculated using all 300 PTC scored	When an average of 2 inclusions per PTC is calculated using all 300 PTC scored	When an average of 3 inclusions per PTC is calculated using all 300 PTC scored	When an average of 4,5,….20 inclusions per PTC is calculated using all 300 PTC scored

a Not applicable - the option 0.5 is not included in BLISS or FSS
b Not applicable - the semiquantitative scoring systems FSS and mFSS included options between 0 and 3 only

Source: Table 2 of the Applicant's responses to the Agency's information request, submitted to BLA761161 (eCTD 0046) on April 6, 2021

Study PB-102-F03 (extension study of Study PB-102-F02)

Study PB-102-F03 is an ongoing open-label extension study of PB-102-F02 administering PRX-102 for up to 60 months. The study drug is administered intravenously at a dose of 1.0 mg/kg every 2 weeks. Patients who had received 0.2 mg/kg or 2 mg/kg of PRX-102 in Study PB-102-F02 were gradually switched to 1 mg/kg given intravenously every 2 weeks. Patients who had originally received 1 mg/kg of PRX-102 in Study PB-102-F02 continued to receive the same dosage in this extension study.

The objective of this study was to evaluate long-term safety, and efficacy endpoints were similar to study PB-102-F02 except for the lack of assessment of Gb3 inclusions in the kidney.

3.2.2 Statistical Analysis Plan (Study PB-102-F01/F02/F03)

Statistical Analysis Plans (Studies PB-102-F01, PB-102-F02, PB-102-F03)
For all three studies listed above, the Applicant's SAPs proposed to use descriptive approaches to summarize efficacy data. Specifically, continuous variables would be summarized using mean, standard deviation, standard error, median, minimum, maximum and interquartile range, while categorical variables were summarized using count and percentages. In the Applicant's clinical study reports, p-values were provided based on paired t-tests for the absolute and percent changes from baseline to 6-month in renal Gb3 BLISS score. The review team conducted non-parametric tests given the small sample size of the study. Given the single-arm design of PB-102-F01/F02/F03, inferential analysis of change from baseline to 6-month in Gb3 BLISS score rests on the assumption that spontaneous decline in Gb3 deposition is unlikely at the population level. Support for this assumption is presented in Appendix 2.

Analysis of Change in Renal Gb3 BLISS Score at the Patient Level
For each patient, the review team conducted an analysis to compare the average number of Gb3 inclusions across the approximately 300 capillaries (i.e., the renal Gb3 BLISS score) at 6 months to the average number at baseline. This comparison was conducted using both a two-sample t-test and permutation test for each of the 14 individual patients. The null hypothesis for these tests is: the mean number of Gb3 inclusions at 6 months = the mean number of Gb3 at baseline. For an individual patient who has n_1 PTCs scored at baseline and n_2 PTCs scored at 6 months, the steps for the permutation testing procedure are as follows:

1. Compute the observed (actual) difference, d, in average scores:
   d = average six-month score – average baseline score
2. Pool the baseline and six-month data.
3. Randomly permute the pooled data.
4. Use the first n_1 observations to compute average baseline score and the remaining n_2 observations to compute 6-month score, and compute their difference as in (1).
5. Repeat steps 3 and 4 10,000 times to generate the null distribution of the difference in (1).

Note: for each patient, the Applicant also provided an estimated density function for the difference in the mean BLISS score between the baseline and 6-month visits using a bootstrap

approach (see Figure 17). The Applicant's proposed bootstrap procedure is as follows:

1. A bootstrap sample size of 300 scores was taken from the patient's baseline dataset
2. Another bootstrap sample size of 300 scores was taken from the patient's six months dataset
3. The difference between the above two averages is computed.
4. The process was then repeated 5000 times to generate the bootstrap distribution of the difference between baseline and six-month scores.

Analysis of Change in Renal Gb3 Inclusions Using mFSS

The Applicant's study report provided summary statistics to examine the Gb3 inclusions as measured by the mFSS. The review team conducted the following additional analyses to examine the treatment effect:

1. Comparison of the change from baseline to 6 months in **the percentage of capillaries with mFSS score of 0 or 0.5**. This analysis is conducted using a permutation test under the null hypothesis of equality of a patient's 6-month and baseline-score in the absence of treatment effect.

2. Comparison of the proportion of patients with **biopsy-level score of 0** at baseline and at 6 months utilizing an exact version of McNemar's test. The biopsy-level score of zero was defined using the following two approaches:
    a. **majority-rule approach**: this approach assigns a biopsy score of 0 if a majority of the capillaries in that biopsy received a score of 0.
    b. **alternate approach**: this approach assigns a biopsy score of 0 if at most 5% of the capillaries have mFSS score > 1 (i.e., at least 95% have mFSS score ≤ 1) **and** at least 47.5% of the capillaries have mFSS score of 0 (i.e., 0 inclusion).

3. Comparison of the patient-level change from baseline to 6 months in the **average biopsy-level score**. The review team defined the average biopsy-level score as the weighted average of the capillary-specific scores. For example, if 30% of capillaries have a score of 3, 49% a score of 2, 20% a score of 1, 10% a score 0.5, and 11% a score of 0, the average biopsy-level score will be 2.13 (= 0.3*3 + 0.49*2 + 0.2*1 + 0.1*0.5 + 0.11*0).

Since the Applicant's stated objective considered the evaluation of efficacy to be exploratory and all inferential analyses were specified post-hoc, all reported p-values are nominal.

Subgroup Analyses

Subgroup analyses were conducted by sex, drug dose group, Fabry disease phenotype (classic vs. non-classic) and anti-drug antibody (ADA) status. A patient was classified as having a positive treatment-induced ADA status if:

1. the patient was IgG negative at baseline and positive at any timepoint post-baseline, or,

2. the patient was IgG positive at baseline and experienced IgG titer increase of at least 4-fold from baseline

The Applicant's definition of classic phenotype required patients meet the following two criteria and applied to both male and female patients:

- **a.** patients with <30% of the mean of the normal range of alpha-galactosidase A (α-Gal A) activity in the leukocyte (normal range: 33 to 144 nmol/hr/mg) and plasma (normal range: 4 to 21.9 nmol/hr/mL),
- **b.** have at least one of the Fabry disease specific symptoms such as neuropathic pain, cornea verticillata, or clustered angiokeratoma.

Based on consultations with the clinical team, the review team's definition of classic phenotype applies only to male patients and used a more stringent threshold of <5% of the mean of the normal range of alpha-galactosidase A (α-Gal A) activity in the leukocyte and plasma. The review team's definition did not require presence of symptoms as described in criteria (b) above. A threshold of <1% was also implemented but there was only one patient who met this criterion, and therefore no further analysis is performed using this latter threshold. All relevant efficacy results will be presented using the review team's definition of classic phenotype.

Sensitivity Analysis Including the Subject with Mislabeled Biopsy Slides

One subject (ID: (b) (6)) was removed from the Applicant's efficacy analysis of Gb3 inclusions as a result of the patient's biopsy slides being mislabeled. For this subject, there was a high level of discrepant scores between readers and the patient's biopsy slides could not be matched to the correct visits (i.e., baseline versus six-month visit times could not be identified). Nonetheless, the review team was able to derive the BLISS score based on the Applicant's raw dataset for each visit, and conduct sensitivity analysis for the following two scenarios:

1. Worst case scenario analysis (assumes the BLISS score increased by attributing the higher of the two scores to the six-month visit)
2. Best case scenario analysis (assumes the BLISS score decreased by attributing the higher of the two scores to the baseline visit)

The results of the sensitivity analysis including this subject's scores are presented in Table 8 and support the results of the main efficacy analysis.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics (Trial PB-102-F01/02/03)

Patient Disposition

Forty-two patients were screened from 13 study sites. Of these, only 19 from 11 study sites were considered eligible for enrollment as the other 23 patients did not meet the inclusion or exclusion criteria. Six patients were enrolled in the 0.2 mg/kg treatment group, nine in the 1.0 mg/kg and four in the 2.0 mg/kg treatment group. The Applicant stopped enrollment into the 2mg/kg cohort after four patients were enrolled after the decision was made that the 1mg/kg was considered the

optimal dose for treatment (see clinical pharmacology review). One patient who was in the 1.0 mg/kg treatment group voluntarily withdrew consent from the study prior to receiving any study treatment. Two patients who were in the 1.0 mg/kg treatment group discontinued the study, one experienced a hypersensitivity reaction (Grade 3 bronchospasm) during the first infusion, and one was found noncompliant to the study and discontinued due to investigator recommendation after the patient received one infusion. Sixteen patients completed study PB-102-F01, and all 16 patients enrolled into study PB-102-F02. All sixteen patients also completed the 9-month extension study PB-102-F02. Of the 16 patients who completed study PB-102-F02, 15 continued into study PB-102-F03, an extension study of up to 60 months. For the main efficacy analysis using the BLISS score, the biopsy data for two out of the 16 patients could not be used because one female patient had biopsy tissue that could not be scored at baseline as it was taken from the medulla of the kidney and one male patient had biopsy slides that were scanned out of focus and mislabeled, and subsequently could not be matched to correct visits (i.e. baseline versus six-month visit times could not be identified).

Demographics/Baseline Characteristics

In this study, 75% of patients were white, 56% of patients were male and 44% of patients were female. Among the nine male patients, seven (78%) had the classic Fabry phenotype.
At baseline, there was a large difference between males and females in terms of Gb3 inclusion burden (females had generally lower average number of Gb3 inclusions per PTC compared to males) which is expected due to the X-linked nature of the disease and the tissue mosaicism of the expression of the abnormal X chromosome in females (who are heterozygous). The more extensive substrate deposition in the PTC is indicative of more severe disease on the histologic level and in general, females tend to have lower (and highly variable) Gb3 burden in tissues and typically milder disease manifestations compared to males. Plasma lyso-Gb3 was also noted to be much larger in the male population than in the females which is consistent with the severity of disease seen in males versus female FD patients. Residual enzyme activity in leukocyte and plasma were much lower among males compared to females.

Table 4: Population Demographic and Baseline Characteristics of the 16 Patients Who Completed Study PB-102-F01/F02

	Female (N=7)	*Male (N=9)*	*Overall (N=16)*
Age (years)			
Mean (SD)	38 (15)	29 (9)	33 (12)
Median (min, max)	34 (20, 54)	27 (17, 50)	30 (17, 54)
Race, n (%)			
White	6 (85.7)	6 (66.7)	12 (75.0)
Black or African American	1 (14.3)	2 (22.2)	3 (18.8)

Other	0 (0.0)	1 (11.1)	1 (6.2)
Ethnicity, n (%)			
Hispanic or Latino	2 (28.6)	1 (11.1)	3 (18.8)
Not Hispanic or Latino	5 (71.4)	8 (88.9)	13 (81.2)
FD Phenotype, n (%)			
Non-classic	7 (100.0)	2 (22.2)	9 (56.2)
Classic[1]	0 (0.0)	7 (77.8)	7 (43.8)
Type of Variant, n (%)			
Nonsense	1 (14.3)	1 (11.1)	2 (12.5)
Missense	3 (42.9)	7 (77.8)	10 (62.5)
Duplication	0	0	0
Duplication and frame shift	0	1 (11.1)	1 (6.3)
Plasma α-Gal A activity (% of mean normal range*[2]*)			
Mean (SD)	[4]—	3.2 (3.0)	—
Median (min, max)	—	2.4 (0.0, 9.3)	—
Leukocyte α-Gal A activity (% of mean normal range*[3]*)			
Mean (SD)	[4]—	1.8 (1.3)	—
Median (min, max)	—	1.3 (0.0, 3.4)	—
***Renal Gb3 score (BLISS)*[5]			
Mean (SD)	1.7 (1.0)	5.7 (3.1)	4.0 (3.1)
Median (min, max)	1.2 (0.8, 3.3)	6.8 (0.4, 9.0)	3.2 (0.4, 9.0)
Plasma Lyso-Gb3 (ng/mL)			
Mean (SD)	9.6 (5.6)	111.2 (79.3)	66.7 (78.0)
Median (min, max)	7.5 (3.4, 19.2)	84.7 (5.1, 272.9)	40.5 (3.4, 272.9)
eGFR CKD (mL/min/1.73m*[2]*)			
Mean (SD)	108.1 (20.7)	116.0 (23.0)	112.6 (21.6)
Median (min, max)	115.1 (77.7, 131.8)	115.8 (82.4, 156.3)	115.1 (77.7, 156.3)
eGFR MDRD (mL/min/1.73m*[2]*)			
Mean (SD)	97.5 (21.9)	110.5 (30.5)	105.0 (27.0)
Median (min, max)	99.5 (69.7, 131.2)	107.2 (74.8, 166.3)	100.8 (69.7, 166.3)
Creatinine (mg/dL)			
Mean (SD)	0.7 (0.1)	0.9 (0.1)	0.8 (0.2)
Median (min, max)	0.7 (0.6, 0.8)	1.0 (0.7, 1.1)	0.8 (0.6, 1.1)
Protein/Creatinine Ratio (mg/g)			
Mean (SD)	208.0 (127.0)	112.4 (72.9)	150.7 (105.6)
Median (min, max)	195.0 (81.0, 405.0)	105.0 (42.0, 298.0)	106.0 (42.0, 405.0)
Total Protein Random Urine (mg/dL)			

Mean (SD)	25.5 (16.1)	13.3 (3.4)	18.1 (11.7)
Median (min, max)	23.5 (9.9, 44.5)	12.5 (8.7, 19.1)	12.5 (8.7, 44.5)
ACEI/ARB use, n (%)			
No	6 (85.7)	6 (66.7)	12 (75.0)
Yes	1 (14.3)	3 (33.3)	4 (25.0)
NSAID use, n (%)			
No	1 (14.3)	2 (22.2)	3 (18.8)
Yes	6 (85.7)	7 (77.8)	13 (81.3)
History of ERT use, n (%)			
Yes	*1 (14.3)*	*5 (55.6)*	*6 (37.5)*
No	6 (85.7)	4 (44.4)	10 (62.5)
PRX-102 Dose, n (%)			
0.2 mg/kg	2 (28.6)	4 (44.4)	6 (37.5)
1.0 mg/kg	2 (28.6)	4 (44.4)	6 (37.5)
2.0 mg/kg	3 (42.9)	1 (11.1)	4 (25.0)

α-Gal A: alpha-galactosidase A; **ACEi:** Angiotensin-converting-enzyme inhibitors; **ARB:** Angiotensin II receptor blockers

[1] The review team's definition of Classic phenotype was restricted to male patients and required patients to have plasma and leukocyte α-Gal A activity < 5% of the mean of the normal range.

[2] The normal range for α-Gal A activity in the plasma is 33 to 144 nmol/hr/mg.

[3] The normal range for α-Gal A activity in the leukocyte is 4 to 21.9 nmol/hr/mL.

[4] Enzyme activity measurements are not reliable in females.

[5] The BLISS methodology counts the number of GbL-3 inclusions in each renal PTC contained in a biopsy specimen. For each biopsy specimen, approximately 300 renal PTCs were scored, and the final biopsy score for each patient was determined as the average number of GbL-3 inclusions per PTC.

Figures on history of ERT use, NSAID use, and type of variant were supplied by the Applicant on April 16, 2021 (eCTD 0048).

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0035) on February 8, 2021.

3.2.4 Results (Trial PB-102-F01/F02)

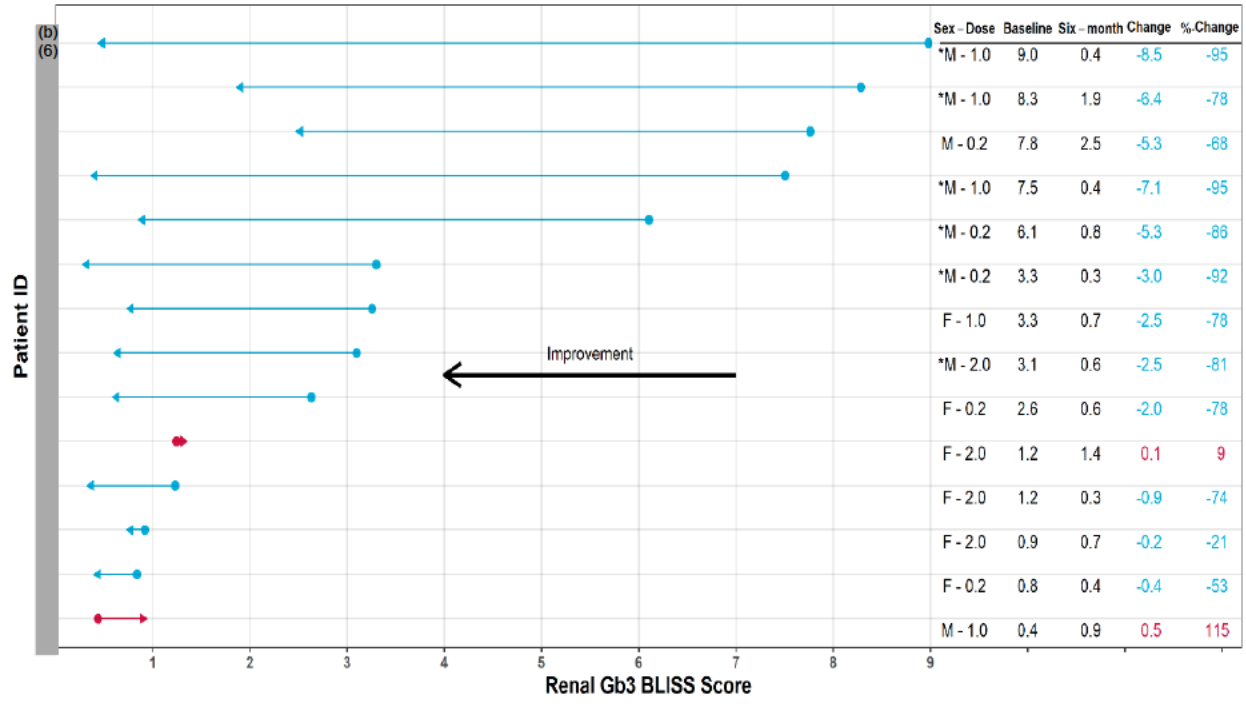
<u>Efficacy Results:</u> Change from Baseline in Renal Gb3 BLISS Score (Average Number of Gb3 Inclusions per PTC)

A total of 14 patients who had Gb3 inclusions assessed at both baseline and 6 months were included in the main efficacy analysis of Gb3 inclusions. Their data are presented in Figure 2. The median absolute reduction in the renal Gb3 BLISS score was -2.5 (95% CI: -5.3, -0.7; p = 0.001), and the median percent reduction was -78% (95% CI: -86%, -53%; nominal p = 0.02) (Table 5). The mean absolute reduction in the number of Gb3 inclusions was -3.1 (95% CI: -4.8, -1.4; nominal p < 0.001), and the mean percent reduction was -55% (95% CI: -88%, -22%;

nominal p = 0.01).

For the nine patients who had a baseline renal Gb3 BLISS score above 2, the minimum percent reduction in Gb3 inclusions at 6 months was 68%. Analysis of change in renal Gb3 BLISS score at the patient level showed that 11/14 (79%) patients had a nominally significant reduction (nominal p<0.001) at 6 months (Figure 16). Both the t-test and permutation testing approach had comparable results. These 11 patients had at least 50% reduction in Gb3 from baseline (ranged from -53% to -95%). Of the remaining three patients, two patients (baseline scores: 0.4 and 1.2) had a minimal increase (change score at six months: 0.5, 0.1) and one patient had a minimal decrease (baseline score: 0.9, change score at six months: -0.2).

Figure 2: Changes in Renal Gb3 BLISS Score (Average Number of Gb3 Inclusions per Kidney PTC) by Patient (Trial PB-102-F01/F02)



Dots (•): Baseline BLISS score Arrow heads (◄): 6-Month BLISS score (*): Classic Fabry Disease

Increase in BLISS score from baseline to six month indicated in red while decrease in BLISS score is indicated in blue

The biopsy data for 2 patients (out of the 16 patients enrolled in PB-102-F01/02) could not be used in the main efficacy analysis; 1 female patient had biopsy tissue that could not be scored at baseline as it was taken from the medulla of the kidney; 1 male patient had biopsy slides that were scanned out of focus and mislabeled, and subsequently could not be matched to correct visits (i e baseline versus six-month visit times could not be identified)

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025)) on November 11, 2020

Table 5. Changes in Renal Gb3 BLISS Score by Sex (Trial PB-102-F01/F02)

	All Patients (N = 16) [a]	Male (N = 9)	Female (N = 7)
Baseline (n)	14	8	6
Mean (SD)	4 (3.1)	5.7 (3.1)	1.7 (1)
Median (Range)	3.2 (0.4, 9)	6.8 (0.4, 9)	1.2 (0.8, 3.3)
Month 6 (n)	14	8	6
Mean (SD)	0.8 (0.6)	1 (0.8)	0.7 (0.4)
Median (Range)	0.7 (0.3, 2.5)	0.7 (0.3, 2.5)	0.7 (0.3, 1.4)
Change from baseline at Month 6 (n)	14	8	6
Mean (SD)	-3.1 (2.9)	-4.7 (2.9)	-1.0 (1.1)
Median (Range)	-2.5 (-8.5, 0.5)	-5.3 (-8.5, 0.5)	-0.7 (-2.5, 0.1)
95% CI for mean	-3.1 (-4.8, -1.4)	-4.7 (-7.1, -2.3)	-1.0 (-2.1, 0.1)
95% CI for median	-2.5 (-5.3, -0.7)	-5.3 (-7.1, -2.5)	-0.7 (-2.3, 0.0)
P-value[b]	<0.001	0.015	0.058
P-value[c]	0.001	0.016	0.063
% Change from baseline at Month 6 (n)	14	8	6
Mean (SD)	-55 (57)	-60 (71)	-49 (36)
Median (Range)	-78 (-95, 115)	-83 (-95, 115)	-63 (-78, 9)
95% CI for mean	-55 (-88, -22)	-	-
95% CI for median	-78 (-86, -53)	-	-
P-value[b]	0.006	0.068	0.066
P-value[c]	0.017	0.195	0.063

[a] Of the 16 patients enrolled in Study PB-102-F01/F02, 14 patients provided renal tissue that could be assessed using the BLISS methodology.
[b] Permutation test p-value for testing the null hypothesis of equality of a patient's baseline and six-month score in the absence of treatment effect.
[c] Exact Wilcoxon signed-rank test p-value.
Confidence interval for the median percent change was based on bootstrap.
All reported p-values are nominal**.**
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025) on November 11, 2020

Subgroup Analyses

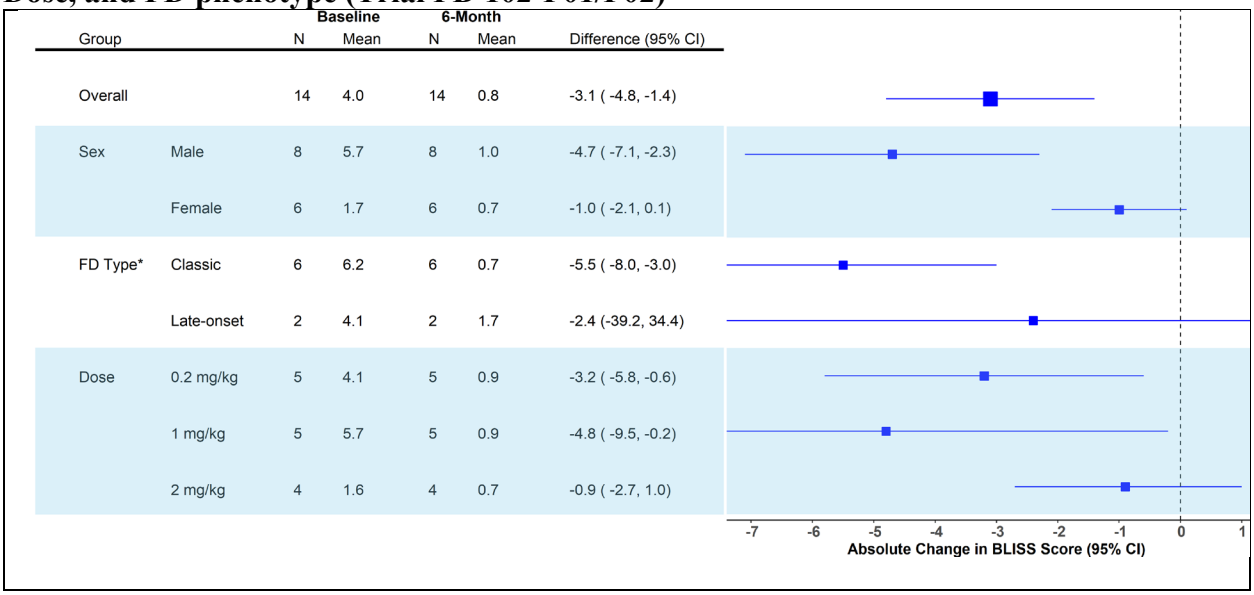
Both male and female patients experienced considerable reductions in renal Gb3 score at 6 months (Table 5). Among the eight male patients, seven of them had relative reductions ranging from 68% to 95%. Among the six female patients, five of them had relative reduction ranging from 21% to 78%. The median absolute reductions were -5.3 (95% CI: -7.1, -2.5) for males and

-0.7 (95% CI: -2.3, -0.04) for females. The median percent reductions were -83% (range: -95%, 115%) for males and -63% (range: -78%, 9%) for females (Table 5). As expected, the observed effect on the female patients was lower compared to the male patients because the baseline values of Gb3 inclusions were significantly lower in the female patients (median of 1.1 for females vs. 6.8 for males).

Regarding the three drug doses of 0.2, 1, and 2 mg/kg, the 2 mg/kg arm had lower median values of Gb3 inclusions at baseline: 3.3 and 7.5, and 1.2 for the three dose arms, respectively. The median percent changes were -78%, -78%, and -47% and the median changes were -3.0, -6.4, and -0.5 for the three dose arms, respectively (Table 6). For the 2 mg/kg arm, the significantly lower median change and percent change from baseline seemed to be driven by the higher proportion of females who had lower numbers of Gb3 inclusions at baseline. The proportion of females was 74% (3/4) in the 2 mg/kg arm compared to 33% (2/6) in the other two arms. Since the three females in the 2 mg/kg arm had a baseline renal Gb3 BLISS score ranging from 0.9 to 1.2 (Figure 2), the possible maximum reductions at 6 months for these patients cannot exceed 1.2. Therefore, given the small sample sizes and the imbalance in the baseline values of Gb3 inclusions, it is challenging to compare the treatment effects among the three dose arms. Of note, the Applicant considered 1 mg/kg dose as the optimal dose and evaluated it in their randomized and controlled phase 3 trial (Trial PB-102-F20) to demonstrate clinical benefit using the eGFR slope endpoint.

A total of six patients met the review team's definition of classic phenotype and they had a 78% or greater reduction in the renal Gb3 BLISS score (Figure 2). The mean and median percent reductions were 88% and 89%, respectively; the mean and median absolute reduction were -5.5 and -5.8.

Figure 3: Absolute Change in Renal Gb3 BLISS Score from Baseline to 6 months By Sex, Dose, and FD phenotype (Trial PB-102-F01/F02)



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025) on November 11, 2020

Table 6: Renal Gb3 BLISS Score by Dose (Trial PB-102-F01/F02)

	All Patients (N = 16) [a]	0.2 mg/kg (N = 6)	1 mg/kg (N = 6)	2 mg/kg (N = 4)
Baseline (n)	14	5	5	4
Mean (SD)	4 (3.1)	4.1 (2.8)	5.7 (3.7)	1.6 (1)
Median (Range)	3.2 (0.4, 9)	3.3 (0.8, 7.8)	7.5 (0.4, 9)	1.2 (0.9, 3.1)
Month 6 (n)	14	5	5	4
Mean (SD)	0.8 (0.6)	0.9 (0.9)	0.9 (0.6)	0.7 (0.4)
Median (Range)	0.7 (0.3, 2.5)	0.6 (0.3, 2.5)	0.7 (0.4, 1.9)	0.7 (0.3, 1.4)
Change from baseline at Month 6 (n)	14	5	5	4
Mean (SD)	-3.1 (2.9)	-3.2 (2.1)	-4.8 (3.7)	-0.9 (1.2)
Median (Range)	-2.5 (-8.5, 0.5)	-3 (-5.3, -0.4)	-6.4 (-8.5, 0.5)	-0.5 (-2.5, 0.1)
95% CI for mean	-3.1 (-4.8, -1.4)	-3.2 (-5.8, -0.6)	-4.8 (-9.5, -0.2)	-0.9 (-2.7, 1)
P-value[b]	0.001	0.066	0.125	0.248
P-value[c]	0.001	0.063	0.125	0.25
% Change from baseline at Month 6 (n)	14	5	5	4
Mean (SD)	-55 (57)	-75 (15)	-46 (90)	-42 (43)
Median (Range)	-78 (-95, 115)	-78 (-92, -53)	-78 (-95, 115)	-47 (-81, 9)
P-value[b]	0.005	0.066	0.378	0.25
P-value[c]	0.017	0.063	0.625	0.25

[a] Of the 16 patients enrolled in Study PB-102-F01/F02, 14 patients provided renal tissue that could be assessed using the BLISS methodology.

[b] Permutation test p-value for testing the null hypothesis of equality of a patient's baseline and six-month score in the absence of treatment effect.

[c] Exact Wilcoxon signed-rank test p-value.

All reported p-values are nominal**.**

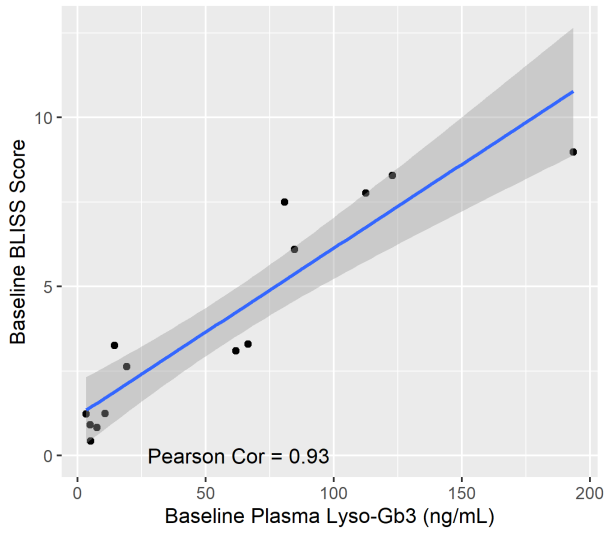
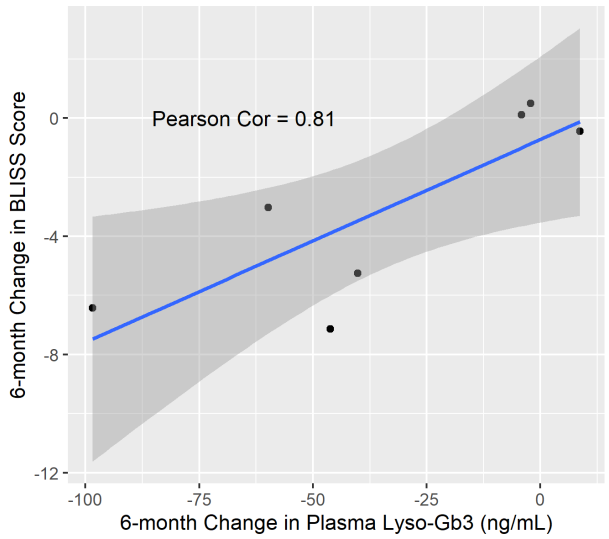
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025) on November 11, 2020

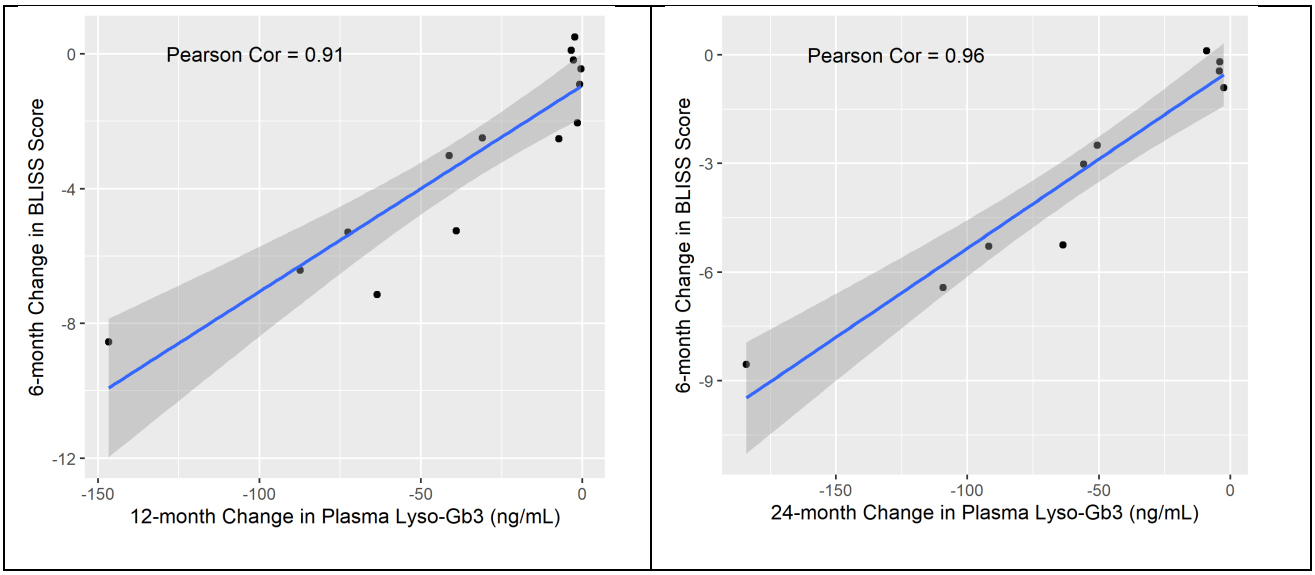
Correlation of Changes in Kidney Gb3 with Changes in Plasma-Lyso Gb3

For detailed analyses of the plasma Lyso-Gb3 endpoint, the reader should consult the Agency's clinical pharmacology review. Overall, there was a mean 49% and 81% reduction in Plasma Lyso-Gb3 at 1 and 2 years, respectively. Female patients had an average reduction of 31% and 72% at 1 and 2 years, respectively, while male patients had an average reduction of 63% and 86% at 1 and 2 years, respectively.

The reduction in kidney Gb3 inclusions was accompanied by a marked reduction in Plasma Lyso-Gb3 with all patients showing a reduction in Plasma Lyso-Gb3 at both 1-year and 2-year visits. At baseline, there was a strong correlation of 0.93 (95% CI: 0.78, 0.98) between kidney Gb3 and Plasma-Lyso Gb3. Furthermore, there was a strong correlation between change in kidney Gb3 inclusions and change in Plasma-Lyso Gb3 (Figure 4). At 6 months the correlation between the two biomarkers was 0.81 (95% CI: 0.15, 0.97). The correlations between six-month change in kidney Gb3 and change in Plasma-Lyso Gb3 at 12-months (n=14) and 24-months (n=10) were 0.91 (95% CI: 0.74, 0.97) and 0.96 (95% CI: 0.85, 0.99), respectively.

Figure 4: Correlation Between Renal Gb3 BLISS Score and Plasma Lyso-Gb3 (Trial PB-102-F01/F02)

A. Baseline BLISS Score vs. Baseline Plasma Lyso-Gb3	**B. 6-Month Change in BLISS Score vs. 6-Month Change in Plasma Lyso-Gb3**
	
C. 6-Month Change in BLISS Score vs. 12-Month Change in Plasma Lyso-Gb3	**D. 6-Month Change in BLISS Score vs. 24-Month Change in Plasma Lyso-Gb3**



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0001 on May 27, 2020 and eCTD 0025 on November 11, 2020)

Gb3 Inclusions in the kidney measured by modified Fabrazyme Scoring System (mFSS)

Individual level data on Gb3 inclusions in the kidney, measured using mFSS, are presented in Figure 25. Overall, there was a significant reduction in the Gb3 inclusions in absolute and relative terms. The mean absolute change in the weighted mFSS score was -0.8 (95% CI: -1.1, -0.4; nominal p <0.001). As shown in Table 7, the mean and median percent reductions were -53% and -70%, respectively.

The average percentage of capillaries with mFSS score of 0-0.5 increased from 47% at baseline to 80% at six-months (nominal p = 0.002; Figure 6). The average proportion of capillaries receiving scores of 1, 2, and 3 were all reduced by 6 months. In addition, the proportion of patients with majority-rule mFSS score of 0 (i.e., whose biopsies had a majority of capillaries scored as 0) increased from 57% (8/14) to 100% after six-months of treatment (p-value < 0.03). The proportion of patients with alternate-approach score of 0 increased from 7% (1/14) at baseline to 64% (9/14) at 6 months (nominal p = 0.008).

Subgroup analysis results using the mFSS approach were comparable to those using the BLISS scoring system. Overall, there was a high correlation between mFSS and BLISS methodologies (**Figure 7**) and both approaches indicate a reduction of Gb3 inclusions at 6 months.

Table 7: Gb3 Inclusions Based on Weighted mFSS Score (Trial PB-102-F01/F02)

	All Patients (N = 14)	Male (N = 8)	Female (N = 6)
Baseline (n)			
Mean (SD)	1.1 (0.7)	1.5 (0.6)	0.6 (0.2)
Median (Range)	1 (0.2, 2.1)	1.7 (0.2, 2.1)	0.5 (0.3, 0.9)
Month 6 (n)	14	8	6

Mean (SD)	0.3 (0.2)	0.4 (0.3)	0.3 (0.2)
Median (Range)	0.3 (0.1, 0.9)	0.3 (0.1, 0.9)	0.2 (0.1, 0.6)
Change from baseline at Month 6 (n)	14	8	6
Mean (SD)	-0.8 (0.6)	-1.1 (0.6)	-0.3 (0.3)
Median (Range)	-0.8 (-1.7, 0.2)	-1.2 (-1.7, 0.2)	-0.3 (-0.7, 0)
95% CI for mean	-0.8 (-1.1, -0.4)	-1.1 (-1.6, -0.6)	-0.3 (-0.6, 0)
P-value[b]	<0.001	0.017	0.065
P-value[c]	<0.001	0.016	0.063
% Change from baseline at Month 6 (n)	14	8	6
Mean (SD)	-53 (50)	-58 (62)	-47 (33)
Median (Range)	-70 (-91, 92)	-79 (-91, 92)	-64 (-73, 0.8)
P-value[b]	0.005	0.072	0.069
P-value[c]	0.017	0.195	0.063

[a] The weighted mFSS score is a biopsy-level score derived by computing the weighted average of the capillary-specific scores. For example, if 30% of capillaries have a score of 3, 49% a score of 2, 20% a score of 1, 10% a score 0.5, and 11% a score of 0, the weighted mFSS score will be 2.13 (= 0.3*3 + 0.49*2 + 0.2*1 + 0.1*0.5 + 0.11*0).

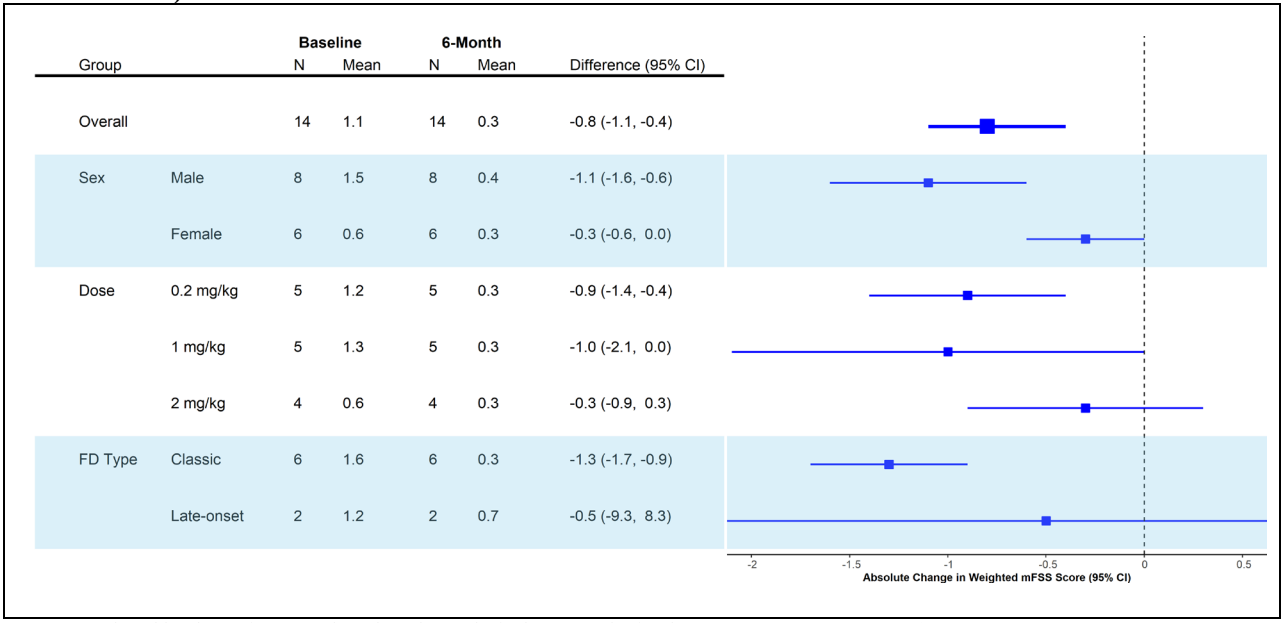
[b] Permutation test p-value for the null hypothesis of equality of a patient's baseline and six-month score in the absence of treatment effect.

[c] Exact Wilcoxon signed-rank test p-value.

All reported p-values are nominal**.**

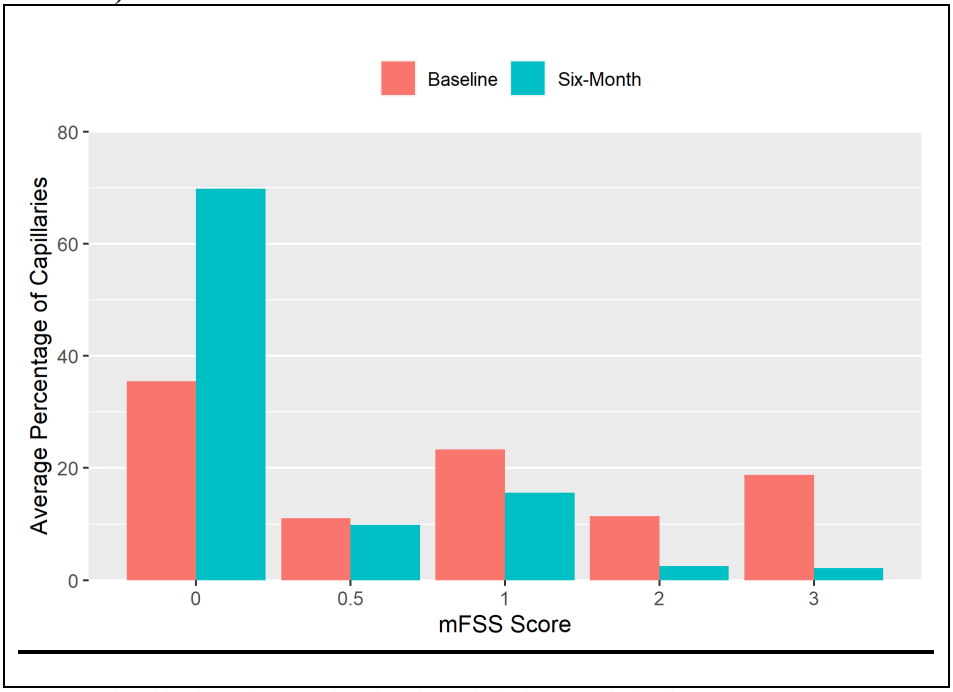
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0001) on May 27, 2020

Figure 5: Absolute Change in Weighted mFSS score from Baseline to 6-months (Trial PB-102-F01/F02)



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0001) on May 27, 2020

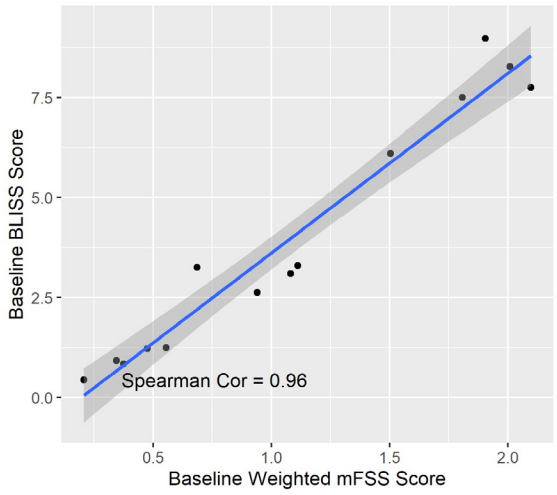
Figure 6: Overall Distribution of the mFSS Score at Baseline and 6 Months (Trial PB-102-F01/F02)



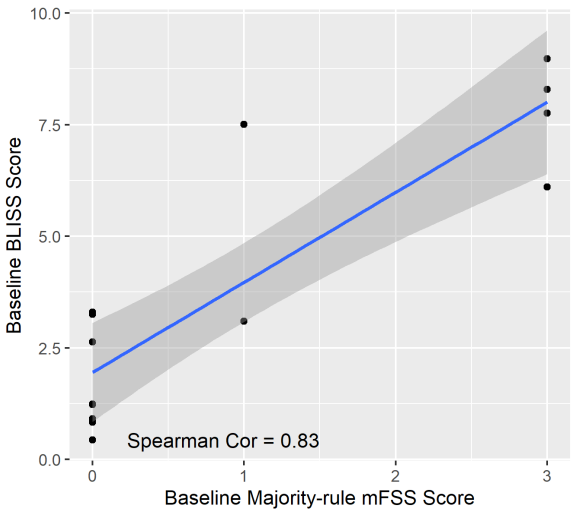
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0001) on May 27, 2020

Figure 7: Correlation of mFSS Scores and BLISS scores (Trial PB-102-F01/F02)

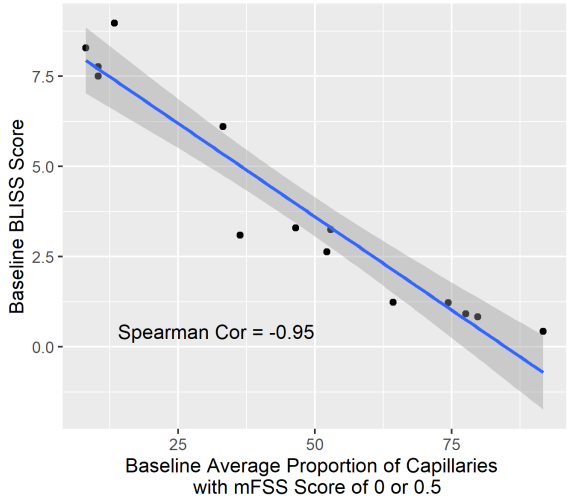
A. BLISS vs. Weighted mFSS Score (Baseline)



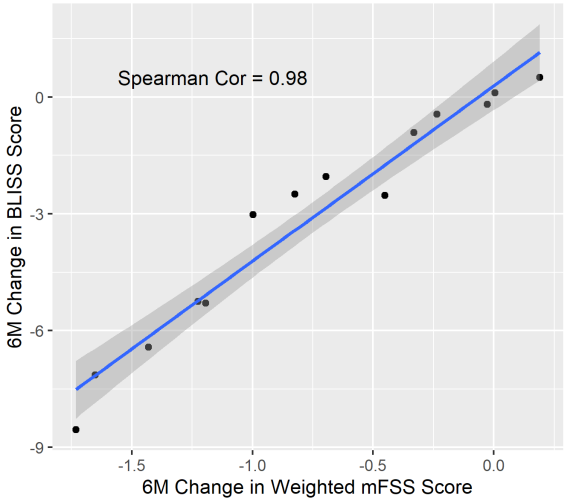
B. BLISS vs. Majority-rule mFSS Score (Baseline)



C. BLISS vs. Average Proportion of Capillaries with mFSS Score of 0 or 0.5 (Baseline)

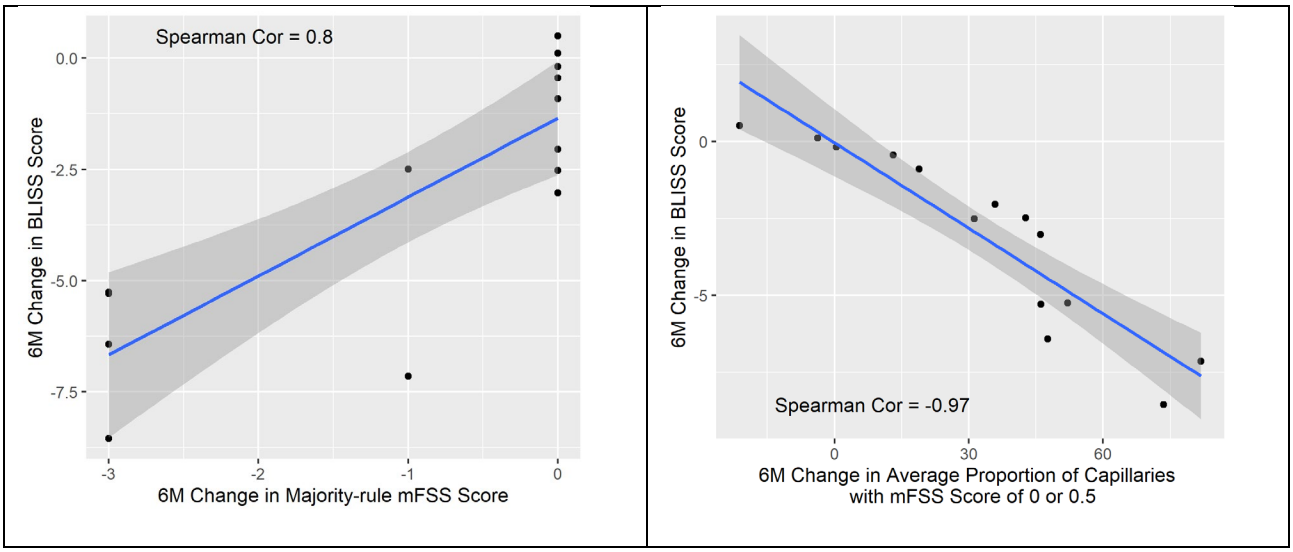


D. BLISS vs. Weighed mFSS Score (Change from Baseline to 6 Months)



E. BLISS vs. Majority-rule mFSS Score (Change from Baseline to 6 Months)

F. BLISS vs. Average Proportion of Capillaries with mFSS Score of 0 or 0.5 (Change from Baseline to 6 Months)



The biopsy-level **weighted mFSS** score is derived by computing the weighted average of the capillary-specific scores. For example, if 30% of capillaries have a score of 3, 49% a score of 2, 20% a score of 1, 10% a score 0.5, and 11% a score of 0, the **weighted mFSS** score will be 2.13 (= 0.3*3 + 0.49*2 + 0.2*1 + 0.1*0.5 + 0.11*0). The biopsy-level **majority-rule mFSS** score corresponds to the score received by the majority of the capillaries. In the above example, the **biopsy-level majority-rule mFSS** score will be 2 since a majority of the capillaries received a score of 2.

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0001 on May 27, 2020 and eCTD 0025 on November 11, 2020)

Sensitivity Analysis Including Subject with Mislabeled Slides

One male subject (ID: (b) (6); classic phenotype) was removed from the main efficacy analysis. For this subject, the biopsy slides were mislabeled and thus could not be matched to the correct visits (i.e., baseline versus six-month visit times could not be identified). The review team derived the BLISS score for each visit based on the Applicant's raw dataset. The two derived BLISS scores were 5.1 and 9.6. The review team conducted sensitivity analysis for the following two scenarios:

1. Worst case scenario analysis (assumes the BLISS score increased by attributing the higher of the two scores to the six-month visit)

2. Best case scenario analysis (assumes the BLISS score decreased by attributing the higher of the two scores to the baseline visit)

The results of the sensitivity analysis support the results of the main efficacy analysis (Table 8).

When assuming the baseline score was 5.1 and the 6-month score was 9.6 (i.e., worst-case scenario), the mean change from baseline in BLISS scores across all patients was -2.6 (95% CI -4.5 ,-0.7; nominal p = 0.01). The inclusion of this subject under this assumption attenuates the main efficacy result of mean reduction of -3.1 (95% CI -4.8, -1.4) by 0.5 units.

When assuming the baseline score was 9.6 and the six-month score was 5.1, the mean change from baseline in BLISS score across all patients was -3.2 (95% CI -4.8, -1.6; nominal p < 0.001). Although the inclusion of this subject will numerically change the main efficacy results of the mean change in BLISS score, the overall efficacy results are qualitatively unchanged and remain nominally statistically significant.

Under the two scenarios considered above, the median change in BLISS score was the same as that from the main analysis (Table 8).

Of note, this subject had the highest plasma Lyso-Gb3 at baseline (273 ng/ML) and a notable decline in plasma Lyso-Gb3 over the course of the study (48%, 75% and 96% percent reduction at 6, 12 and 24 months, respectively). Given the high correlation between change in plasma lyso-Gb3 and change in BLISS score observed in this study (e), this subject likely had a reduction in BLISS score at 6 months; consequently, for this subject, the baseline and 6-month BLISS scores were likely 9.6 and 5.1, respectively.

No sensitivity analyses were done for the one female patient whose biopsy tissue who could not be scored at baseline as it was taken from the medulla of the kidney. For this patient, the missing Gb3 data is assumed to be missing completely at random.

Table 8: Sensitivity Analysis Including Subject with Mislabeled Slides (Trial PB-102-F01/F02)

Population	N	Mean Difference (95% CI)	Exact P-value	Median Difference	Exact Signed-rank P-value
Main Efficacy Population	14	-3.1 (-4.8, -1.4)	<0.001	-2.5	0.001
EP + (b) (6) (Worst-case)[1]	15	-2.6 (-4.5, -0.7)	0.011	-2.5	0.008
EP + (b) (6) (Best-case)[2]	15	-3.2 (-4.8, -1.6)	<0.001	-2.5	<0.001

[1]Since subject (b) (6) 's scores could not be attributed to a visit, the "worst case" analysis assumed the baseline score is 5.1 and the six-month score is 9.6.

[2]The "best case" analysis assumed the baseline score is 9.6 and the six-month score is 5.1.

All reported p-values are nominal.

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025) on November 11, 2020

Efficacy Results: Mean eGFR and Annualized eGFR Slope

The mean (SE) eGFR at baseline was 111.7 (5.5) mL/min/1.73 m², ranging from 78 to 156 mL/min/1.73 m² at baseline. The mean (SE) change from baseline in eGFR was -0.4 (1.3) mL/min/1.73 m² (range -5.9 to 8.5) at Month 24 and -10.9 (2.0) mL/min/1.73 m² (range -19.2 to 1.1) at Month 60 (Table 9).

Table 9: eGFR (mL/min/1.73 m²) Over Time (Trial F01/F02/F03)

Timepoints[1] Parameters		**Male/Classic Patients N=8**	**Female/Non-classic Patients N=7**	**Treated ≥5 years N=10**	**Overall N=15**
Baseline					
Absolute value	n	8	7	10	15
	Mean (SE)	118.1 (7.7)	104.4 (7.5)	107.9 (6.0)	111.7 (5.5)
Month 12 (Visit 27)					
Absolute value	n	8	6	10	14
	Mean (SE)	117.1 (9.0)	101.1 (9.6)	108.5 (7.7)	110.3 (6.7)
Change from baseline	n	8	6	10	14
	Mean (SE)	-1.0 (3.0)	-1.1 (3.2)	0.6 (2.4)	-1.0 (2.1)
Month 24 (Visit 54)					
Absolute value	n	7	4	10	11
	Mean (SE)	110.2 (6.4)	101.1 (10.9)	107.5 (6.1)	106.9 (5.5)
Change from baseline	n	7	4	10	11
	Mean (SE)	-2.5 (0.9)	3.1 (2.4)	-0.3 (1.4)	-0.4 (1.3)
Month 48 (Visit 106)					
Absolute value	n	6	4	10	10
	Mean (SE)	105.9 (4.2)	97.1 (12.0)	102.4 (5.2)	102.4 (5.2)
Change from baseline	n	6	4	10	10
	Mean (SE)	-8.6 (4.6)	-0.9 (5.7)	-5.5 (3.6)	-5.5 (3.6)
Month 60 (Visit 132)					
Absolute value	n	6	4	10	10
	Mean (SE)	100.0 (8.3)	92.4 (11.4)	97.0 (6.4)	97.0 (6.4)
Change from baseline	n	6	4	10	10
	Mean (SE)	-14.5 (1.7)	-5.6 (2.6)	-10.9 (2.0)	-10.9 (2.0)

[1] Baseline values were those from either baseline (i.e. Visit 1) or screening (whichever was the latest observation) in study PB-102-F01 and the presented timepoints correspond to an overall treatment period of 72 months with PRX-102 (i.e. 3 months in study PB-102-F01, 9 months in study PB-102-F02 and 60 months in study PB-102-F03).

Source: Applicant's *Clinical Study Report*, Table 16, page 73

The mean (SE) annualized eGFR slope was -1.6 (0.8) mL/min/1.73 m²/year, with this value

ranging from -6.5 to 4.9 mL/min/1.73 m²/year (Table 10). Overall, male patients had a faster rate of eGFR loss compared to females.

Table 10: eGFR Slope (mL/min/1.73 m²/year) Over Time (Trial F01/F02/F03)

	Male/Classic Patients N=8	Female/Non-classic Patients N=7	Overall N=15
Mean (SE)	-2.4 (0.9)	-0.7 (1.3)	-1.6 (0.8)
Median (min, max)	-2.8 (-5.2, 2.3)	-1.3 (-6.5, 4.9)	-1.5 (-6.5, 4.9)

max = maximum; min = minimum; SE = standard error.

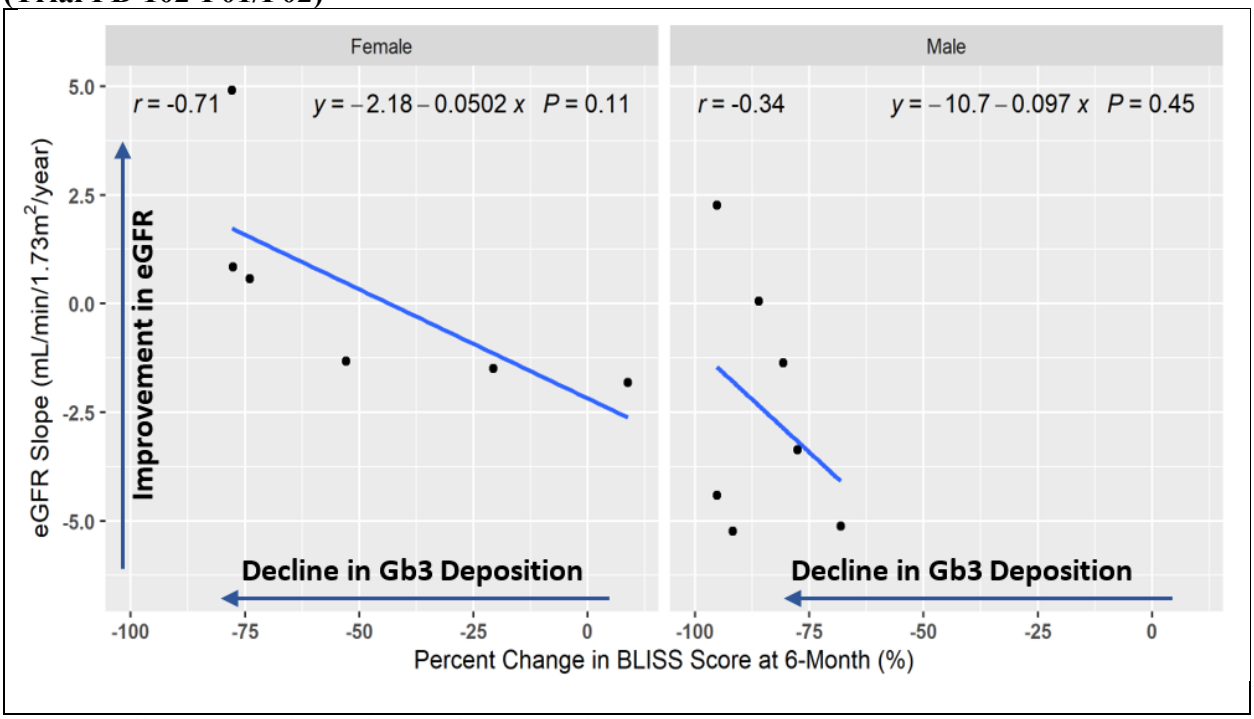
Source: Applicant's *Summary of Clinical Efficacy*, Table 17, page 64

Given the lack of concurrent control arm and data on the expected trajectory of eGFR in the absence of treatment, the reviewer finds the interpretation of the results on the eGFR endpoint is limited. However, since eGFR is a well-known established measurement of kidney function, the review team performed additional exploratory analysis to examine the relationship between decline in Gb3 deposition in kidney PTCs (BLISS score) and improvement in kidney function as measured by eGFR.

Relationship between Change in BLISS Score and eGFR Slope

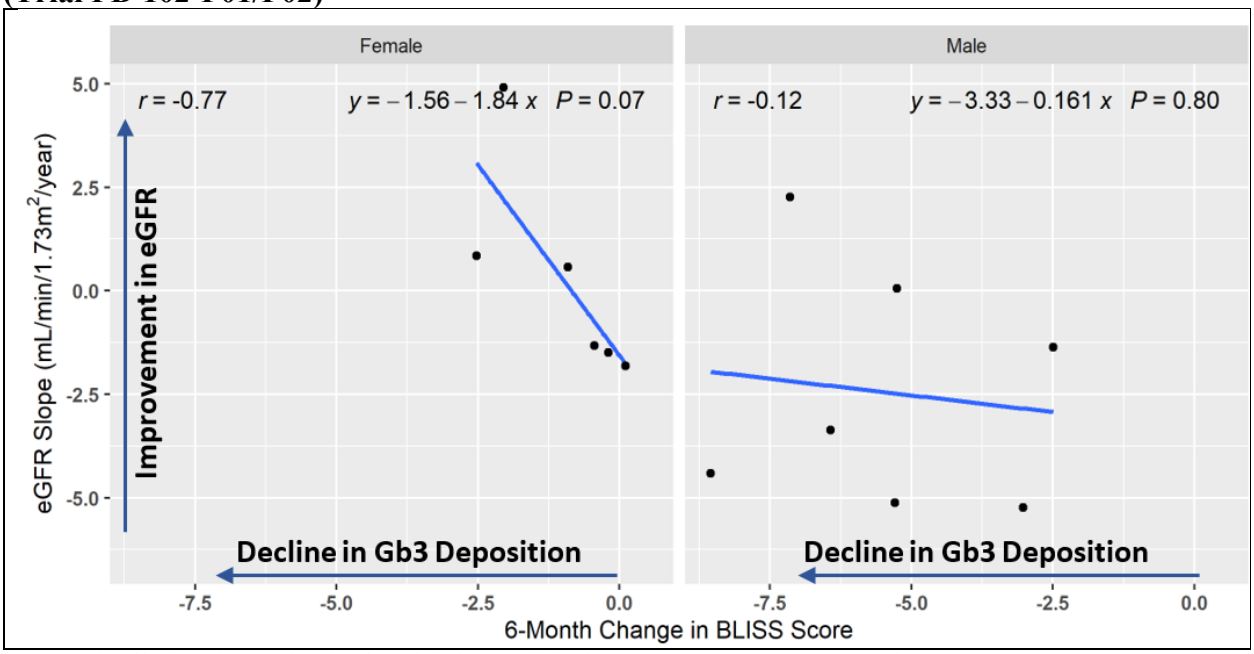
The relationship between change in BLISS score and eGFR slope was explored in Trial F01/F02/F03 (Figure 8 and Figure 9). The eGFR slope was calculated based on data obtained over a period ranging from 12 months up to 60+ months. Among female subjects (n =6), there was a strong inverse correlation between percent change in BLISS score and eGFR slope (correlation = -0.71; 95% CI: -0.97, 0.24). Among males (n=7), there was a weak inverse correlation of -0.34 (95% CI: -0.87, 0.55). Overall, reduction in renal Gb3 at 6-month appeared to associate with better outcome in eGFR slope.

Figure 8: Correlation between 6-Month Percent Change in BLISS score and eGFR Slope (Trial PB-102-F01/F02)



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0058)) on November 9, 2022

Figure 9: Correlation between 6-Month Absolute Change in BLISS score and eGFR Slope (Trial PB-102-F01/F02)



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0058) on November 9, 2022

3.3 Evaluation of Efficacy in Trial PB-102-F20

Key timelines and events

The trial protocol was finalized on July 14, 2017. The first patient was enrolled on August 22, 2016 and the last patient completed the trial on October 12, 2021. The last SAP (dated September 24, 2020) was submitted to the FDA on October 8, 2020 prior to the conduct of the pre-planned 12-month interim analysis. The database lock for the pre-planned 12-month interim analysis took place in April of 2021. After receiving the Agency's CR letter (dated April 27, 2021) on their original BLA, for the primary analysis, the Applicant proposed changing the original superiority test on the mean eGFR slope to an NI test on the median eGFR slope using an NI margin of -3 mL/min/1.73m^2/year at the End-of-Review meeting (held on September 9, 2021).

3.3.1 Study Design and Endpoints (Trial PB-102-F20)

Trial PB-102-F20 was a randomized, multi-center, active-controlled, parallel-group study. The primary objective of the study as stated in the protocol was to evaluate the efficacy of PRX-102 compared to agalsidase beta in Fabry disease patients with impaired renal function. Patients were randomized 2:1 to either switch to PRX-102 or continue treatment with agalsidase beta. Randomization was stratified according to whether the urine protein-to-creatinine ratio (UPCR), a

measure of kidney function, was above or below 1 gr/gr. Both study products were administered as an intravenous infusion every 2 weeks, at a dosage of 1 mg/kg, for up to 24 months.

The key inclusion criteria for this trial were:

(1) patients should be between 18 to 60 years old
(2) patients should have received agalsidase beta treatment for at least a year prior to screening visit
(3) patients' eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation should be between 40 to 90 mL/min/1.73 m^2 at screening visit
(4) patients should have an annualized rate of loss of eGFR of at least 2 mL/min/1.73m^2/year at screening visit

Trial PB-102-F20 was conducted at 29 study centers in 12 countries: the United States, the United Kingdom, The Netherlands, Spain, France, Italy, Norway, Slovenia, Switzerland, Finland, Hungary, and the Czech Republic.

Primary Efficacy Endpoint

The protocol-defined primary efficacy endpoint was the annualized rate of change (slope) of eGFR.

For the derivation of the primary endpoint, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was employed (Figure 10). Serum creatinine values (used in the CKD-EPI) formula were collected at baseline, and either every 2 weeks or every 4 weeks for a planned total of 30 assessments over the duration of two years.

Figure 10: Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Formula

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

where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. Age is the actual age when the patient's serum creatinine is collected.

Secondary Efficacy Endpoints

The SAP specifies the following secondary efficacy endpoints:

1. Change from baseline to all time points in the following measures:
    a. Plasma globotriaosylsphingosine (Lyso-Gb3)
    b. Left Ventricular Mass Index (LVMI) (g/m^2) by Magnetic Resonance Imaging (MRI)
    c. Plasma globotriaosylceramide (Gb3)

d. Urine Lyso-Gb3
e. Protein/Creatinine ratio spot urine test
f. Frequency of pain medication use
g. Exercise tolerance (Stress Test)
h. Short Form Brief Pain Inventory (BPI)
i. Mainz Severity Score Index (MSSI)
j. Quality of life (EQ-5D-5L)

2. Occurrence of Fabry Clinical Events (FCE): a composite of cardiac events, cerebrovascular events, renal events, and deaths

3. Achieving Fabry Kidney Disease therapeutic goals

The review team notes that:

1. *The secondary endpoint of occurrence of FCE was not included in the study protocol (finalized on July 14, 2017). This endpoint was included in the four draft SAPs (dated on 09/05/2019, 06/29/2020, 09/24/2020, and 11/28/2021) and the final SAP (dated on 01/30/2022). FCE were evaluated by the Applicant's medical monitor in a blinded manner.*
2. *Although the Applicant pre-specified several secondary efficacy endpoints, the Agency's evaluation of secondary endpoints was focused on Plasma Lyso-Gb3 and occurrence of FCE which were considered most important by the clinical and clinical pharmacology teams. The review team is uncertain of the clinical meaningfulness of the other secondary endpoints in the context of Fabry disease. Furthermore, some of the secondary endpoints had high rates of missing data rendering the efficacy analysis results as uninterpretable.*

Additional Efficacy Endpoints Evaluated by the Review Team

- Change in eGFR from baseline at week 104. For patients who do not have eGFR data at week 104, their last available eGFR is used to define this endpoint.
- Change in eGFR from baseline at week 100. For patients who do not have eGFR data at week 100, their last available eGFR (prior to week 100) is used to define this endpoint.
- Average change in eGFR from baseline at last two visits (Week 100 and Week 104). This endpoint was defined by averaging the week 100 and week 104 values to minimize the variability observed at week 100 and week 104 separately.

3.3.2 Statistical Analysis Plan (Trial PB-102-F20)

3.3.2.1 Primary Analysis Populations

The primary efficacy analysis population was defined as all randomized patients who received at least one dose (including partial dose) of the study medication (PRX-102 or agalsidase beta). The Sponsor referred to this as the Intent to Treat (ITT) population. The secondary efficacy analysis population was the per protocol (PP) population consisting of all ITT patients who completed at least 24 months of treatment for the final analysis, with study drug compliance of at least 80%, and with no major protocol violations before database lock which may impact their primary

endpoint. Both ITT and PP analysis populations will be used together to inform interpretation of the overall study results.

3.3.2.2 Primary and Supportive Analysis Methods

Prior to unblinding of the 12-month interim data in 2021, the SAP dated September 24, 2020 was submitted to the FDA on October 8, 2020. In this SAP, the primary analysis aimed at testing superiority of PRX-102 over agalsidase beta on the mean eGFR slope using a random intercept and random slope mixed effect model (RIRS) that includes the randomization stratification factor of UPCR (UPCR <1 g/g; >=1 g/g; UPCR is the variable denoting the urine protein to creatinine ratio, a measure of kidney function known as proteinuria) as a covariate. Additionally, the SAP-defined key supportive analysis was a two-stage analysis of covariance (ANCOVA). Using this analysis, in the first stage, patient-specific eGFR slope is estimated using the following linear regression model based on each patient's eGFR data:

$$eGFR_t = \alpha + \beta * t$$

where *t* is time from baseline measured in years, β is the eGFR slope for the patient. The eGFR slope is estimated only for patients with at least four eGFR measurements; for patients with fewer than four eGFR measurements, the eGFR slope is set to missing. In the second stage, the mean eGFR slope is compared between the treatment arms using an ANCOVA that includes the randomization stratification factor as a covariate.

The review team recommended the two-stage ANCOVA as the primary analysis at the pre-BLA meeting (held in 2019) since the RIRS relies on a specific covariance structure for the eGFR data and the missing-at-random assumption for missing data. Additionally, the review team notes that the RIRS does not account for the variability of the eGFR slope contributed by the covariate.

After unblinding of the 12-month interim data, the Applicant made a significant change to their primary analysis in the SAP. The original superiority test on the mean slope was changed to a non-inferiority test on the median eGFR slope using a two-stage analysis. In the first stage, patient-specific eGFR slopes are estimated. In the second stage, the median eGFR slope is compared between the treatment arms using a quantile regression model that includes treatment arm indicator as a covariate. The Applicant intended to claim non-inferiority if the lower bound of the confidence interval for the treatment difference (PRX-102 minus agalsidase beta) was greater or equal to -3.0 mL/min/1.73 m^2/year (Applicant's proposed NI margin).

However, the review team does not agree with the Applicant's NI test because there are no data to support their proposed NI margin for agalsidase beta in the setting of Trial PB-102-F20 (see Appendix 3 for review team's evaluation on the Applicant's NI margin justification).

To examine the robustness of the efficacy results and to provide further understanding of the treatment effect, the following supportive analyses were conducted by the review team:

1. Supportive Analysis (SA) 1**:** ANCOVA model for the mean eGFR slopes adjusting for continuous baseline UPCR. The bootstrap approach was used to construct confidence intervals for the mean treatment difference since this approach does not rely on the

assumptions of normality and homoscedasticity.
The rationale for performing an analysis adjusting for proteinuria as a continuous covariate is as follows: first, UPCR is known to be a strong predictor of eGFR decline, second, although the binary proteinuria variable appeared balanced between the two treatment arms, there was a noted imbalance in the continuous proteinuria variable (see Table 19 and Figure 21) and lastly, baseline proteinuria had the strongest correlation with eGFR slope over 2 years ($r = 0.57$; $p<0.0001$) and was the strongest predictor of Fabry clinical events (HR associated with 1 unit increase was 3.1 (95% CI: 1.6, 5.9; $p<0.001$). Regarding the correlation between eGFR slope and proteinuria, it is noteworthy that one subject on the PRX-102 arm who had the highest baseline proteinuria of 3.1, also had the worst baseline eGFR slope of -30.5 mL/min/1.73m2/year, and the worst post-baseline eGFR slope of -45.3 mL/min/1.73m2/year. This patient experienced an end-renal disease around 6 months post-baseline.

2. SA2: ANCOVA model for the mean eGFR slopes adjusting for binary proteinuria variable (UPCR). The bootstrap approach was used to construct confidence intervals.
3. SA3: quantile regression for the median eGFR slopes adjusting for binary proteinuria variable (UPCR). This is the Applicant's proposed primary analysis model after unblinding of the 12-month interim data. This analysis was performed using the PROC QUANTREG procedure in SAS with the resampling option for the estimation of standard error. However, based on the reviewer's experience, the Applicant's proposed quantile regression analysis cannot provide reliable treatment effect estimates in small sample settings.
4. SA4: ANCOVA model for mean change in eGFR from baseline at Week 104 adjusting for baseline continuous UPCR and baseline eGFR.
5. SA5: ANCOVA model for mean change in eGFR from baseline at Week 100 including baseline continuous UPCR and baseline eGFR.
6. SA6: ANCOVA model for mean average change in eGFR from baseline at last two visits (Week 100 and Week 104) adjusting for baseline continuous UPCR and baseline eGFR.

3.3.2.3 Sensitivity Analyses for Missing Data

Among the ITT patients (N = 77), five patients (6.5%) discontinued the study prematurely. Among these five patients, three of them stated that they discontinued the study for reasons not related to study drug, and the remaining two patients dropped due to AE (Table 13). The primary analysis specified in the original SAP included all available eGFR data across all ITT patients, relied on the missing-at-random assumption for missing data, and did not involve any explicit imputation for missing data. Based on the reasons presented in Table 13 and the eGFR profile over time (Figure 20), the missing-at-random assumption appears reasonable for three out of five subjects who dropped out for reasons other than an AE.

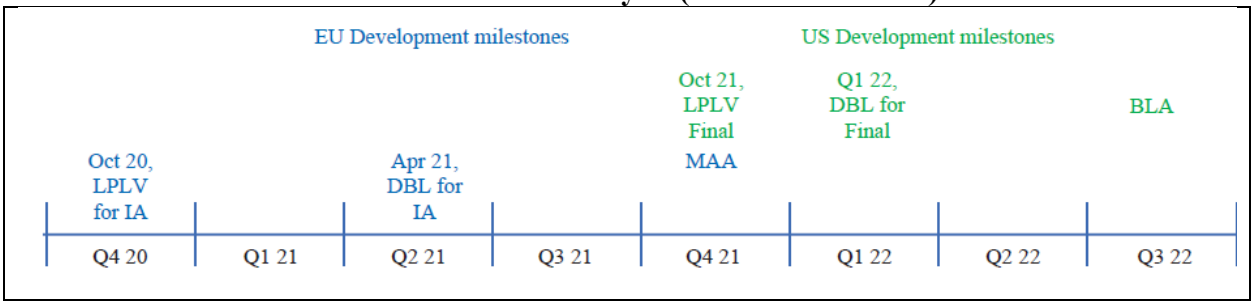
The original SAP planned to perform a sensitivity analysis using a reference-based multiple imputation approach to examine the robustness of the primary analysis results with respect to the missing-at-random assumption. This sensitivity analysis would have been appropriate in the context of a superiority test. However, since the Applicant changed the primary testing from

superiority to non-inferiority in their final SAP, the proposed sensitivity analyses was not considered to be appropriate, and the Applicant removed this analysis from their final SAP. The Agency's two-stage ANCOVA used all available eGFR data to derive each individual's slope, targeting a while-on-treatment estimand. This approach estimated the slope for four out of the five dropouts; the remaining one person had only two eGFR measures and was not included in the two-stage ANCOVA as prespecified in the SAP. Given the small amount of missing data and the similar results from the Applicant's primary analysis and the two-stage ANCOVA, the review team concluded that the impact of missing data was minimal.

3.3.2.4 Interim Analysis for the European Medicines Agency

To submit Marketing Authorization Application (MAA) to the European Medicines Agency (EMA), the Applicant performed an analysis to demonstrate non-inferiority of PRX-102 to agalsidase beta at 12 months. Since the Applicant's interim analysis was not intended to stop the study for either futility or efficacy for the FDA, there was no adjustment to the alpha-level to be used for the final analysis at 24 months. However, it is important to acknowledge that the Applicant would have had access to comparative analysis results after these interim analyses. When trial data are examined in a comparative interim analysis, data analyses that were not prospectively planned as the basis for adaptations may unexpectedly appear to indicate that some specific design change (e.g., changing analysis methods) is justified or might increase the potential for a statistically significant final trial result. Unplanned modifications based on non-prospectively planned analyses can create difficulty in controlling the Type I error probability and in interpreting the trial results. Therefore, the review team considered the primary analysis defined in the SAP (dated September 24, 2020) prior to the unblinding of the 12-month interim analysis for the EMA to be the Applicant's primary analysis. Additional information regarding the timeline of interim analysis for EMA and final analysis for FDA are shown in Table 11.

Table 11: Timeline of Interim and Final Analysis (Trial PB-102-F20)



LPLV: Last Patient Last Visit; **IA:** Interim Analysis; **DBL:** Database Lock; **MAA:** Marketing Authorization Application; **BLA:** Biologics License Application
Source: Figure 1, Statistical Analysis Plan

3.3.3 Patient Disposition, Demographic and Baseline Characteristics (Trial PB-102-F20)

Patient Disposition

Table 12. summarizes the patient disposition for trial PB-102-F20. A total of 127 patients were

screened for eligibility in this study. Of these, 78 met the inclusion criteria and were randomized, and 49 failed to be eligible for study inclusion. The reasons for screen failure were not meeting all the inclusion/exclusion criteria (n=39), withdrawal of consent prior to randomization (n=3), and "other" (n=7).

Patients who met the inclusion criteria (n = 78) were randomized to receive either PRX-102 (n = 53) or agalsidase beta (n = 25). All but one patient in the PRX-102 arm received at least one dose of study product. A total of five patients in the PRX-102 arm and one patient in the agalsidase beta arm terminated the study prematurely while 48 (90.6%) and 24 (96.0%) patients, respectively, completed the 24-month study period. Reasons for discontinuation were AE (2 patients in the PRX-102 arm, none in the agalsidase beta arm) and voluntary withdrawal (3 and 1, respectively). One of the AEs that led to withdrawal, a drug hypersensitivity reaction, was considered related to study treatment. Both subjects with AEs withdrew consent to participate and were not subsequently followed up. Detailed reasons for study withdrawal are described in Table 13.

Table 12: Patient Disposition (PB-102-F20)

		PRX-102 N=53	AGALSIDASE BETA N=25	OVERALL N=78
Number of Subjects Screened	n			127
Reason for Screen Failures+	n			49 (38.6%)
Subject Withdrew Consent	n(%)			3 (2.4%)
Subject Did Not Meet Inclusion/Exclusion Criteria	n(%)			39 (30.7%)
Other	n(%)			7 (5.5%)
Number of Subjects Randomized	n	53	25	78
Number of Subjects Exposed to Treatment&	n(%)	52 (98.1%)	25 (100.0%)	77 (98.7%)
Number of Subjects Completed 12 Months&	n(%)	49 (92.5%)	25 (100.0%)	74 (94.9%)
Number of Subjects Completed at 24 Months&	n(%)	48 (90.6%)	24 (96.0%)	72 (92.3%)

Note 1: + The denominator is Number of Subject Screened.
Note 2: & The denominator is Number of Subject Randomized.
Note 3: Number of Subjects Completed 12 Months presents how many subjects reached the 12 months study milestone. This includes the one subject who withdrew consent before 1st infusion.
Note 4: Number of Subjects Completed at 24 Months presents how many subjects have completed the study (as per protocol or discontinued) at the 24 months milestone.
Note 5: Number of Subjects Discontinued (regardless of whether discontinuation was before or after the 12 months milestone).
Cross-reference: Listing 16.2.1.1, 16.2.1.2

Source: Table 14.1.1, Applicant's Clinical Study Report

Table 13: Demographics and discontinuation reasons for the six subject who withdrew prior to 24 months (Trial PB-102-F20)

ID	Treatment	Age	Sex	Reason for withdrawal
1	PRX-102	38	M	Subject withdrew due to travel distance and financial reasons. Was randomized but **did not receive any study treatment**.
2	PRX-102	34	M	Got a new job and felt he did not have time for this study. Was offered home infusions but declined.

3	PRX-102	36	F	Subject had a family situation that was interfering with her ability to come in for her infusions.
4	PRX-102	27	M	End stage kidney failure (AE). This subject had the worst pre- and post-baseline eGFR slope (-30 and -45 mL/min/1.73m^2/year, respectively), the worst baseline proteinuria (3.12), and the lowest plasma lyso-Gb3 (0.8 nM) in the trial.
5	Agalsidase beta	46	M	Personal reasons
6	PRX-102	39	M	Moderate infusion drug allergy (AE)

AE = Adverse event,
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0058)) on November 9, 2022

Demographic and Baseline Characteristics

Demographic and baseline data are summarized in Table 14. Most of the trial participants were white (94%) and male (61%). The Fabrazyme group had more male patients than the PRX-102 group (18/25 = 72% vs 29/52 = 56%). The patients in the Fabrazyme group were slightly older (median age of 48 years for Fabrazyme and 44 years for PRX-102) and treated for a longer duration prior to randomization (5.7 years vs 4.3 years).

Kidney function as measured by eGFR appeared balanced between the two treatment arms (mean of 73.5 mL/min/1.73m^2 for PRX-102 arm vs. mean of 74.2 mL/min/1.73m^2 for Fabrazyme arm). The eGFR slope at baseline, Fabry disease subtype (classic vs. non-classic), ADA status and plasma lyso-Gb3 appeared balanced between the treatment arms. However, the baseline slope appeared more variable in the PRX-102 arm (SD = 6.6) than the Fabrazyme arm (SD = 4.3). There was a marked difference in the distribution of the baseline proteinuria between the two treatment groups (Table 19). While the proportions of patients with baseline proteinuria ≥ 1 g/g were similar in both groups (13.5% for PRX-102 and 12% for Fabrazyme), both the mean and median of baseline proteinuria in the PRX-102 group were more than 50% higher than those in the Fabrazyme group (mean: 0.44 vs 0.28; median: 0.13 vs 0.07; 75% quantile: 0.65 vs 0.24; maximum: 3.12 vs 2.10; Figure 21**.** shows empirical cumulative distribution function for proteinuria by treatment). This imbalance in UPCR persisted across many important subgroups including males, females, classic, non-classic, ADA +, ADA-, US, non-US, eGFR<60 and eGFR≥60 (Table 19).

Table 14: Demographic and Baseline Characteristics by Treatment Group and Overall (Trial PB-102-F20)

	PRX-102 N=52	Fabrazyme N=25	Overall N=77
Age (Years)			
Mean (SD)	43.9 (10.2)	45.2 (9.6)	44.3 (10.0)
Median (min ; max)	44.0 (20 ; 60)	48.0 (18 ; 58)	46.0 (18 ; 60)
Gender			
Male, n (%)	29 (55.8%)	18 (72.0%)	47 (61.0%)
Female, n (%)	23 (44.2%)	7 (28.0%)	30 (39.0%)
Race			
White, n (%)	49 (94.2%)	23 (92.0%)	72 (93.5%)
Duration of Previous Continuous Fabrazyme Treatment (Months)			
Mean (SD)	65.03 (47.98)	77.34 (41.25)	69.03 (46.00)
Residual Enzyme Activity in Leukocytes (%)			
Mean (SD)	18.0 (18.17)	25.1 (58.99)	20.3 (36.49)
Median (min ; max)	11.0 (1.0 ; 71.9)	8.9 (1.9 ; 297.0)	9.7 (1.0 ; 297.0)
Residual Enzyme Activity in Plasma (%)			
Mean (SD)	24.0 (35.00)	2526.8 (12387.64)	836.6 (7060.55)
Median (min ; max)	13.1 (0.3 ; 206.1)	3.6 (0.0 ; 61984.6[b])	12.4 (0.0 ; 61984.6)
eGFR (mL/min/1.73 m^2) [a]			
Mean (SD)	73.46 (20.21)	74.16 (20.97)	73.69 (20.32)
Median (min ; max)	73.45 (30.2 ; 125.9)	74.85 (34.1 ; 107.6)	74.51 (30.2 ; 125.9)
Annualized eGFR Slope at Baseline (mL/min/1.73 m^2/year)			
Mean (SD)	-8.03 (6.60)	-8.25 (4.27)	-8.10 (5.92)
Median (min ; max)	-6.70(-30.5 ; 6.3)	-7.84 (-20.3 ; -2.8)	-7.25 (-30.5 ; 6.3)
UPCR Categories at Baseline, n (%)			
UPCR ≤0.5 g/g	36 (69.2%)	20 (80.0%)	56 (72.7%)
0.5 < UPCR <1 g/g	9 (17.3%)	2 (8.0%)	11 (14.3%)
1 ≤ UPCR g/g	7 (13.5%)	3 (12.0%)	10 (13.0%)
Plasma Lyso-Gb3 (nM)			
Mean (SD)	26.22 (27.27)	32.14 (35.38)	28.14 (30.04)
Median (min ; max)	15.20 (0.8 ; 143.9)	17.60 (2.1 ; 142.0)	17.30 (0.8 ; 143.9)
Fabry Disease Classification [c]			
Classic, n (%)	27 (51.9%)	14 (56.0%)	41 (53.2%)
Non-classic, n (%)	25 (48.1%)	11 (44.0%)	36 (46.8%)
Treatment with ACEi or ARB			
Yes, n (%)	26 (50.0%)	16 (64.0%)	42 (54.5%)
No, n (%)	26 (50.0%)	9 (36.0%)	35 (45.5%)

	PRX-102 N=52	Fabrazyme N=25	Overall N=77
Premedication Use for ERT Infusion prior to Enrolment			
Yes, n (%)	20 (38.5%)	15 (60.0%)	35 (45.5%)
No, n (%)	32 (61.5%)	10 (40.0%)	42 (54.5%)
ADA Status to PRX-102 [d]			
Positive, n (%)	18 (34.6%)		
Negative, n (%)	34 (65.4%)		
ADA Status to Fabrazyme [d]			
Positive, n (%)		8 (32.0%)	
Negative, n (%)		17 (68.0%)	

ACEi = Angiotensin converting enzyme inhibitors; ADA = anti-drug antibody; ARB = angiotensin receptor blocker; CKD-EPI = Chronic Kidney Disease – Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; ERT = enzyme replacement therapy; IgG = Immunoglobulin G; Lyso-Gb3 = globotriaosylsphingosine; Max = maximum; Min = minimum; SD = standard deviation; UPCR = urine protein to creatinine ratio.

a. Estimated using the CKD-EPI equation;
b. Very high value is probably incorrect but could not be verified/corrected;
c. Classic Fabry disease defined as a patient with ≤ 5% mean of laboratory normal ranges residual enzymatic activity in plasma or leukocytes at baseline (V1, Day 1) and at least one Fabry-specific symptom (cornea verticillata, acroparesthesias and/or angiokeratomas)
d. ADA status for PRX102/Fabrazyme based on the results of the IgG for PRX102/Fabrazyme at baseline.

Source: Table 4, Summary of Clinical Efficacy (Module 2)

3.3.4 Results (Trial PB-102-F20)

Efficacy Results: Primary Endpoint of eGFR Slope

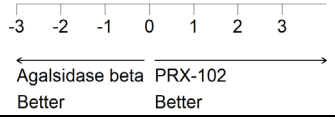
All analyses (discussed in Section 3.3.2) yielded comparable results between the two treatment arms (Figure 11). Based on the Applicant's original primary analysis (RIRS), the estimated mean eGFR slopes were -2.4 and -2.3 mL/min/1.73 m^2/year in the PRX-102 and agalsidase beta arms, respectively, and the treatment difference was -0.1 (95% CI: -2.2, 2.1) mL/min/1.73 m^2/year. Based on the ANCOVA adjusted for continuous baseline proteinuria, the estimated mean eGFR slopes were -2.0 and -3.1 mL/min/1.73 m^2/year in the PRX-102 and agalsidase beta arms, respectively, and the treatment difference was 1.1 (95% CI: -0.8, 3.1) mL/min/1.73 m^2/year.

The results of the analyses on eGFR slopes were supported by the analysis of change from baseline in the average eGFR at the last two visits (100 and 104 weeks). The estimated mean changes were -3.0 and -3.8 mL/min/1.73 m^2 in the PRX-102 and agalsidase beta arms, respectively. The difference in mean change (PRX-102 – agalsidase beta) was 0.8 (95% CI: -3.0, 4.6) mL/min/1.73 m^2 or annualized change of 0.4 (95% CI: -1.5, 2.3) mL/min/1.73 m^2/year.

Additionally, the analysis results in the PP population (n = 72) were consistent with those in the ITT population (n = 77).

Figure 11: Primary and Supportive Analyses Results (Trial PB-102-F20)

Analysis Type (Population): Summary Measure (Model)	eGFR Slope PRX-102	Agalsidase beta	Treatment Difference (95% CI)
PA (ITT): Mean eGFR Slope (RIRS)	-2.4	-2.3	-0.1 (-2.2, 2.1)
PA (PP): Mean eGFR Slope (RIRS)	-2.4	-2.3	0.0 (-2.2, 2.2)
SA1 (ITT): Mean eGFR Slope (ANCOVA)	-2.0	-3.1	1.1 (-0.8, 3.1)
SA1 (PP): Mean eGFR Slope (ANCOVA)	-2.2	-2.6	0.4 (-1.0, 1.8)
SA2 (ITT): Mean eGFR Slope (ANCOVA)	-2.3	2.4	0.1 (-2.0, 2.2)
SA2 (PP): Mean eGFR Slope (ANCOVA)	-2.3	-2.3	0.0 (-1.4, 1.5)
SA3 (ITT): Median eGFR Slope (QR)	-1.8	-2.2	0.4 (-1.7, 2.4)
SA3 (PP): Median eGFR Slope (QR)	-2.2	-2.3	0.1 (-1.9, 2.1)
SA4 (ITT): Mean eGFR Change (ANCOVA)	-1.5	-1.3	-0.3 (-2.5, 1.9)
SA4 (PP): Mean eGFR Change (ANCOVA)	-1.6	-1.1	-0.5 (-2.7, 1.8)
SA5 (ITT): Mean eGFR Change (ANCOVA)	-1.4	-2.8	1.3 (-0.9, 3.5)
SA5 (PP): Mean eGFR Change (ANCOVA)	-1.6	-2.6	1.0 (-1.2, 3.3)
SA6 (ITT): Mean eGFR Change (ANCOVA)	-1.5	-1.9	0.4 (-1.5, 2.3)
SA6 (PP): Mean eGFR Change (ANCOVA)	-1.6	-1.8	0.3 (-1.7, 2.2)



PA = Primary Analysis. **SA** = Supportive Analysis. ITT = Intention to Treat Population (N = 51 for PRX-102 arm, N = 25 for Agalsidase beta arm). PP = Per Protocol Population (N = 48 for PRX-102 arm, N = 24 for Agalsidase beta arm).

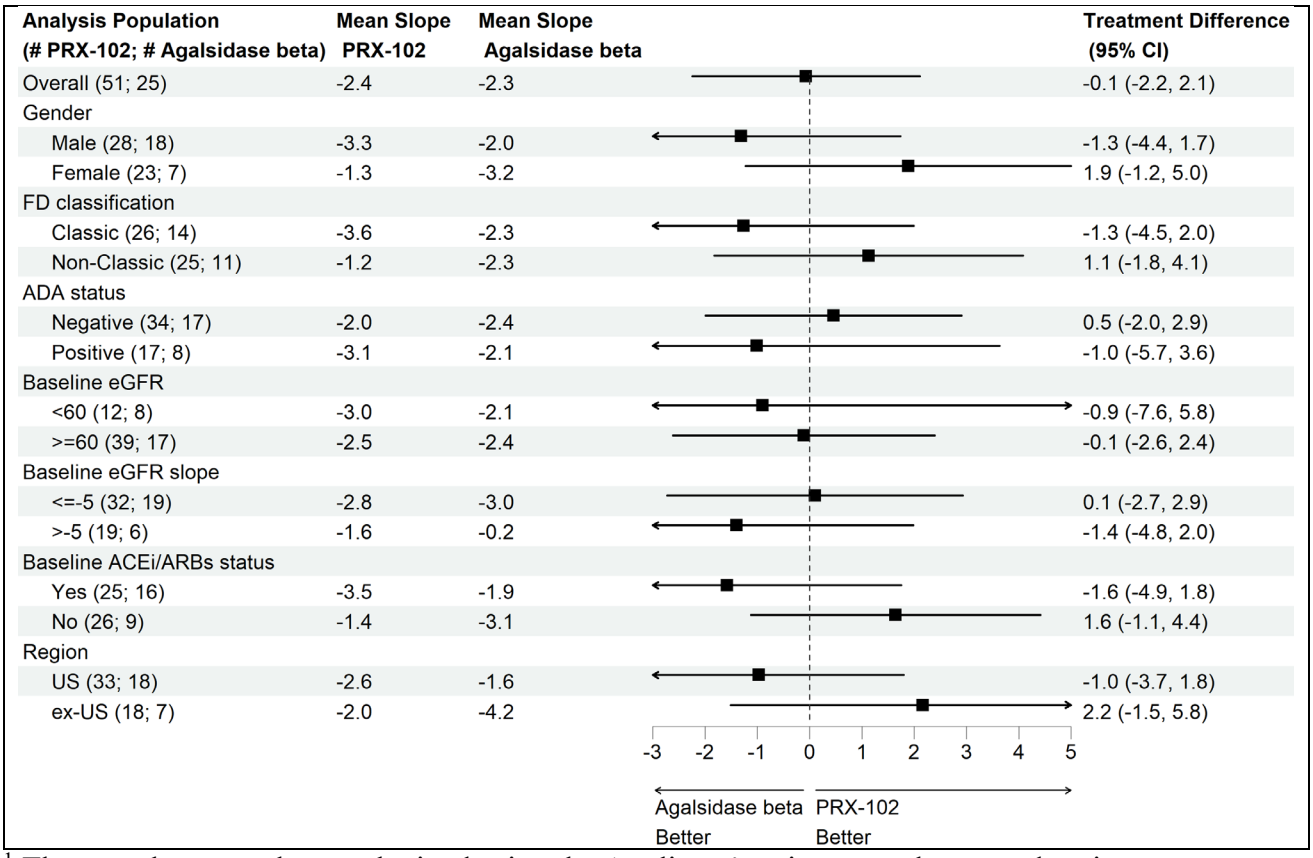
SA1: ANCOVA model for the mean eGFR slopes adjusting for continuous baseline UPCR. **SA2**: ANCOVA model for the mean eGFR slopes adjusting for binary proteinuria variable (UPCR). **SA3**: quantile regression for the median eGFR slopes adjusting for binary proteinuria variable (UPCR). **SA4**: ANCOVA model for mean change in eGFR from baseline at Week 104 adjusting for baseline continuous UPCR and baseline eGFR. **SA5**: ANCOVA model for mean change in eGFR from baseline at Week 100 including baseline continuous UPCR and baseline eGFR. **SA6**: ANCOVA model for mean average change in eGFR from baseline at last two visits (Week 100 and Week 104) adjusting for baseline continuous UPCR and baseline eGFR.
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0057)) on August 23, 2022

Subgroup Analyses Results

The results of key subgroup analyses based on the Applicant's original primary analysis model (RIRS) are presented in Figure 12. The confidence interval for treatment difference within each subgroup was wide and contained 0 suggesting the lack of significant difference between the treatment arms. Given the small overall treatment difference of -0.1 (-2.2, 2.1) mL/min/1.73 m^2/year, it is not surprising that the numerically favorable estimated treatment effect in a specific subgroup is counter-balanced by numerically unfavorable treatment effect in the complementary subgroup. Overall, the findings from the subgroup analyses were consistent with the analysis

results from the overall population.

Figure 12: Subgroup Analyses[1] of eGFR Slope (mL/min/1.73 m2/year) in PB-102-F20

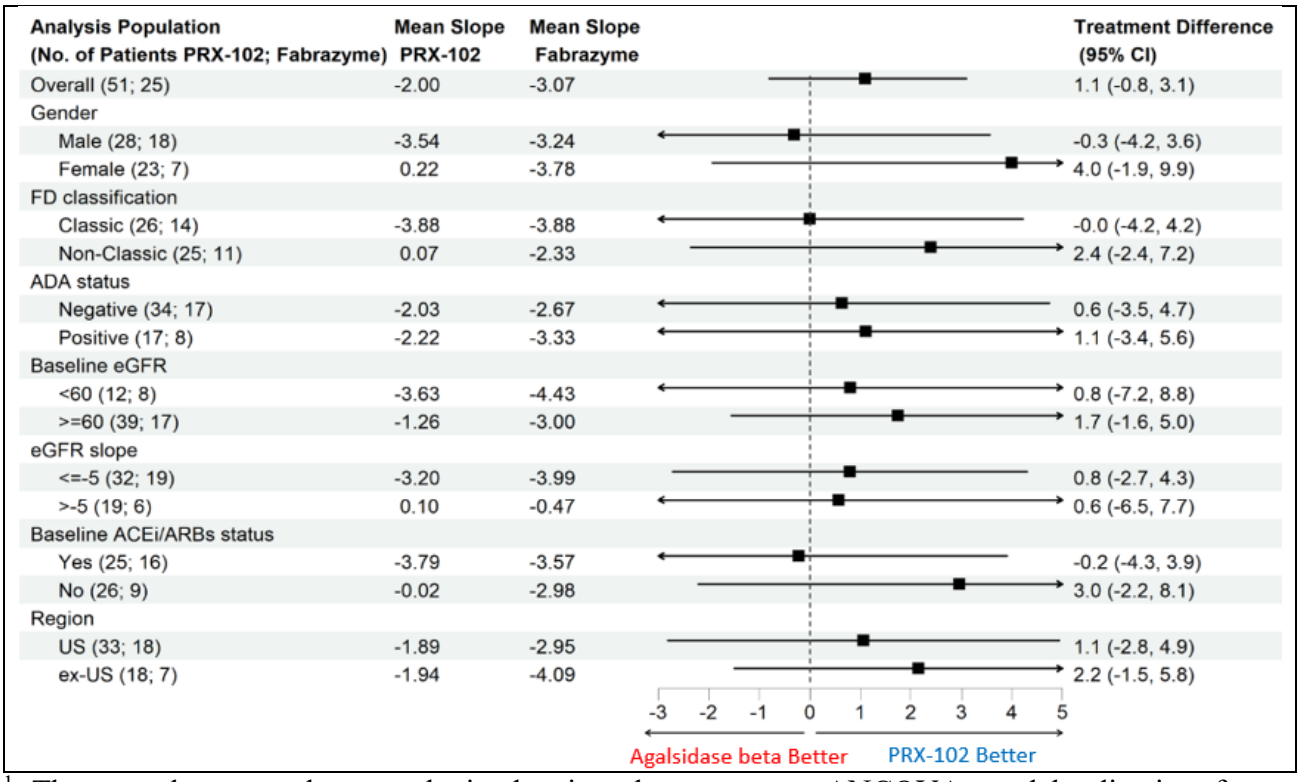


[1] These analyses results are obtained using the Applicant's primary analyses random intercept random slope mixed model.

Additional subgroup analyses were performed using the Agency's two-stage ANCOVA model adjusting for continuous proteinuria variable. The results of these subgroup analyses are presented in Figure 13. Although these results were slightly numerically more favorable towards the PRX-102 arm, the overall conclusion is similar to that from the Applicant's primary analysis

model (Figure 12).

Figure 13: Subgroup Analyses[1] of eGFR Slope (mL/min/1.73 m2/year) in PB-102-F20



[1] These analyses results are obtained using the two-stage ANCOVA model adjusting for continuous proteinuria.

Conclusions on the eGFR Results

An important aspect of any trial is assay sensitivity, i.e., the ability to differentiate an effective treatment from a less effective or ineffective treatment. In an NI study, this means we are able to conclude that a lack of observed differences between arms would reliably indicate that the two treatments are similarly effective. Given the absence of a placebo control arm in an NI study, this relies on the assumption that the active control had its expected effect in the NI study. In this case, there is a lack of previous data to determine the treatment effect of agalsidase beta compared to placebo for a patient population the same as that in Trial PB-102 F20 (e.g., ERT-experienced), such that the expected effect of this active control is not well characterized. Without a known magnitude of the treatment effect of the comparator, an NI margin cannot be identified. Therefore, the design of Trial PB-102 F20 does not allow for inference regarding non-inferiority of PRX-102 to agalsidase beta. However, to aid in the interpretation of the comparable results of the eGFR slope between the two treatment arms, the review team noted the following observations which provide information on the expected effect of agalsidase beta in the population studied in Trial PB-102 F20:

- In an observational study, Weideman et al. (2014)[6] showed significant worsening in eGFR and albumin-to-creatinine ratio in patients who switched to half the normal dose of ERT treatment compared to those who continued on the regular dose.
- A long-term observational study showed that Fabrazyme-treated patients had a slower rate of decline in eGFR compared to untreated patients, as described in the Fabrazyme label (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103979s5309lbl.pdf).
- Trial PB-102-F20: The agalsidase beta arm had point estimates of the mean eGFR slopes ranging from -3.1 to -2.6 mL/min/1.73 m^2/year depending on the analysis used. These estimated slopes were favorable compared to those previously reported for the untreated or placebo-treated patients as shown in Table 15. This observation was supported by considering the baseline median eGFR values in the placebo and untreated patients relative to those in Trial PB-102-F20. Compared to the patients in Trial PB-102-F20 who had a median baseline eGFR of 74 mL/min/1.73 m^2, overall, the placebo-treated patients in the Fabrazyme phase 4 trial had more advanced disease with a median baseline eGFR of 52 mL/min/1.73 m^2 whereas the untreated patients in the observational study had less advanced disease with median baseline eGFR of 93 mL/min/1.73 m^2. Thus, it is reasonable to expect that if a placebo arm were enrolled with patients that had a similar baseline eGFR as those in Trial PB-102-F20, its mean eGFR slope would likely fall between -4.1 and -3.2 mL/min/1.73 m^2/year. There are notable limitations to this comparison including that it relies on non-randomized data from different studies and that the untreated and placebo-treated patients were treatment naïve whereas the patients enrolled in Trial PB-102-F20 were treatment-experienced. Nonetheless, this information helps to contextualize the results in Trial PB-102-F20.

Table 15: Estimated eGFR Slopes: patients in Trial PB-102-F20 and untreated patients from external studies

Study	Treatment	N	Baseline eGFR (mL/min/1.73m^2)	Point Estimation of Mean or Median Post-baseline eGFR slope (mL/min/1.73m^2/year)
PB-102-F20	Agalsidase beta	25	74 (median)	-2.6 to -3.1
Observational Study[(a)]	Untreated	122	93 (median)	-3.2 (mean)
Fabrazyme Phase 4[(b)]	Placebo	30	52 (median)	-4.1 (median)

[(a)] Fabrazyme label (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103979s5309lbl.pdf).
[(b)] Baseline eGFR from Fabrazyme label and Median eGFR slope from Oritz et al. 2021.

Therefore, despite the limitations of the external and observational data used to evaluate the

[6] Weidemann, Frank, et al. "Patients with Fabry disease after enzyme replacement therapy dose reduction versus treatment switch." Journal of the American Society of Nephrology 25.4 (2014): 837-849.

assay sensitivity, the review team concludes that the comparable results of the eGFR endpoint between PRX-102 and agalsidase beta provide informative and supportive evidence.

Efficacy Results – Secondary Endpoint of Fabry Clinical Event

A total of 9 (17%) subjects (11 events) and 2 (8%) subjects (2 events) experienced a FCE event on PRX-102 and agalsidase beta respectively; and the treatment difference was 9% (95% CI: -10%, 24%; nominal p = 0.49). There was a numerical imbalance that did not favor PRX102. However, as reflected by the wide confidence intervals, there is considerable uncertainty around the estimates due to the small number of subjects experiencing an event. In addition, the clinical reviewer's independent evaluation of the Applicant's adverse event dataset identified three additional FCE events – one on PRX-102 and two on agalsidase beta. The resultant total FCE events were 10 (19%) and 4 (16%) on PRX-102 and agalsidase beta, respectively, and the treatment difference was 3% (-19, 21%; nominal p > 0.90). Regarding the process of identifying and evaluating potential FCE events, we refer the reader to the clinical team's review.

Efficacy Results – Secondary Endpoint of Change in Plasma Lyso-Gb3

For detailed analyses of the plasma Lyso-Gb3 endpoint, the reader should consult the Agency's clinical pharmacology review. Summary statistics for baseline, week 104 (2 years) and change in plasma Lyso-Gb3 is provided in Table 16. At baseline, the mean (SE) plasma concentration of Lyso-Gb3 was similar between the arms: 26.3 (3.8) nM for pegunigalsidase alfa vs. 32.1 (7.1) nM for agalsidase beta. At Week 104, the concentration had increased slightly (3.30 (1.38) nM) in the PRX-102 arm and decreased slightly (-8.74 [4.85] nM) in the Fabrazyme arm. These results favor the agalsidase beta arm.

Table 16: Change in Plasma Lyso-Gb3 Concentrations from Baseline to Week 104 in ERT (agalsidase beta)-Experienced Patients (Trial PB-102-F20)

	PRX-102 N = 52	**Agalsidase beta N = 25**
Plasma Lyso-Gb3 Concentration (nM)		
Baseline		
n	52	25
Mean (SE)	26.3 (3.8)	32.1 (7.1)
Median (Min, Max)	15.2 (0.8, 143.9)	17.6 (2.1, 142.0)
Change from Baseline at Week 104 (nM)		
n	46	22
Mean (SE)	3.3 (1.4)	-8.7 (4.8)
Median (Min, Max)	1.2 (-32.2, 32.7)	-1.5 (-102.3, 2.4)
Percent Change from Baseline at Week 104		
Mean (SE)	10.3 (3.8)	-12.7 (4.6)
Median (Min, Max)	10.0 (-47.2, 73.0)	-11.4 (-72.0, 22.5)

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

There were several challenging statistical issues concerning the design and analysis of studies PB-102-F01/F02 and PB-102-F20. These issues were:

1. **Trial PB-102-F01/F02**: **Single Arm**

   Given the single arm design of PB-102-F01/F02, the adequacy of the efficacy results of Gb3 endpoint relied on the following assumption: in the absence of treatment, the average change in Gb3 deposition over a short period of time (5 to 6 months) is zero or higher. In other words, Gb3 deposition is not expected to decline spontaneously at the population level. As discussed in Appendix 2, the data from the placebo arm of two randomized, controlled trials provides support for this assumption. However, the review team acknowledges this cross-study comparison may be limited due to difference between the patient populations across the studies, and difference in the assessment of kidney Gb3. Nonetheless, given the large magnitude of Gb3 reduction in the kidney accompanied by a large decline in plasma lyso-Gb3 and no biologic plausibility for spontaneous reduction in renal Gb3 at population-level, the review team concludes the observed results are unlikely to have arisen due to spontaneous improvement.

2. **Trial PB-102-F20: Applicant's proposed noninferiority margin of -3 ml/min/1.73m^2/year**

   The review team does not agree with the Applicant's proposed non-inferiority margin because there are no data to support this margin for agalsidase beta in the setting of Trial PB-102-F20 (see Appendix 3 for review team's evaluation on the Applicant's NI margin justification). The design of Trial PB-102 F20, therefore, does not allow for inference regarding non-inferiority of PRX-102 to agalsidase beta.

3. **Trial PB-102-F20: Assay Sensitivity**

   For a detailed discussion on the issues of assay sensitivity and interpretation of the comparable results of eGFR slope between the two arms, the reader is referred to Section 3.3.4. Briefly, to aid in the interpretation of the comparable results of the eGFR slope between the two treatment arms, the review team made several observations which provide information on the expected effect of agalsidase beta in the population studied in Trial PB-102-F20. Despite the limitations of the external data used to evaluate the assay sensitivity, the review team concludes that the comparable results of eGFR slope between PRX-102 and agalsidase beta provide informative and supportive evidence of efficacy for PRX-102.

4.2 Collective Evidence

The collective evidence of this application supports the effectiveness of PRX-102 for the treatment of adults with confirmed Fabry disease. In trial PB-102-F01/F02, after treatment with PRX-102 for 6 months, patients experienced a median 78% reduction from baseline in the number of kidney Gb3 inclusions per PTC. The mean absolute reduction at 6 months compared to baseline was 3.1 fewer Gb3 inclusions per PTC (95% CI: 1.4, 4.8). Additional analyses performed at the patient level showed that 11 out of the 14 patients who had data available had a nominally significant reduction in Gb3 inclusions. The reduction in kidney Gb3 inclusions was accompanied by a marked reduction in Plasma Lyso-Gb3 with all patients showing a reduction in Plasma Lyso-Gb3 at both 1-year and 2-year visits.

In Trial PB-102-F20, a randomized, double-blind, active-controlled trial comparing PRX-102 to the approved ERT agalsidase beta, the eGFR slopes were comparable between the arms. Based on the Applicant's primary analysis adjusted for the binary baseline proteinuria (< 1 vs ≥ 1 gr/gr), the estimated mean eGFR slope between the two arms were comparable (-2.4 for PRX-102 and -2.3 for agalsidase beta), and the estimated treatment difference was -0.1 (95% CI: -2.3, 2.1) mL/min/1.73 m^2/year. These comparable results were supported by the review team's post-hoc analyses, including an analysis adjusted for the continuous baseline proteinuria. This analysis yielded the estimated mean eGFR slopes of -2.0 and -3.1 mL/min/1.73 m^2/year in the PRX-102 and agalsidase beta arms, respectively, and the treatment difference of 1.1 (95% CI: -0.8, 3.1) mL/min/1.73 m^2/year.

Regarding the Applicant's intent to rely on PB-102-F20 to demonstrate non-inferiority between PRX-102 and agalsidase beta, the review team determined that Trial PB-102-F20 cannot support a non-inferiority claim due to the lack of data to support a non-inferiority margin for agalsidase beta. However, to aid in the interpretation of the results of the eGFR slope between the two treatment arms and to provide information on the expected effect of agalsidase beta in the population studied, the review team considered additional external data. There are notable limitations to this evaluation including that it relies on observational and non-randomized data from different studies and that the untreated and placebo-treated patients were treatment naïve whereas the patients enrolled in Trial PB-102-F20 were treatment-experienced. Nonetheless, this information helps to contextualize the results in Trial PB-102-F20 and the review team concluded that the comparable results of the eGFR endpoint between PRX-102 and agalsidase beta provide informative and supportive evidence.

The renal Gb3 endpoint evaluated in trial PB-102-F01/F02 is not a clinical endpoint because it does not directly measure how a patient functions or feels in daily life, or how long a patient survives. Nonetheless, the compelling drug effect on this endpoint observed in PB-102-F01/F02 is clinically relevant given the following published literature on the central pathophysiologic role of Gb3 accumulation in Fabry disease: (1) when it accumulates, the Gb3 substrate is toxic to tissues and causes damage to organ systems, (2) Gb3 accumulates in tissues/organs which exhibit structural damage and functional impairment due to Fabry disease, and (3) the degree of accumulation of the substrate appears to correlate with the degree of damage in renal tissue. Additionally, despite the small sample size, reduction in renal Gb3 at 6-month appeared to

associate with better outcome in eGFR slope (Section 3.2.4). In addition, we gave importance to analyses of the PB-102-F20 trial which evaluated the well-established endpoint of rate of loss of renal function (as measured by annualized change in estimated eGFR). Though there were additional limitations in PB-102-F20 as discussed above, the observed comparability between treatment arms observed in F20 increased our confidence that the compelling treatment effect observed on the reduction in Gb3 is reflective of an overall clinical benefit.

4.3 Conclusions and Recommendations

The collective evidence from the two clinical studies discussed in this review, the well-established etiology of the disease, and the mechanism of action of PRX-102 supports the effectiveness of PRX-102 for the treatment of adults with confirmed Fabry disease. The statistical review team found there to be limitations and uncertainties in both trials (PB-102-F01/F02 and PB-102-F20) as discussed in this review. However, when considering the trials together and incorporating information from other disciplines, the statistical team concluded that this BLA provided substantial evidence of effectiveness for PRX102. From a statistical perspective, the team recommends traditional approval of PRX102.

4.4 Labeling Recommendations

The review team made significant revisions to the Applicant's proposed *Clinical Studies* (section 14) of the labeling document. Specifically, the review team implemented the following changes:

1. Re-wrote the description of trial PB-102-F01/F02 and provided tabular summary of the primary efficacy results of this study
2. Revised the description of trial PB-102-F20 and updated the Applicant's primary analysis using the primary analysis model that was pre-specified prior to unblinding of the 12-month interim data.

All other changes implemented by the review team are reflected in the final version of the labeling.

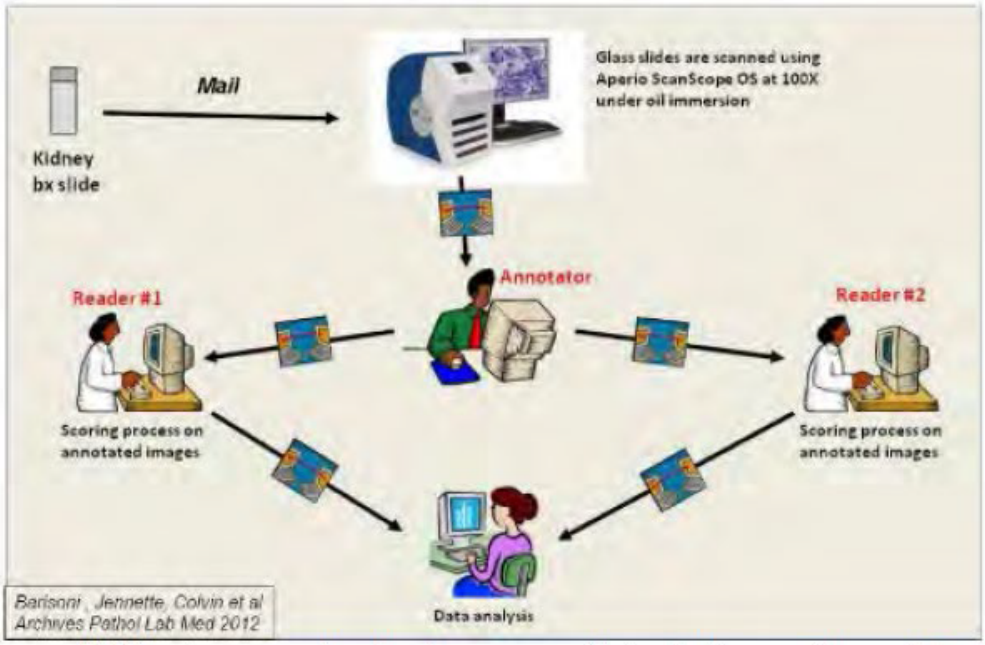
Appendix 1: BLISS Methodology

BLISS Scoring Algorithm

The implementation of the BLISS protocol requires three pathologists: one pathologist who serves as the annotator and two pathologists who serve as readers. The annotator and reader roles were assigned to the pathologists on a rotation basis and therefore, each pathologist served as the annotator for 1/3 of the kidney biopsies and as the reader for the remaining 2/3 of the kidney biopsies. All pathologists are blinded to each other's scores, the treatment assignment and biopsy collection timepoints (i.e., baseline vs. 6-month visit).

The annotator-pathologist identifies approximately 300 capillaries on the Whole Slide Images (WSI) and marks each with an arrow. Once the annotation is complete, two identical copies of the WSI are distributed to the reader-pathologists (Figure 14), and each pathologist will independently count the number of Gb3 inclusions at each capillary (these are the capillary-level scores). Regarding the selection of the capillaries and differential tissue sampling, the applicant states:
"Criteria for the selection of capillaries for digital annotation were established so that the size of the peritubular capillaries was consistent across all specimens as previously described. The selection of the 300 capillaries was random across all blocks processed for each biopsy. This protocol was created to assure a broad and standardized representation of peritubular capillaries across all areas of the cortical renal tissue available (Barisoni 2012). This process served to minimize any possible variation in results due to differential tissue sampling."
Applicant's Late-Cycle Meeting Discussion Supplement, page 6

Figure 14: Flowchart of the BLISS Scoring Procedure (Trial PB-102-F20)



Glass slides are mailed to an imaging center where they are scanned into virtual images. The annotator pathologist annotates PTC on WSI. Annotated WSI are triplicated and distributed to two reader-pathologists for scoring and one copy was maintained in the database at the image coordinating center. Abbreviation: bx, biopsy.

Source: Figure 1, Applicant's Histology Report, Page 9

Adjudication Process

To improve the reliability of the scoring system and reconcile large disagreements between the readers, the following adjudication process was pre-specified. As stated in the Applicant's Histology Report, the adjudication process was to be implemented in the following two scenarios:

- For capillary-level scores ≤ 10 (by both readers): if there is a difference > 5 units between the two readers' scores
- For capillary-level scores >10 (by one or both readers): if there's ≥50% difference between the two readers' scores

Once the capillaries that meet the above adjudication rules are identified, the data-management center will provide the adjudicator pathologist (original annotator) with a list of the capillaries that need to be re-scored. The adjudicator, who is blinded to the scores from the two original readers, will then count the number of Gb3 inclusions at each of the capillaries in question. Once adjudication is complete, the two closest (of the three scores) will be assigned as the capillary-level scores. In case the differences between the scores were equal (e.g., 0, 5, 10), the middle score will be taken as the final capillary-level score.

Derivation of the Renal Gb3 BLISS Score (Average Number of Gb3 Inclusions per Kidney PTC)

The biopsy-level score was determined as the average number of Gb-3 inclusions per kidney PTC (i.e., total number of Gb3 inclusions summed across all annotated-capillaries divided by the number of capillaries scored). The final score used for primary efficacy assessment is obtained by averaging the biopsy-level score from each reader-pathologist (i.e. [Reader 1 Biopsy-level Score + Reader 2 Biopsy-level Score]/2).

We examined sensitivity of the primary efficacy analysis to the Applicant's scoring strategy whenever adjudication was done. In addition to the Applicant's scoring strategy of picking two closest (of three scores), the review team implemented the following scoring strategies:

1. Capillary-level scores determined as the average score of the three readers
2. Capillary-level scores determined as the median score of the three readers

For each of the scoring strategies shown in (1) and (2) above, the biopsy-level score is determined as the average number of inclusions per PTC defined as the total sum of capillary-level scores divided by the total number of capillaries. Results of this sensitivity analysis are described in the subsection entitled: *BLISS Protocol: FDA Assessment of Applicant's Adjudication Procedure* (Figure 18).

Reliability of the BLISS Approach for Renal Gb3 BLISS Score (Average Number of Gb3 Inclusions per Kidney PTC)

The Applicant examined agreement between readers in the overall trial population using a Bland-Altman plot. In addition, to minimize variability due to female tissue mosaicism, we examined the inter-reader variability in the population of male patients (Figure 15).

BLISS Assay Variability: FDA's Assessment of Inter-reader agreement, intra-reader agreement and sampling variability

The mean inter-reader difference was 0.0002 (95% CI: -0.35, 0.35) for the overall population and 0.06 (95% CI: -0.45, .57) for male patients indicating a high level of agreement between readers (Figure 15). The mean inter-reader differences were much smaller than the mean observed reductions at 6 months (-3.1 units for the overall population and -4.7 units for male patients), suggesting that the observed reductions were unlikely to be due to inter-reader variability.

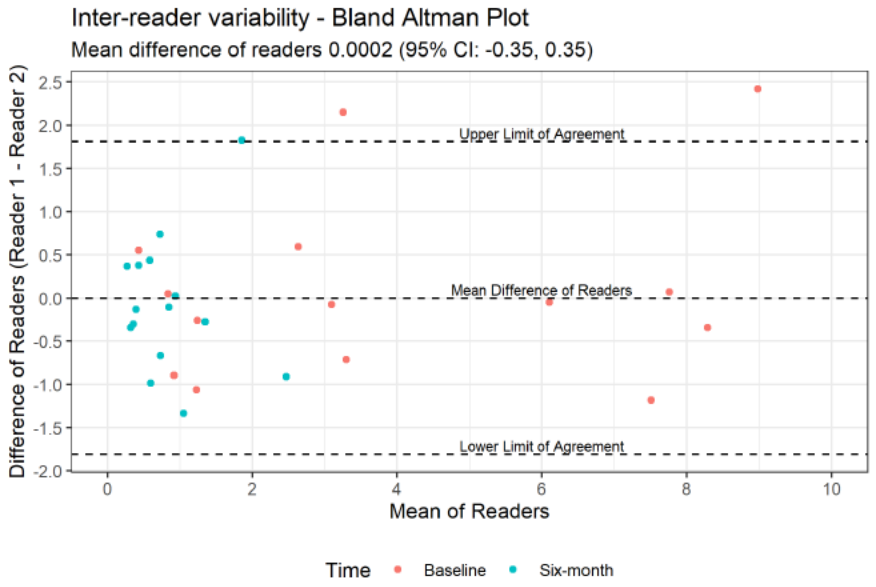
The review team notes that intra-reader variability of the BLISS procedure could not be assessed in this study. However, since the pathologists who implemented the BLISS methodology in this study of PRX-102 also implemented it in the Galafold trial in the same manner, it is reasonable to borrow information on intra-reader variability from the Galafold trial (Barisoni et al. 2012). According to Barisoni et al. (2012), the mean intra-reader difference is 0.07 (95% CI: -0.34 to 0.49). This intra-reader variability is much lower than the mean reduction in Gb3 inclusions at 6 months (-3.1 with 95% CI: -4.8, -1.4) and suggests that the observed reduction is not a result of intra-rater variability.

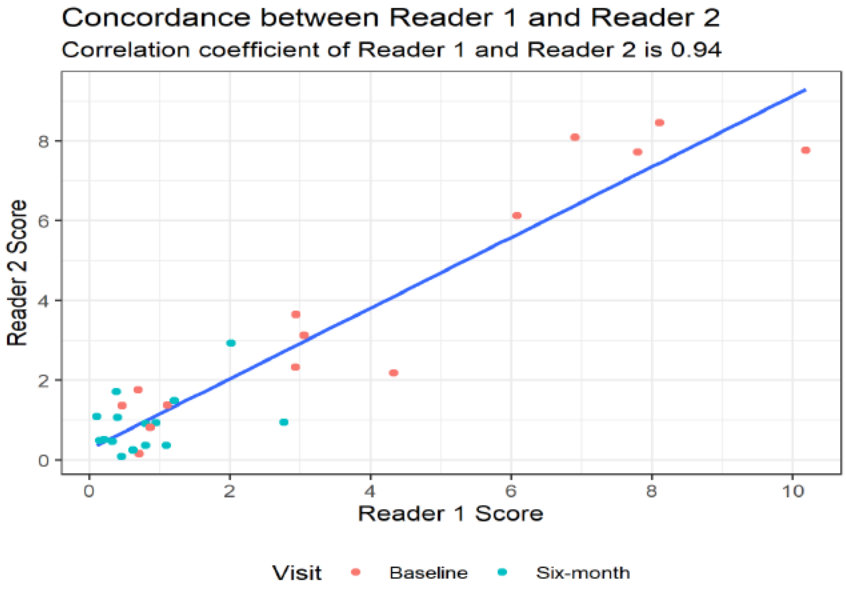
The bootstrap and permutation analyses showed that 11 out of 14 (79%) subjects showed significant reductions that were more than what would have been expected due to sampling variability (**Figure 16** and Figure 17). Of the remaining three patients, one subject had a minimal (from 0.4 at baseline to 0.9 at six-months) yet nominally statistically significant increase, while the other two patients had small changes that were within the range of what would have been expected due to sampling variability.

Overall, given the small inter-reader and intra-reader variability, and the small sampling variability of the BLISS methodology, the reductions observed in this study are not likely to be attributed to variability in the BLISS methodology.

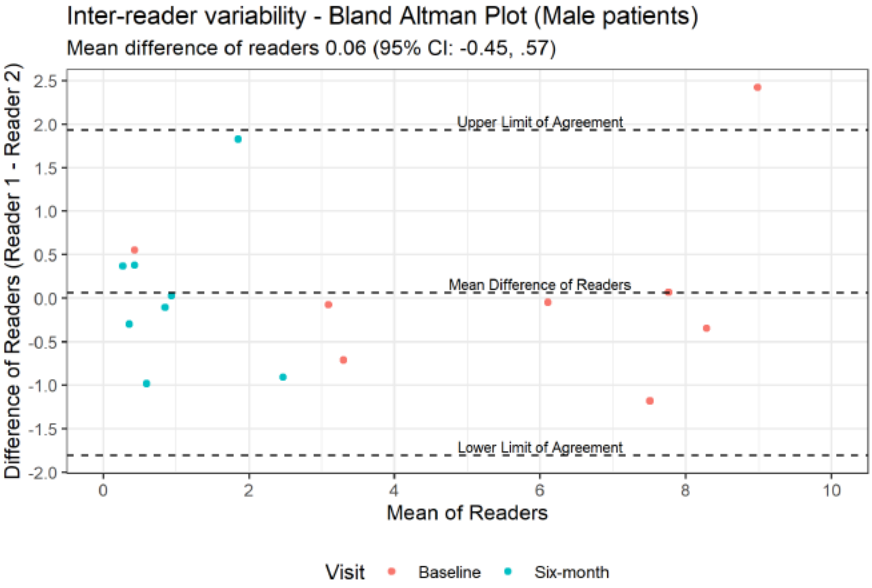
Figure 15: Inter-reader Variability (Trial PB-102-F01/F02)

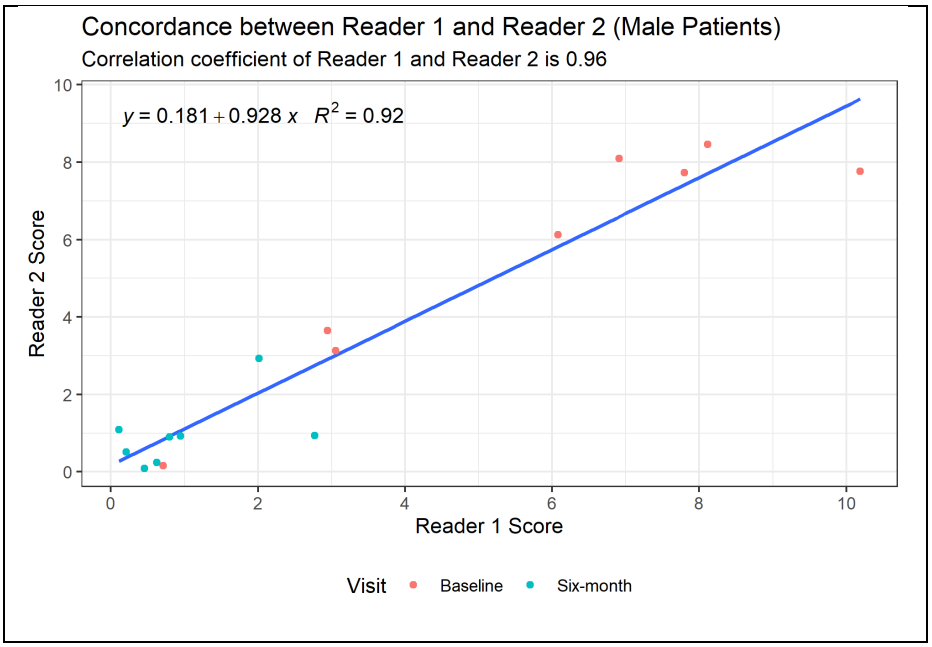
All patients





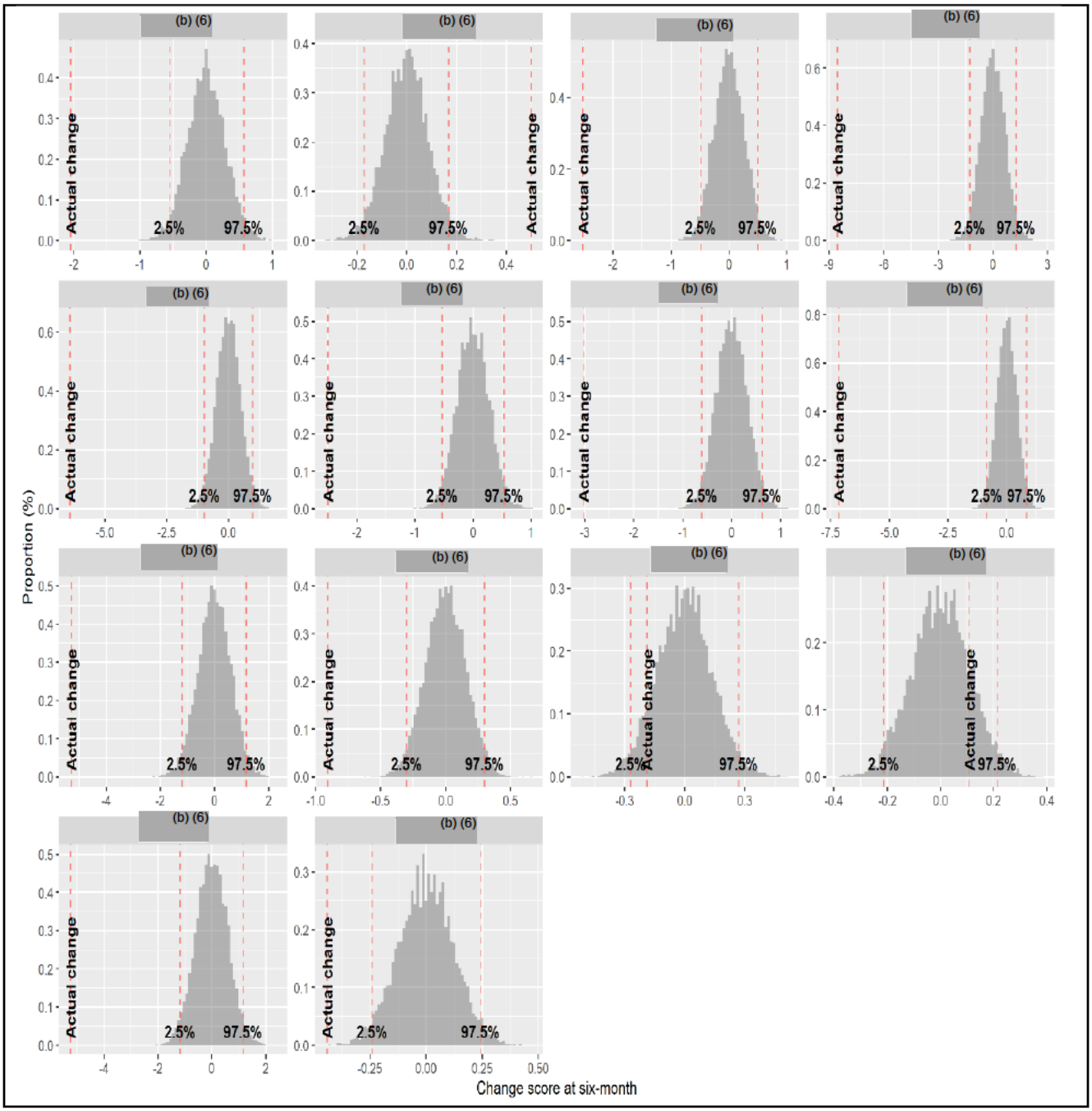
Male Patients





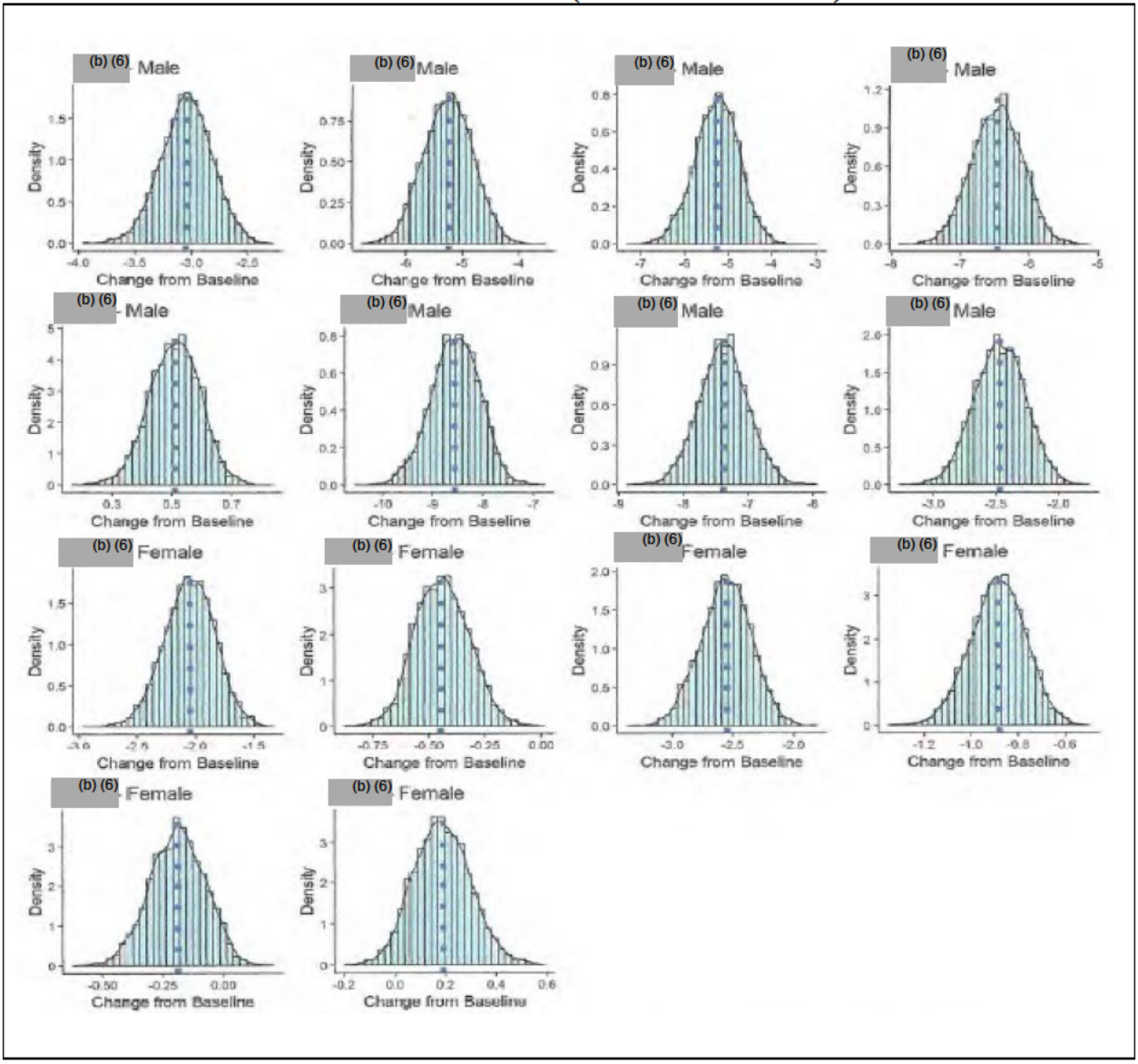
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025) on November 11, 2020

Figure 16: Permutation Sampling Distribution of Change in BLISS Score Assuming the Distribution of Six-month Gb3 Score is Identical to the Distribution of Baseline Gb3 Score (Trial PB-102-F01/02)



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025) on November 11, 2020

Figure 17: Bootstrap Based Estimated Density Function of the Difference in Average BLISS Score Between Baseline and 6 Months (Trial PB-102-F01/02)



Source: Figure 2 of Applicant's histology report

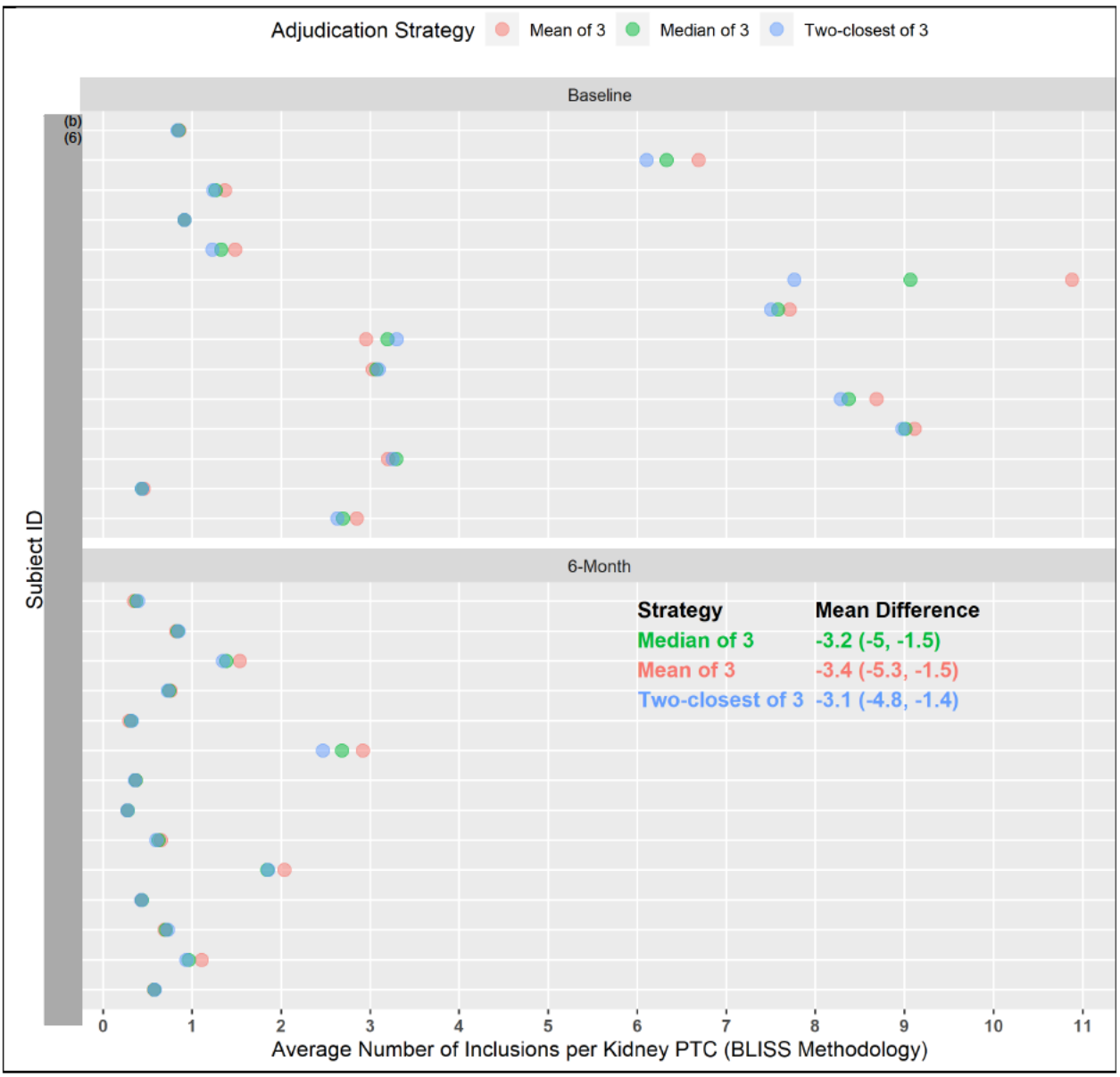
All but three patients (b) (6) had a significant reduction in Gb3 inclusions.

BLISS Protocol: FDA Assessment of Applicant's Adjudication Procedure

Overall, 13% of the capillary-level scores needed adjudication. When the mean of the scores from each of the three pathologists was used to derive the capillary-level score, the mean reduction in BLISS scores was -3.4 (95% CI: -5.3, -1.5). When the median of the scores from each of the three pathologists was used to derive the capillary-level score, the mean reduction in BLISS scores was -3.2 (95% CI: -5.0, -1.5). Both of these results were similar to the primary

efficacy result which was based on the Applicant's adjudication strategy of taking the two-closest of the three scores (Figure 18).

Figure 18: Comparison of Strategies for BLISS Score Determination in the Presence of Adjudication



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025) on November 11, 2020

Appendix 2: Absence of Spontaneous Reduction in Kidney Gb3

The Applicant has argued that concerns regarding the single-arm design of study PB-102-F01/F02 are mitigated by the lack of evidence for spontaneous decrease of Gb3 inclusions in the kidney as evidenced by the results of the following two placebo-controlled trials:

1. In the placebo-controlled trial for Galafold, in the placebo arm (n = 20 patients with amenable GLA variant), the mean change from baseline in the BLISS score was 0.07 after 6 months of treatment with placebo (Figure 19). Furthermore, as shown in Table 17**.** presented in Galafold's labeling, the median change in BLISS score ranged from -0.05 to -0.02 for four subgroups (female vs male, baseline BLISS score < 0.3 vs ≥ 0.3) of placebo-treated patients.
2. In the placebo-controlled trial for Fabrazyme, in the placebo-arm (n = 29) patients, there was minimal change[7] (-0.07 units on the Fabrazyme Scoring System) in Gb3 deposition after 5 months of treatment with placebo. The placebo arm data are graphically presented in Figure 19.

These results from the placebo arm of two placebo-controlled trials indicate spontaneous reduction of kidney Gb3 is unlikely at the population level.

[7] Clinical Review of Genzyme STN103979, Table 17 and Table 19 (page 31 and page 32) [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/agalgen042403r5.pdf]

Figure 19: Summary Data on Gb3 Inclusions Based on Prior Placebo-controlled Trials (Figures Extracted from Applicant's Histology Report)

Figure 15: Kidney Biopsy Data from the Published Phase 3 Development Program for Fabrazyme® (Thurberg et al., 2002)

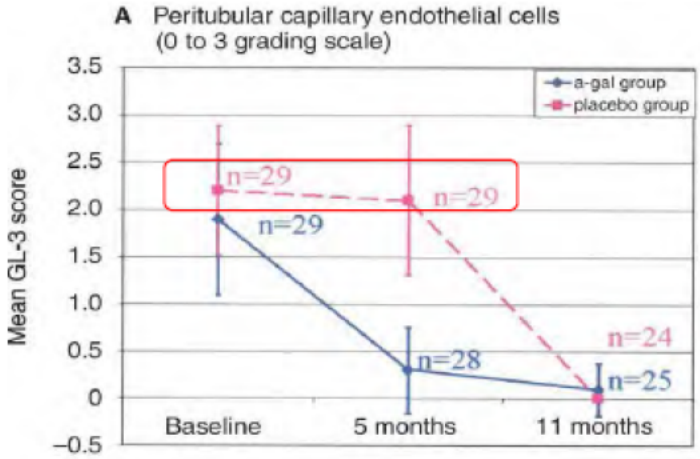


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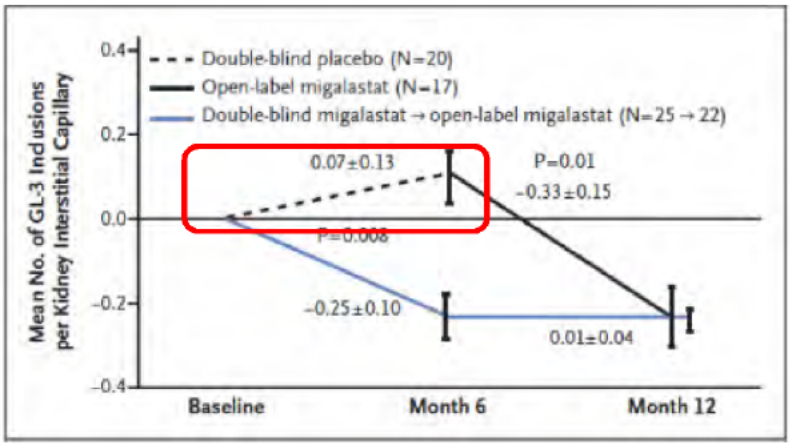
Figure 16: Change from Baseline of Gb3 Inclusions in Kidney PTC in Patients with Mutations That Were Suitable for Migalastat Therapy (Germain et al., 2016)



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Source: Applicant's Histology Report, Page 29-33

Table 17: Changes from Baseline to Month 6 in Average Number of GL-3 Inclusions

	GALAFOLD n/N (%) with ≥ 50% reduction Median change from baseline (range)	Placebo n/N (%) with ≥ 50% reduction Median change from baseline (range)
All patients (N = 45)	13/25 (52%) -0.04 (-1.94, 0.26)	9/20 (45%) -0.03 (-1.00, 1.69)
Females (N = 29)	8/18 (44%) -0.02 (-0.46, 0.26)	5/11 (46%) -0.03 (-0.35, 0.10)
Males (N = 16)	5/7 (71%) -1.10 (-1.94, -0.02)	4/9 (44%) -0.03 (-1.00, 1.69)
Patients with baseline GL-3 ≥ 0.3 (N = 17; 9 males, 8 females)	7/9 (78%) -0.91 (-1.94, 0.19)	2/8 (25%) -0.02 (-1.00, 1.69)
Patients with baseline GL-3 < 0.3 (N = 28; 7 males, 21 females)	6/16 (38%) -0.02 (-0.10, 0.26)	7/12 (58%) -0.05 (-0.16, 0.14)

Source: Galafold USPI (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208623lbl.pdf)

Appendix 3: Evaluation of the Applicant's Proposed Noninferiority Margin

Summary of the Applicant's communication with FDA regarding the design and analysis of PB-102-F20 can be found in Section 2.1.2. Briefly, submitted for special protocol assessment in 2016, Trial PB-102-F20 was designed as a non-inferiority trial; however, the Agency did not agree with this design and recommended a superiority design due to the lack of data to support the Applicant's proposed non-inferiority margin of -3 mL//min/1.73m^2/year. Following the Agency's recommendation, the final protocol (submitted in 2017) stated that the trial primary objective was to demonstrate superiority of PRX-102 compared to agalsidase beta. However, while Trial PB-102-F20 was ongoing, Fabrazyme received full approval from the Agency on 03/11/2021. The full approval was supported by a phase 3 trial, a phase 4 trial, and a long-term observational study (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103979s5309lbl.pdf) as well as other clinical studies and published literature.

After unblinding of the 12-month interim data analysis and receiving the Agency's Complete Response letter on the original BLA in April of 2021, the Applicant proposed to change the primary analysis at 2 years from a superiority to non-inferiority comparison. Although the Agency agreed to the non-inferiority analysis in principle, no agreement was reached regarding the Applicant's proposed non-inferiority margin of -3 mL/min/1.73m^2/year. Regarding their proposed NI margin, the Applicant argued that this margin is appropriate given the following factors:

- a rare disease with unmet need

- limited natural history study data to guide selection of NI margin
- significant heterogeneity in the Fabry population with respect to eGFR slope
- high degree of intra-subject variability in eGFR measurements
- recruitment challenges if a smaller margin were to be selected

Specifically, regarding the rational for choosing the NI margin of -3 mL/min/1.73m^2/year, the Sponsor provided the following information:

1. Evidence on the natural history of the disease suggests that untreated patients tend to present progressive kidney deterioration by showing an eGFR slope worse than 3 mL/min/1.73 m^2/year (from around -4 to -12 mL/min/1.73 m^2/year), therefore we can consider achieving -3 mL/min/1.73 m^2/year as a relevant threshold for assessing the benefit of a disease specific treatment.
2. The European Therapeutic Goals published by Wanner 2018 has used the same threshold for defining patients considered clinically stable with regards to renal function (one of the main goals for long-life treatment of progressing diseases), thus confirming that -3 mL/min/1.73 m^2/year is a reasonable threshold from a clinical perspective.
3. Finally, this threshold was pre-defined and used for the first 12 months NI interim analysis, mainly on the basis of what was already known on the natural history of the disease and on what is published in literature on the treatments effect. Considering that the slope is an annualized measure, the applicant considers the use of the same margin an appropriate approach (since we are testing the NI hypothesis on the same population, with additional data).

Source: Type-C Briefing Document submitted on December 2, 2021

Based on the review team's assessment, the studies cited by the Applicant are not adequate to estimate effect size of agalsidase beta over placebo in the setting of Trial PB-102-F20. However, based on the best available data comparing agalsidase beta to placebo among treatment-naïve patients, an acceptable statistical margin would have been 0.5 – 0.6 mL/min/1.73 m^2/year (Table 18). But this margin requires a sample size of more than 1000 patients to obtain adequate statistical power in an NI trial; consequently, conducting an adequately powered NI trial relying on eGFR as the primary efficacy endpoint is not feasible given the rarity of the Fabry disease.

Table 18: Effect of agalsidase beta over placebo in previous studies

Data Source	eGFR Slope (mL/min/1.73 m^2/year)		Treatment Difference	Margin
	Placebo / Untreated	Fabrazyme		
Fabrazyme label[1]	-3.2	-1.5	1.7 (0.5, 3.0)	0.5
Ortiz et al.[2]	-3.47	-1.01	2.5 (0.6, 4.3)	0.6

[1] Fabrazyme label (https://www.accessdata fda.gov/drugsatfda_docs/label/2021/103979s5309lbl.pdf)

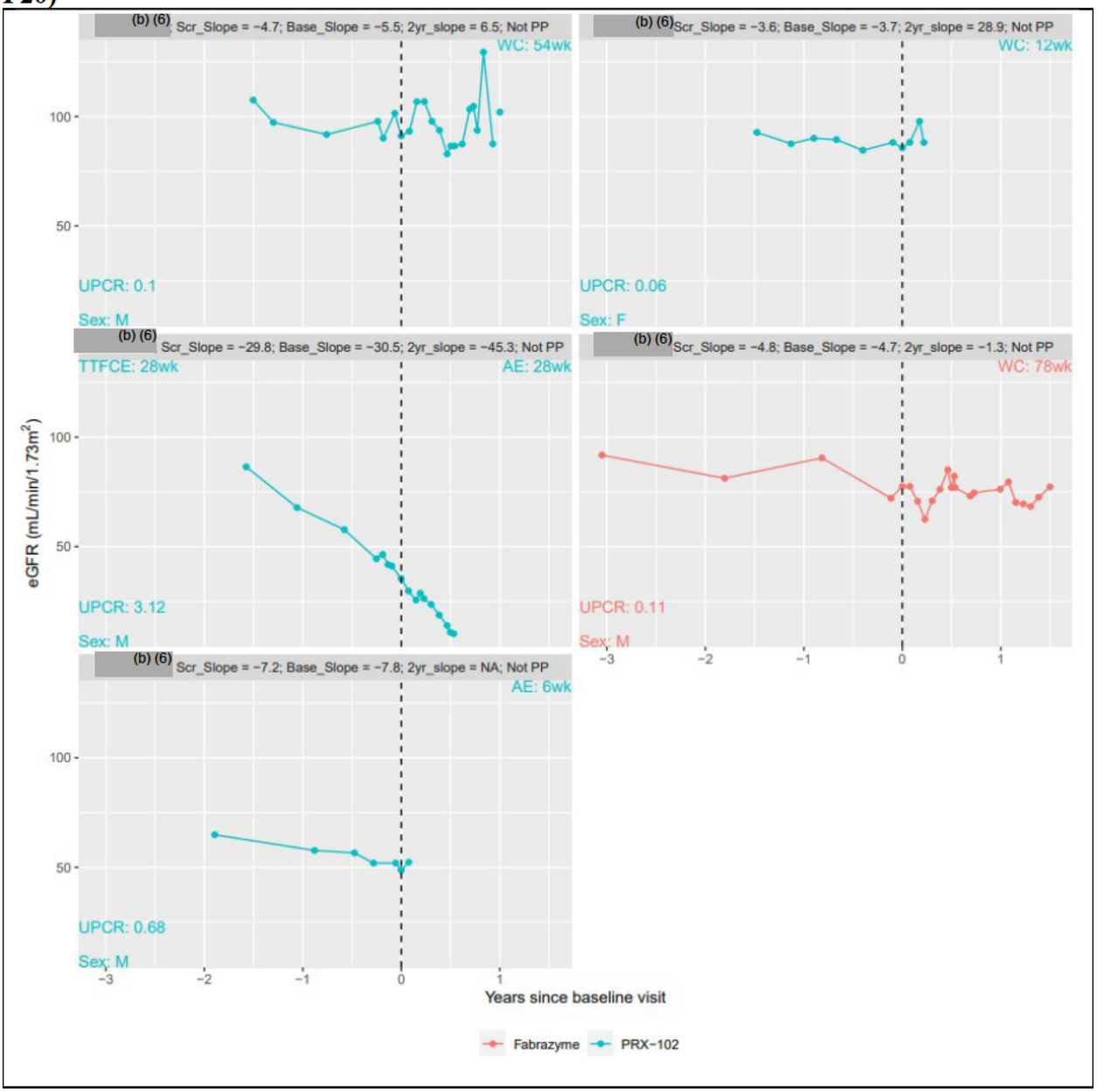
[2] Ortiz A, et al. Agalsidase beta treatment slows estimated glomerular filtration rate loss in classic Fabry disease

patients: results from an individual patient data meta-analysis. Clin Kidney J. 2020 May 22;14(4):1136-1146. doi: 10.1093/ckj/sfaa065.

Note: To support their proposed analysis for the median slope, the Applicant cited the paper by Oritz et al. (2021) that used a quantile regression analysis to estimate the treatment effect of agalsidase beta in slowing glomerular filtration rate loss in treatment-naïve patients with classic Fabry disease.

Appendix 4: Supplemental Tables and Figures

Figure 20: eGFR Profile for Subjects who Prematurely Discontinued Study (Trial PB-102-F20)



WC = Withdrawal of Consent. AE = Adverse Event. TTFCE = Time to Fabry Clinical Event.

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0057)) on August 23, 2022

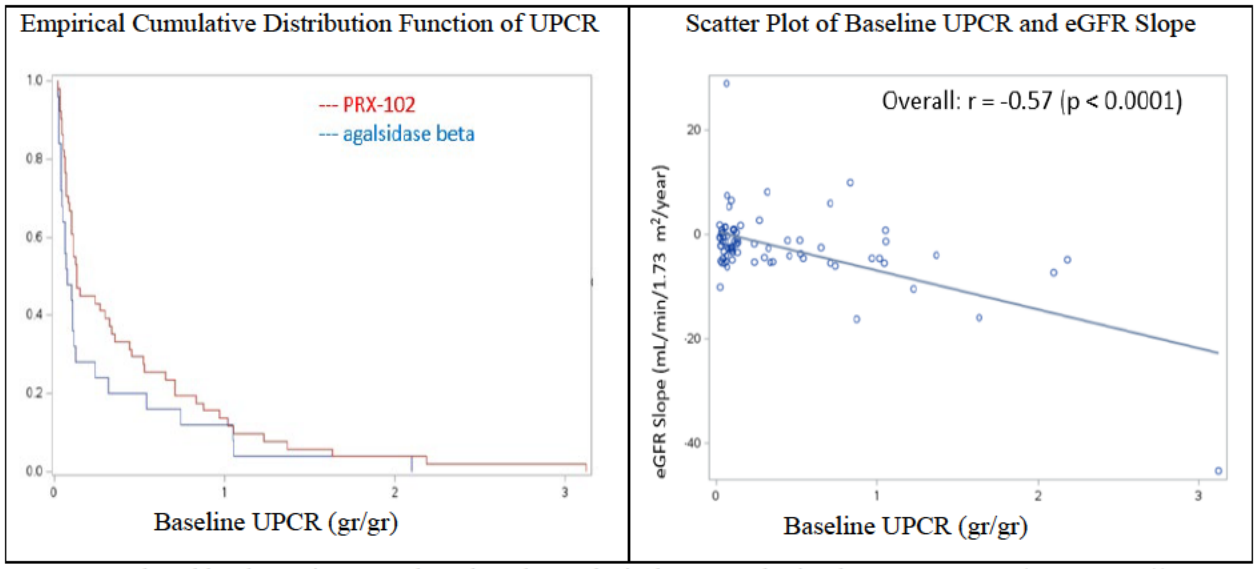
Table 19: Imbalance between Treatment Arms in Baseline Proteinuria (Trial PB-102-F20)

Population	Treatment Group	N	Mean	Median	Max	P75	P25	Min	STD
Overall		77	0.38	0.11	3.12	0.52	0.06	0.02	0.57
Overall	Agalsidase beta	25	0.28	0.07	2.10	0.24	0.04	0.02	0.49
Overall	PRX-102	52	0.43	0.13	3.12	0.59	0.07	0.02	0.60
Sex: Female	Agalsidase beta	7	0.05	0.04	0.10	0.07	0.02	0.02	0.03
Sex: Female	PRX-102	23	0.18	0.09	1.02	0.13	0.05	0.02	0.27
Sex: Male	Agalsidase beta	18	0.38	0.11	2.10	0.54	0.06	0.02	0.55
Sex: Male	PRX-102	29	0.63	0.35	3.12	0.83	0.10	0.03	0.72
Phenotype: Classic	Agalsidase beta	14	0.37	0.10	2.10	0.54	0.04	0.02	0.59
Phenotype: Classic	PRX-102	27	0.64	0.35	3.12	0.87	0.10	0.03	0.74
Phenotype: Non-classic	Agalsidase beta	11	0.18	0.06	1.04	0.24	0.03	0.02	0.30
Phenotype: Non-classic	PRX-102	25	0.20	0.09	1.02	0.13	0.06	0.02	0.28
ADA: Negative	Agalsidase beta	17	0.29	0.07	2.10	0.24	0.04	0.02	0.53
ADA: Negative	PRX-102	34	0.33	0.10	3.12	0.44	0.06	0.02	0.59
ADA: Positive	Agalsidase beta	8	0.27	0.08	1.04	0.43	0.05	0.02	0.39
ADA: Positive	PRX-102	18	0.61	0.34	2.19	0.87	0.11	0.03	0.61
Baseline eGFR<60	Agalsidase beta	8	0.58	0.15	2.10	1.05	0.06	0.02	0.75
Baseline eGFR<60	PRX-102	12	0.99	0.77	3.12	1.30	0.39	0.08	0.89
Baseline eGFR>=60	Agalsidase beta	17	0.15	0.07	0.74	0.11	0.04	0.02	0.20
Baseline eGFR>=60	PRX-102	40	0.26	0.10	1.63	0.31	0.06	0.02	0.35
Baseline slope <=-5	Agalsidase beta	19	0.33	0.07	2.10	0.54	0.03	0.02	0.55
Baseline slope <=-5	PRX-102	33	0.54	0.27	3.12	0.83	0.07	0.02	0.71
Baseline slope >-5	Agalsidase beta	6	0.13	0.11	0.32	0.12	0.06	0.04	0.10
Baseline slope >-5	PRX-102	19	0.24	0.11	0.96	0.32	0.07	0.03	0.28
ACEi/ARBs: No	Agalsidase beta	9	0.06	0.04	0.11	0.10	0.03	0.02	0.04
ACEi/ARBs: No	PRX-102	27	0.14	0.07	0.71	0.13	0.04	0.02	0.16
ACEi/ARBs: Yes	Agalsidase beta	16	0.41	0.11	2.10	0.64	0.06	0.02	0.57
ACEi/ARBs: Yes	PRX-102	25	0.75	0.52	3.12	1.02	0.15	0.06	0.74
Region: USA	Agalsidase beta	18	0.20	0.05	1.05	0.12	0.03	0.02	0.33
Region: USA	PRX-102	34	0.38	0.11	3.12	0.33	0.06	0.02	0.63

Population	Treatment Group	N	Mean	Median	Max	P75	P25	Min	STD
Region: ex-USA	Agalsidase beta	7	0.49	0.11	2.10	0.74	0.10	0.06	0.75
Region: ex-USA	PRX-102	18	0.53	0.40	2.19	0.83	0.10	0.04	0.56
UPCR <1 g/g	Agalsidase beta	22	0.13	0.07	0.74	0.11	0.04	0.02	0.18
UPCR <1 g/g	PRX-102	45	0.24	0.11	0.96	0.33	0.06	0.02	0.26
UPCR >=1 g/g	Agalsidase beta	3	1.40	1.05	2.10	2.10	1.04	1.04	0.61
UPCR >=1 g/g	PRX-102	7	1.66	1.37	3.12	2.19	1.05	1.02	0.76

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0057)) on August 23, 2022

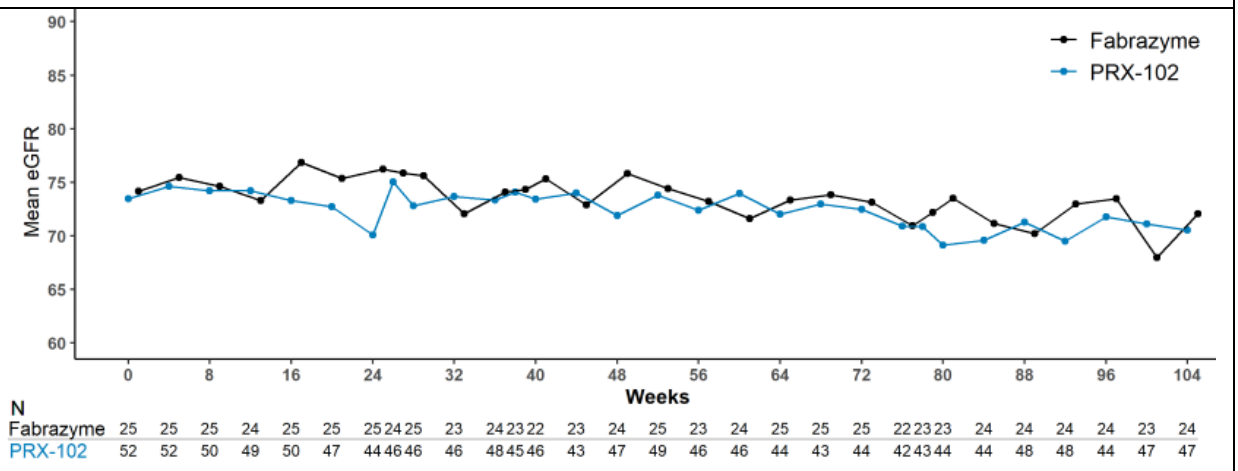
Figure 21: Empirical Cumulative Distribution Function of UPCR (gr/gr) and Scatter Plot of Baseline UPCR and Post-baseline eGFR Slope Over 2 Months (Trial PB-102-F20)



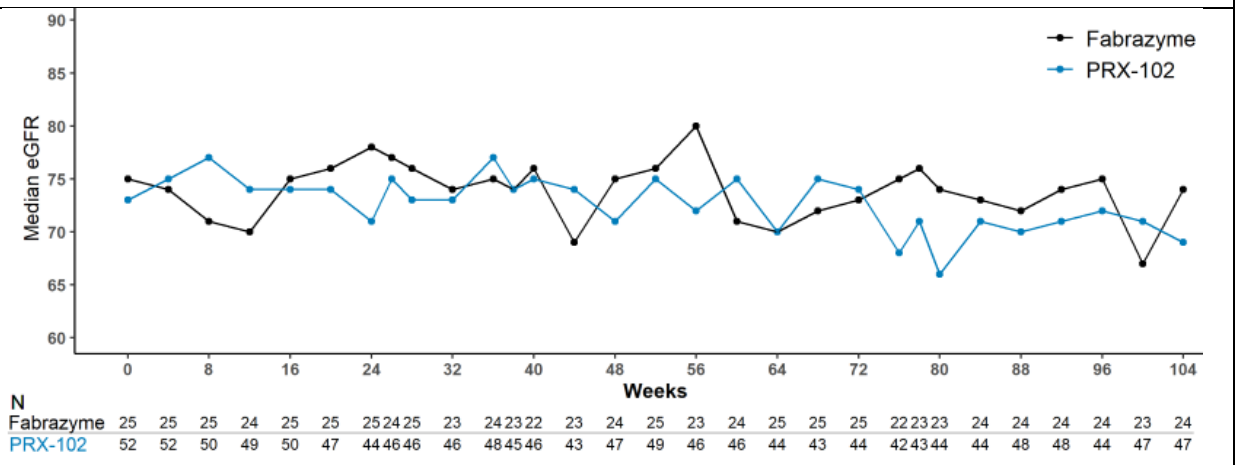
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0057)) on August 23, 2022

Figure 22: eGFR (ml/min/1.73$m2$) by Visit (Trial PB-102-F20)

A). Mean eGFR by Visit (ml/min/1.73m^2)



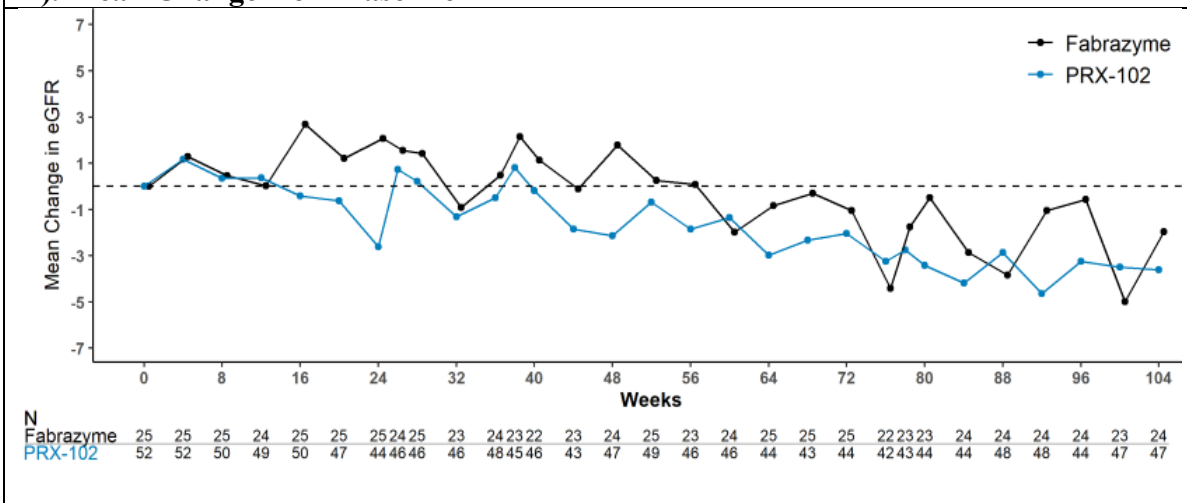
B). Median eGFR by Visit (ml/min/1.73m^2)



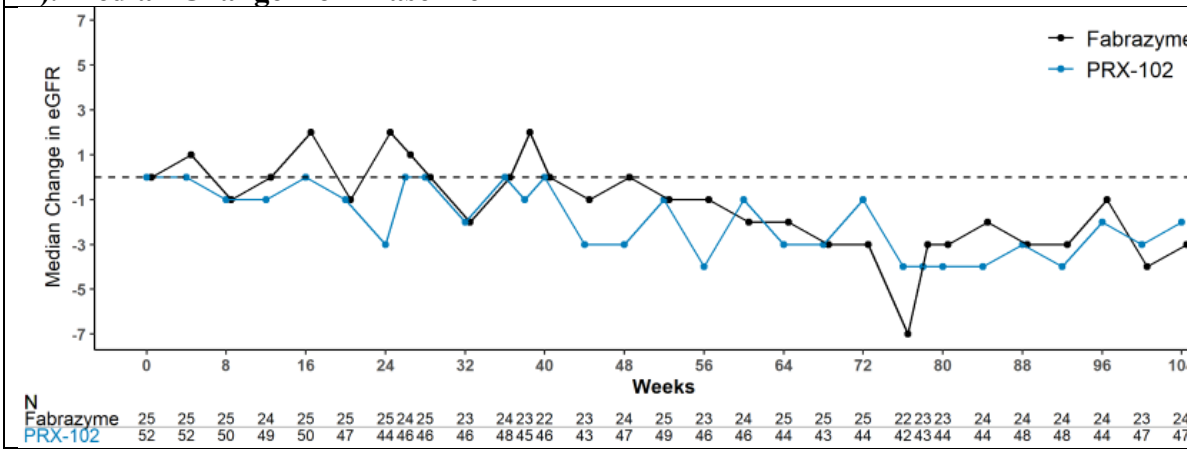
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0057)) on August 23, 2022

Figure 23: Change from Baseline in eGFR (ml/min/1.73m^2) by Visit (Trial PB-102-F20)

A). Mean Change from Baseline



B). Median Change from Baseline



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0057)) on August 23, 2022

Table 20: eGFR (mL/min/1.73m^2) by Visit

	PRX-102				Fabrazyme			
	N	Mean (SD)	Median	Min, Max	N	Mean (SD)	Median	Min, Max
Week 0	52	73 (20)	73	30, 126	25	74 (21)	75	34, 108
Week 4	52	75 (19)	75	30, 120	25	75 (24)	74	38, 120
Week 8	50	74 (21)	77	26, 117	25	75 (23)	71	33, 118
Week 12	49	74 (21)	74	26, 120	24	73 (22)	70	39, 112
Week 16	50	73 (22)	74	24, 112	25	77 (23)	75	34, 114
Week 20	47	73 (22)	74	19, 115	25	75 (22)	76	31, 111
Week 24	44	70 (22)	71	14, 125	25	76 (22)	78	39, 112
Week 26	46	75 (21)	75	11, 128	24	76 (22)	77	38, 117
Week 28	46	73 (23)	73	10, 129	25	76 (21)	76	38, 114
Week 32	46	74 (22)	73	33, 124	23	72 (22)	74	34, 111
Week 36	48	73 (21)	77	34, 117	24	74 (22)	75	36, 116
Week 38	45	74 (19)	74	35, 108	23	74 (22)	74	32, 120
Week 40	46	73 (21)	75	33, 123	22	75 (23)	76	33, 109
Week 44	43	74 (22)	74	34, 129	23	73 (21)	69	33, 107
Week 48	47	72 (22)	71	27, 120	24	76 (24)	75	29, 114
Week 52	49	74 (21)	75	27, 116	25	74 (23)	76	32, 108
Week 56	46	72 (22)	72	28, 127	23	73 (23)	80	24, 110
Week 60	46	74 (20)	75	30, 109	24	72 (22)	71	25, 109
Week 64	44	72 (20)	70	29, 112	25	73 (22)	70	30, 113
Week 68	43	73 (20)	75	29, 122	25	74 (24)	72	27, 115
Week 72	44	72 (21)	74	26, 119	25	73 (23)	73	23, 115
Week 76	42	71 (21)	68	24, 121	22	71 (22)	75	23, 108
Week 78	43	71 (21)	71	23, 122	23	72 (23)	76	23, 109

	PRX-102				Fabrazyme			
	N	Mean (SD)	Median	Min, Max	N	Mean (SD)	Median	Min, Max
Week 80	44	69 (21)	66	25, 123	23	74 (21)	74	29, 115
Week 84	44	70 (21)	71	25, 113	24	71 (20)	73	29, 101
Week 88	48	71 (21)	70	29, 110	24	70 (21)	72	29, 108
Week 92	48	70 (20)	71	26, 112	24	73 (21)	74	30, 109
Week 96	44	72 (22)	72	29, 116	24	73 (21)	75	25, 106
Week 100	47	71 (22)	71	24, 120	23	68 (22)	67	24, 109
Week 104	47	71 (22)	69	28, 114	24	72 (23)	74	24, 115

Table 21: Change in eGFR (mL/min/1.73m^2) by Visit

	PRX-102				Fabrazyme			
	N	Mean (SD)	Median	Min, Max	N	Mean (SD)	Median	Min, Max
Week 4	52	1 (6)	0	-21, 14	25	1 (8)	1	-20, 22
Week 8	50	0 (8)	-1	-14, 16	25	0 (11)	-1	-26, 20
Week 12	49	0 (7)	-1	-21, 22	24	0 (9)	0	-17, 21
Week 16	50	0 (8)	0	-22, 16	25	3 (8)	2	-11, 23
Week 20	47	-1 (8)	-1	-25, 18	25	1 (8)	-1	-14, 20
Week 24	44	-3 (8)	-3	-21, 17	25	2 (14)	2	-32, 45
Week 26	46	1 (8)	0	-25, 17	24	2 (7)	1	-11, 20
Week 28	46	0 (8)	0	-25, 21	25	1 (7)	0	-14, 14
Week 32	46	-1 (6)	-2	-16, 15	23	-1 (9)	-2	-17, 20
Week 36	48	0 (7)	0	-18, 13	24	0 (8)	0	-13, 18
Week 38	45	1 (10)	-1	-37, 21	23	2 (8)	2	-13, 22
Week 40	46	0 (7)	0	-16, 13	22	1 (6)	0	-6, 17
Week 44	43	-2 (9)	-3	-15, 38	23	0 (8)	-1	-19, 16
Week 48	47	-2 (8)	-3	-22, 23	24	2 (9)	0	-13, 18
Week 52	49	-1 (8)	-1	-14, 31	25	0 (10)	-1	-16, 21
Week 56	46	-2 (7)	-4	-14, 20	23	0 (9)	-1	-18, 14
Week 60	46	-1 (8)	-1	-21, 16	24	-2 (8)	-2	-25, 12
Week 64	44	-3 (8)	-3	-25, 15	25	-1 (6)	-2	-15, 10
Week 68	43	-2 (8)	-3	-23, 21	25	0 (8)	-3	-12, 17
Week 72	44	-2 (8)	-1	-19, 21	25	-1 (8)	-3	-14, 17
Week 76	42	-3 (9)	-4	-32, 17	22	-4 (8)	-7	-18, 10
Week 78	43	-3 (9)	-4	-29, 16	23	-2 (9)	-3	-18, 15
Week 80	44	-3 (9)	-4	-32, 17	23	0 (10)	-3	-21, 17

	PRX-102				Fabrazyme			
	N	Mean (SD)	Median	Min, Max	N	Mean (SD)	Median	Min, Max
Week 84	44	-4 (9)	-4	-22, 18	24	-3 (8)	-2	-20, 12
Week 88	48	-3 (11)	-3	-35, 19	24	-4 (9)	-3	-21, 11
Week 92	48	-5 (11)	-4	-36, 14	24	-1 (9)	-3	-21, 16
Week 96	44	-3 (9)	-2	-32, 14	24	-1 (11)	-1	-19, 33
Week 100	47	-3 (9)	-3	-29, 11	23	-5 (11)	-4	-27, 18
Week 104	47	-4 (11)	-2	-37, 22	24	-2 (7)	-3	-18, 17

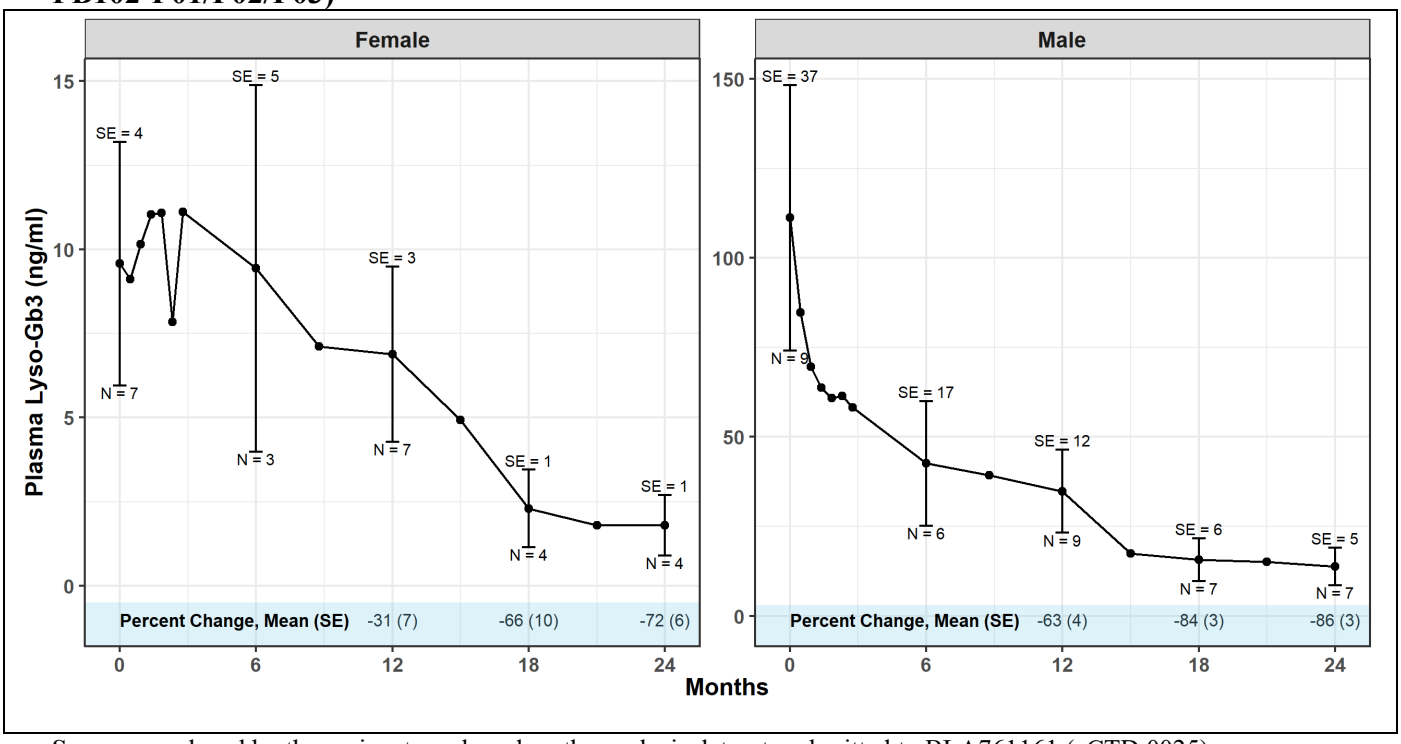
Table 22: Individual Renal Gb3 BLISS Score and Plasma Lyso-Gb3 Levels in Trial PB102-F01/F02

Subject ID	Treatment (mg/kg)	Sex	Renal Gb3 BLISS Score			Plasma Lyso-Gb3 (ng/mL)				
			Baseline	Month 6	% Change at Month 6	Baseline	Month 6	Month 12	% Change at Month 6	% Change at Month 12
(b) (6)	0.2	F	2.6	0.6	-77.8	19.2	NA	17.7	NA	-7.8
	1	M	0.4	0.9	114.9	5.1	2.9	2.8	-43.1	-45.1
	1	F	3.3	0.7	-77.6	14.4	NA	7.1	NA	-50.7
	1	M	9.0	0.4	-95.2	193.4	NA	46.7	NA	-75.9
	1	M	8.3	1.9	-77.6	123.0	24.5	35.6	-80.1	-71.0
	2	M	3.1	0.6	-80.7	61.8	NA	30.8	NA	-50.2
	0.2	M	3.3	0.3	-91.7	66.5	6.7	25.2	-89.9	-62.1
	1	M	7.5	0.4	-95.2	80.8	34.7	17.2	-57.1	-78.7
	1	F	NA	1.1	NA	6.8	5.5	4.2	-19.1	-38.2
	0.2	M	7.8	2.5	-68.2	112.5	NA	40.0	NA	-64.5

(b) (6)	2	F	1.2	0.3	-74.0	3.4	NA	2.6	NA	-23.5
	2	F	0.9	0.7	-20.7	5.0	NA	2.2	NA	-55.6
	0.2	M	NA	NA	NA	272.9	142.3	69.5	-47.9	-74.5
	2	F	1.2	1.4	8.8	10.8	6.6	7.3	-38.9	-32.4
	0.2	M	6.1	0.8	-86.1	84.7	44.5	45.7	-47.5	-46.0
	0.2	F	0.8	0.4	-52.9	7.5	16.2	7.1	116.0	-5.3

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025) on November 11, 2020

Figure 24: Average Absolute and Percent Change in Plasma Lyso-Gb3 by Sex (Trial PB102-F01/F02/F03)



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025) on November 11, 2020

Figure 25: Individual Level Distribution of the mFSS Score, Majority-rule Based mFSS Score, Weighted mFSS Score and BLISS Score (Trial PB102-F01/F02)

mFSS: modified Fabrazyme Scoring System; **Majority:** Majority rule mFSS score; **Weighted:** weighted mFSS score;

The biopsy score for each scoring system is represented using the notation x → y, where x represents the baseline score, and y represents the six-month score.

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0001) on May 27, 2020

The above figure shows each patient's Gb3 burden using the semi-quantitative mFSS and quantitative BLISS methodology. In the mFSS, each capillary receives a severity score of 0, 0.5, 1, 2, or 3 and, the proportion of capillaries receiving the given score is calculated. The biopsy-level **weighted mFSS** score is derived by computing the weighted average of the capillary-specific scores. For example, if 30% of capillaries have a score of 3, 49% a score of 2, 20% a score of 1, 10% a score 0.5, and 11% a score of 0, the **weighted mFSS** score will be 2.13 (= 0.3*3 + 0.49*2 + 0.2*1 + 0.1*0.5 + 0.11*0). The biopsy-level **majority-rule mFSS** score corresponds to the score received by the majority of the capillaries. In the above example, the **biopsy-level majority-rule mFSS** score will be 2 since a majority of the capillaries received a score of 2. Compared to the BLISS methodology, the semi-quantitative mFSS is less sensitive to small changes in the number of Gb3 inclusions. For example, the individual shown in the top right panel has a majority-rule score of 0 both at baseline and at six-month, however, the BLISS scores for this individual are 0.8 and 0.4 at baseline and six-month, respectively.

Table 23: Baseline Kidney Function Parameters

	PRX-102 N=52	Agalsidase Beta N=25	Overall N=77
eGFR (mL/min/1.73 m^2)			
Mean (SD)	73.46 (20.21)	74.16 (20.97)	73.69 (20.32)
Median (Min, Max)	73.45 (30.2 ; 125.9)	74.85 (34.1 ; 107.6)	74.51 (30.2 ; 125.9)
eGFR Category (mL/min/1.73 m^2), n (%)			
≤ 60	13 (25.0%)	8 (32.0%)	21 (27.3%)
60 < and ≤ 90	28 (53.8%)	11 (44.0%)	39 (50.6%)
>90	11 (21.2%)	6 (24.0%)	17 (22.1%)
eGFR slope at screening (mL/min/1.73 m^2/year) [1]			
Mean (SD)	-8.42 (6.96)	-7.79 (4.74)	-8.22 (6.30)
Median (Min, Max)	-6.10 (-32.7; -2.1)	-5.97 (-19.5; -2.3)	-6.07 (-32.7; -2.1)
eGFR slope at baseline (mL/min/1.73 m^2/year) [2]			
Mean (SD)	-8.03 (6.60)	-8.25 (4.27)	-8.10 (5.92)
Median (Min, Max)	-6.70 (-30.5 ; 6.3)	-7.84 (-20.3 ; -2.8)	-7.25 (-30.5 ; 6.3)
Baseline eGFR slope categories (mL/min/1.73 m^2/year), n (%)			
≤ -5	33 (63.5%)	19 (76.0%)	52 (67.5%)
> -5	19 (36.5%)	6 (24.0%)	25 (32.5%)
UPCR stratification (at screening), n (%)			
< 1 gr/gr	41 (78.8%)	21 (84.0%)	62 (80.5%)
≥ 1 gr/gr	11 (21.2%)	4 (16.0%)	15 (19.5%)
UPCR categories at baseline, n (%)			
UPCR ≤ 0.5 gr/gr	36 (69.2%)	20 (80.0%)	56 (72.7%)
0.5 < UPCR < 1 gr/gr	9 (17.3%)	2 (8.0%)	11 (14.3%)
1 ≤ UPCR gr/gr	7 (13.5%)	3 (12.0%)	10 (13.0%)
Treatment with ACEi or ARBs, n (%)			
Yes	26 (50.0%)	16 (64.0%)	42 (54.5%)
No	26 (50.0%)	9 (36.0%)	35 (45.5%)

ACEi = Angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; eGFR = estimated glomerular filtration rate; UPCR = urine protein-to-creatinine ratio

[1] eGFR slope at screening was based on historical serum creatinine and screening serum creatinine.

[2] eGFR slope at baseline was based on historical, screening, and baseline serum creatinine.

Source: Table 11.3, Applicant's CSR

Appendix 5: Efficacy results from Trial PB-102-F30 and Trial PB-102-F50

Trial PB-102-F30

Study PB-102-F30 was an open-label, switch-over study that enrolled 22 adult Fabry patients who have been receiving agalsidase alfa treatment for at least 2 years prior to enrollment. Once enrolled, patients switched over to PRX-102 delivered intravenously at a dose of 1.0 mg/kg every other week for a period of 12 months. Efficacy results for the endpoints of eGFR and eGFR slope are summarized in the table below. The mean (SE) eGFR values were 79.5 (4.9) ml/min/1.73m^2 at baseline and 76.9 (5.2) at 12 months. The mean (SE) change in eGFR from baseline to 12 months was -2.6 (2.1) ml/min/1.73m^2. The mean (SE) eGFR slopes were -5.9 (1.3) ml/min/1.73m^2 /year at baseline and -1.2 (1.8) at 12 months. The mean (SE) change in eGFR slope from baseline to 12 months was 4.7 (2.3) ml/min/1.73m^2/year.

Table 24: eGFR and eGFR Slope Pre- to Post-switch to PRX-102 in PB-102-30

	Male Patients N=13	Female Patients N=7	Overall N=20
eGFR (mL/min/1.73 m^2)			
Baseline Mean (SE)	75.87 (6.62)	86.14 (6.72)	79.46 (4.92)
Median (min; max)	69.75 (49.4; 113.9)	87.71 (55.3; 109.2)	82.18 (49.4; 113.9)
Month 12 Mean (SE)	74.27 (7.15)	81.80 (7.09)	76.91 (5.22)
Median (min; max)	71.36 (41.1; 118.3)	89.41 (44.1; 100.5)	77.43 (41.1; 118.3)
Change in eGFR from Baseline to Month 12			
Mean (SE)	-1.60 (2.76)	-4.34 (3.54)	-2.56 (2.14)
Median (min; max)	-3.96 (-17.0; 16.3)	0.31 (-19.8; 4.4)	-3.39 (-19.8; 16.3)
eGFR slope (mL/min/1.73 m^2/year)			
Pre-switch Mean (SE)	-6.36 (1.89)	-5.03 (1.65)	-5.90 (1.34)
Median (min; max)	-4.55 (-20.5; 4.8)	-3.68 (-11.2; 1.5)	-4.41 (-20.5; 4.8)
Post-switch Mean (SE)	-1.73 (2.64)	-0.21 (1.47)	-1.19 (1.77)
Median (min; max)	-1.11 (-18.6; 14.2)	1.39 (-6.3; 4.1)	-0.72 (-18.6; 14.2)
Change in eGFR Slope from Pre- to Post-switch			
Mean (SE)	4.63 (3.48)	4.83 (1.09)	4.70 (2.26)
(95% CI for the Mean) [b]	(-2.95, 12.22)	(2.16, 7.49)[a]	(-0.03, 9.43)
Median (min; max)	3.16 (-17.7; 22.1)	5.93 (-0.1; 7.6)	5.00 (-17.7; 22.1)
p-value[2]			0.051

CI = confidence interval; eGFR = estimated glomerular filtration rate; max = maximum; min = minimum; SE = standard error.
a. suggesting statistical significance as 0 is not included in 95% Confidence Intervals (CI).
b. p-values and 95% CIs are based on t-distribution (paired t-test).

Source: Table 21, Applicant's Summary of Clinical Efficacy (Module 2)

Trial PB-102-F50

Trial PB-102-F50 was an open-label, switch-over study that enrolled 30 adult Fabry patients who have been receiving agalsidase alfa or Replagal treatment for at least 3 years prior to enrollment. Once enrolled, patients switched over to PRX-102 delivered intravenously at a dose of 2.0 mg/kg every 4 weeks for a period of 12 months. Efficacy result for eGFR slope endpoint is summarized in the table below. The mean (SE) eGFR slopes were -1.8 (0.7) ml/min/1.73m^2 /year at baseline and -2.9 (1.1) ml/min/1.73m^2 /year at 12 months.

Table 25: eGFR Slope Pre- to Post-switch to PRX-102 in PB-102-50

Population/Subgroup	Pre-switch	Post-switch
Efficacy Population		
N	29	
Mean (SE)	-1.79 (0.69)	-2.77 (0.54)
Median (min ; max)	-1.06 (-13.6 ; 3.6)	-2.47 (-8.7 ; 1.4)

Source: Table 19, Applicant's Summary of Clinical Efficacy (Module 2)

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/s/

YARED GURMU
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YAN WANG
05/08/2023 05:31:33 PM
I concur.

REBECCA R CHIU
05/08/2023 05:32:43 PM

U.S. FOOD & DRUG ADMINISTRATION

PHARMACOLOGY/TOXICOLOGY MEMORANDUM

Date:	May 8, 2023
Subject:	BLA 761161
Author:	Shawna L Weis, PhD Acting Team Leader, Division of Pharmacology/Toxicology for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine Center for Drug Evaluation and Research

Secondary Review Memorandum

On April 27, 2021, the Division issued a complete response letter to Chiesi's Biologics License Application (BLA) 761161 for accelerated approval of pegunigalsidase alfa for the treatment of Fabry disease, due to inspection-related concerns with the (b) (4) (b) (4) manufacturing facility, and because of the full approval of Fabrazyme in March 2022, which blocked approval of pegunigalsidase alfa by the accelerated approval route.

The nonclinical review of this BLA was performed by Dr. Jackye Peretz, who concluded that, aside from the lack of a pre- and postnatal development (PPND) study, the nonclinical toxicology and pharmacology dataset was sufficient to support an approval of pegunigalsidase for the treatment of patients with Fabry disease. She recommended a post-marketing requirement (PMR) for the PPND study.

BLA 761121 was resubmitted on November 9, 2022. Because the nonclinical review was final and no additional nonclinical data were submitted, the nonclinical review of the resubmission focused on the adequacy of the nonclinical confirmatory evidence to support an effect of pegunigalsidase alfa on the clinical biomarker, GL3, in relation to a change in a clinically-meaningful endpoint in animals.

The nonclinical confirmatory evidence supplied by the Applicant included studies in agalsidase alpha-deficient mice (αGAL KO mice) in which the Applicant performed single- and repeat-dose biodistribution and pharmacodynamic studies to evaluate enzyme uptake and GL3 clearance in multiple tissues, including the skin, liver, heart, spleen, kidney, and brain. These studies were problematic for a number of reasons, however, because the methods used were not validated or appropriately quantitative or specific for GL3, and therefore were unable to provide independent nonclinical confirmation of the clinical results.

The Sponsor used thin layer chromatography with primuline staining, which is nonquantitative and nonspecific. Primuline staining is not capable of differentiating between GL3 and other lipids, so the study was not sufficiently informative about the relationship between exposure to pegunigalsidase alfa and reduction in GL3. Moreover, the αGAL KO mouse model does not exhibit clinical signs of disease, so the study was

not capable of assessing effects on the clinical outcome of interest (estimated glomerular filtration rate, eGFR). In addition, the distribution results were potentially confounded by the lack of perfusion to eliminate residual blood, so it is unclear how much of the measured enzyme in target tissues was reflective of uptake versus how much was accounted for by residual drug in the plasma.

Conclusions and Recommendations:

Taken together, the data do not provide an independent line of evidence to support the association between pegunigalisidase administration, an effect on the clinical biomarker (GL3), and an effect on the clinical endpoint (eGFR) in a nonclinical model; thus, the nonclinical confirmatory data are weak. Consequently, we defer to the clinical team to establish the adequacy of confirmatory evidence to support the approval of pegunigalsidase alfa. In addition to the PMR for the pre- and postnatal development study in the rat, a post-marketing commitment (PMC) has been requested to address the deficiencies related to measurement of GL3 in tissues and plasma. From a nonclinical perspective, there are no approvability issues that preclude approval of this marketing application.

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/s/

SHAWNA L WEIS
05/08/2023 12:13:40 PM

MUKESH SUMMAN
05/08/2023 12:20:26 PM

BLA 761161 Clinical Review and Evaluation

Application Type	BLA
Application Number(s)	761161
Priority or Standard	Class 2 Resubmission (6 months)
Submit Date(s)	11/9/2022
Received Date(s)	11/9/2022
PDUFA Goal Date	5/9/2023
Division/Office	DRDMG/ORPURM
Review Completion Date	5/8/2023
Established/Proper Name	Pegunigalsidase alfa
(Proposed) Trade Name	Elfabrio
Pharmacologic Class	Hydrolytic lysosomal neutral glycosphingolipid-specific enzyme
Code name	PRX-102
Applicant	Chiesi Farmaceutici S.p.A
Dosage form	Injection, Solution Concentrate
Applicant proposed Dosing Regimen	1 mg/kg (actual body weight) intravenously every 2 weeks (b) (4)
Applicant Proposed Indication(s)/Population(s)	Fabry Disease
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	16652001 Fabry Disease (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	ELFABRIO is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme indicated for the treatment of adults with confirmed Fabry disease.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	16652001 Fabry Disease (disorder)
Recommended Dosing Regimen	1 mg/kg every 2 weeks

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AKI	acute kidney injury
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ERT	Enzyme Replacement Therapy
ETASU	elements to assure safe use
FD	Fabry Disease
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FCE	Fabry Clinical Events
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NI	Non-inferiority
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SE	surrogate endpoint
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
UPCR	Urinary Protein:Creatinine ratio

1 Executive Summary

1.1. Product Introduction

PRX-102 (pegunigalsidase alfa) is being developed as an enzyme replacement therapy for treatment of Fabry Disease. It is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme. It is a PEGylated, recombinant human alpha-Gal-A enzyme that is expressed in plant (Nicotiana tabacum Bright Yellow 2, BY2) cells.

The dosage form is a clear, colorless, preservative-free, and sterile solution (b) (4) intended for IV infusion. Each vial contains 20 mg/10 mL (2 mg/mL). One carton can contain either a single dose, 5 single dose or 10 single dose vials in a carton.

PRX-102 is a new molecular entity and has not been approved outside the U.S.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for PRX-102 was established with findings from a single adequate and well-controlled trial taken together with adequate confirmatory evidence described below.

Adequate and well-controlled trial: demonstration of a large and statistically significant treatment effect on the surrogate endpoint (SE) of reduction of accumulated globotriaosylceramide (GL-3/Gb-3) in biopsied renal peritubular capillaries, assessed using Barisoni Lipid Inclusion Scoring System (BLISS) methodology, in the single-arm, PB-102-F01/02 study. Despite its single-arm (baseline control) design, PB-102-F01/02 provides compelling evidence of PRX-102's efficacy given that resolution of GL-3/Gb-3 deposition in the kidney does not spontaneously occur.[1][2]

Several publications establish the central pathophysiologic role of Gb3 accumulation in Fabry Disease (FD) which has progressive, detrimental effects on tissue structure and organ function.[3] Published literature collectively shows that: a) accumulation of Gb3 is toxic to tissues, b) Gb3 accumulates in tissues/organs which exhibit structural damage and functional impairment due to Fabry disease, and c) Gb3 accumulation in affected tissues correlates with tissue and end-organ damage and functional impairment. There is strong biological rationale that a reduction in Gb3 accumulation would be expected to modify the

[1] Thurberg BL, Kidney International 2002, pg 1933-1946
[2] Germain DP, NEJM 2016, pg 545-555
[3] sBLA 103979 Unireview

pathophysiology of FD beneficially, which is further supported in this development program based on comparable effects of PRX-102 and agalsidase beta on renal function.

Confirmatory evidence:

- In a multicenter, randomized, double-blind, active-control (agalsidase beta) study (PB-102-F20, or F20), the effects of PRX-102 on eGFR annualized slope, an accepted clinical endpoint, appear comparable to agalsidase beta. Although limitations of this trial preclude its ability to establish that PRX-102 is non-inferior to agalsidase beta, as the applicant intended, the data nonetheless are sufficient to provide confirmatory evidence of the drug's effect to treat Fabry disease.
- Additional confirmatory evidence includes the effects of PRX-102 on reducing plasma lyso-Gb3 levels as observed in the F01/02 study in enzyme replacement therapy naïve subjects. The changes in plasma lyso-Gb3 showed statistical correlation with renal Gb3 inclusion changes in F01/02.
- Confirmatory evidence also includes strong mechanistic support. The well-established etiology of the disease as a monogenic inborn error of glycosphingolipid metabolism from a single enzymatic deficiency. The targeted mechanism of action of PRX102 as an exogenous enzyme replacement for the deficient/absent endogenous enzyme.

Taken together, the review team concludes that substantial evidence of effectiveness of PRX-102 for the treatment of Fabry disease has been demonstrated by the combination of a substantial reduction of accumulated globotriaosylceramide (Gb-3) in renal peritubular capillaries along with data suggesting a comparable effect on renal function between PRX-102 and an approved enzyme replacement therapy with the same mechanism of action (agalsidase beta).

The safety profile of PRX-102 was generally consistent with the known safety profile of other ERTs. The main safety concern is the risks of severe hypersensitivity reactions, including anaphylaxis, and infusion-associated reactions. These known safety risks can be adequately mitigated through product labeling, which will include a boxed warning for severe hypersensitivity reactions, and further monitored through routine pharmacovigilance. One subject receiving PRX-102 in the PRX-102 program experienced an adverse reaction of membranoproliferative glomerulonephritis due to immune-mediated complexes to PRX confirmed by biopsy. This risk can also be mitigated through product labeling. Although there were numerically a higher percentage of Fabry Clinical Events (FCE) in the PRX-102 arm compared to the agalsidase beta arm, the number of events was small and the process of identifying and evaluating potential FCE events was not robust. Due to multiple uncertainties, it was not possible to reliably determine whether the imbalances were due to drug (PRX102), prior exposure to agalsidase beta, disease progression, or to a chance finding.

In summary, in the context of Fabry Disease as a rare, serious disease with limited therapeutic options that may not be suitable to all individual patients, the review team concludes PRX-102's benefit outweighs its risks when used as recommended in the approved labeling and traditional approval is recommended for the treatment of adults with confirmed Fabry disease.

1.3. Benefit-Risk Assessment

Fabry disease (FD) is a rare and serious inborn error of glycosphingolipid metabolism characterized by deficiency of a single lysosomal enzyme, alphagalactosidase A. This single enzyme defect leads to progressive accumulation of the upstream substrate globotriaosylceramide (Gb3 or GL3) and its metabolite lyso-Gb3 due to the enzymatic block in the pathway of its degradation.

Current FDA-approved treatments for Fabry include Fabrazyme, an ERT analogous to PRX-102. The limitations of Fabrazyme include the occurrence of hypersensitivity reactions, other infusion related reactions, and development of anti-drug antibodies which may impact efficacy and/or safety. It requires bi-weekly IV infusions which can sometimes last several hours. Galafold is an additional treatment available in the U.S. for the treatment of Fabry disease. It is an orally administered therapy that received accelerated approval in 2018. Its use is limited to a subset of patients with amenable *GLA* variants.

PRX-102 (pegunigalsidase alfa) is a pegylated, covalently cross-linked recombinant human protein α-galactosidase A enzyme that replaces the deficient enzyme in FD. In the pivotal F01/02 study, PRX-102 administered to ERT-naïve (naïve or off-ERT for at least 6 months with no evidence of ADA) adult FD subjects significantly reduced from baseline Gb3 inclusions in the peritubular capillaries in the kidney, as assessed by using BLISS methodology. At Month 6, 11 of 14 evaluable subjects (79%) had at least a 50% reduction from baseline in renal Gb3 inclusions; the median absolute reduction was -2.5 units, and the median percent reduction was -78%. The consistency and magnitude of clearance of renal Gb3 inclusions observed in the study population are highly unlikely to occur spontaneously. Therefore, the results from F01/02 contribute compelling evidence of PRX-102's efficacy. Reductions in GL-3/Gb-3 inclusions in the kidney would be expected to modify the pathophysiology of FD beneficially including the rate of decline in renal function as measured by eGFR. Consistent with this, the effects of PRX-102 on annualized eGFR slope, an accepted clinical endpoint, appear comparable to agalsidase beta, an approved enzyme replacement therapy with a similar mechanism of action as PRX-102.

With respect to safety, the overall safety profile is consistent with that expected for an enzyme replacement therapy. No deaths were reported in the F20 study. The incidence of serious adverse events was comparable between PRX-102 and agalsidase beta. There were 3 (of 52) subjects in the PRX-102 arm that withdrew from the study due to adverse events: one due to a severe allergic reaction, one due to development of end stage kidney disease, one due to an event of membranoproliferative glomerulonephritis. Zero (of 25) subjects in the agalsidase beta arm withdrew from the study due to adverse events. The overall incidence of hypersensitivity and infusion related reactions was comparable in the PRX-102 and agalsidase beta arms.

In the context of Fabry Disease as a rare, serious disease with limited therapeutic options that may not be suitable to all individual patients, the review team has determined the benefit-risk of PRX-102 favorable for the treatment of adults with confirmed Fabry disease.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 1.4
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	Patient experience data was not submitted as part of this application.			

Data on Brief Pain Inventory Scale (BPI) were discussed in Section 11.4.2.8 of the PB-102-F20 CSR (page 116). In addition, data on EQ-5D-5L are discussed in Section 11.4.2.9 of F20 CSR (page 117). In the context of an active control study design, these patient experience data do not meaningfully inform a decision on approvability and thus are not discussed further in this review. Qualitatively, the data in PRX-102 and agalsidase beta arms appear similar.

2 Therapeutic Context

2.1. Analysis of Condition

Fabry disease (FD) is an X-linked, slowly progressive, lysosomal disease affecting both males and females. With an estimated incidence of approximately 1:40,000[4], it is the second most common lysosomal storage disorder after Gaucher disease. FD is caused by biallelic variants in the *GLA* gene, which encodes the lysosomal enzyme alpha-galactosidase A (alpha-Gal A) that breaks down the glycosphingolipid globotriaosylceramide (Gb3) in lysosomes. Pathogenic *GLA* variants result in complete or partial deficiency of alpha-Gal A, which in turn causes progressive intralysosomal accumulation of the substrate glycosphingolipids globotriaosylceramide (Gb3) and its metabolite globotriaosylsphingosine (lyso-Gb3) in vascular, endothelial, epithelial, smooth muscle, and ganglion cells of the kidneys, cardiovascular system, cerebrovascular system, gastrointestinal (GI) tract, peripheral nerves, and skin. Gb3 and lyso-Gb3 are the tissue toxic intermediates that directly contribute to the pathophysiology of Fabry disease. A reduction of accumulated Gb-3 (sometimes referred to as GL-3) in affected tissues is expected to ameliorate and/or prevent the adverse clinical outcomes from the cellular and tissue damage and organ dysfunction caused by this single enzyme deficiency.

FD spans a spectrum of disease severity ranging from severe, early-onset disease (classic FD) to later-onset, milder disease (late-onset FD) in males. Affected females can have either symptomatic or asymptomatic disease and a wide range of manifestations and severity (depending on the extent of X-inactivation in the corresponding cells/tissues and the amount of residual alpha-Gal A enzyme activity). The first clinical manifestations in the classic form of the disease in males typically appear in childhood starting around age 5 years with development of diarrhea or abdominal pain, neuropathic pain crises (i.e., acroparesthesia with excruciating pain in the hands and feet), angiokeratomas (clusters of red to blue rash-like discolorations on the skin) and hypo/anhidrosis (markedly decreased or absent sweating). Typically, chronic renal insufficiency (initially manifesting as proteinuria, on average appearing in the 20s in classic FD males) slowly progresses to renal failure and end-stage renal disease. Gradual decline in renal function and the development of azotemia typically occur in the third to fifth decades and are managed with hemodialysis and renal transplantation. Males with classic FD with untreated end-stage renal disease (ESRD) typically die in their early 40s. Major causes of mortality in FD include life-threatening cardiovascular (sudden cardiac death, arrhythmias, myocardial infarction) and cerebrovascular complications (stroke). The cardiovascular manifestations can include hypertension, left ventricular hypertrophy, and ischemic heart disease, which can progress to heart failure, myocardial infarction, or arrhythmias. Cardiac disease is progressive and is typically present in most males with classic FD by middle age. Certain cardiac phenotypes

[4] OMMBID Book Chapter on Alpha-galactosidase deficiency: Fabry Disease

can develop hypertrophic cardiomyopathy that may lead to cardiovascular events. Cardiac manifestations tend to occur earlier in affected males than in females. The disease course in late-onset FD is highly variable with some patients experiencing severe manifestations and a more rapid rate of disease progression, while others only have mild or slowly progressive symptoms over their lifetime. Typically, affected males experience more severe disease manifestations and a faster rate of disease progression compared to females due to the X-linked nature of the disease but this is highly variable.

2.2. Analysis of Current Treatment Options

Fabrazyme (agalsidase beta) is a recombinant human alpha-Gal A. It is given as an IV infusion once every 2 weeks at a dose of 1 mg/kg. It was originally approved under subpart E, section 351 of the PHS act in 2003 for the treatment of FD based on histological clearance of the substrate Gb-3 inclusions in the kidney interstitial capillary cell globotriaosylceramide (Gb- 3). This randomized, placebo-controlled, phase 3 trial of Fabrazyme included patients with a diagnosis of FD, plasma alpha-Gal A activity ≤ 1.5 nmol/hr/mL, and plasma Gb-3 level ≥ 5 ng/μL. Treatment with Fabrazyme resulted in a statistically significant clearance of Gb-3 inclusions in 20 of 29 (69%) treated subjects (based on the Genzyme renal histologic methodology) compared to no clearance among subjects treated with placebo. Directionally consistent reductions in Gb-3 inclusions were also obtained in heart and skin biopsy specimens. Fabrazyme received traditional approval in March 2021 based on evidence establishing that the reductions in Gb-3 inclusions are expected to result in clinical benefit based on data within the Fabrazyme clinical development program. This evidence included several published studies establishing that the central pathophysiological role of tissue Gb-3 accumulation in FD has a progressive, detrimental effect on tissue structure and organ function in FD. In addition, exploratory analyses from a long-term observational study suggested that treatment may be associated with slower renal disease progression (eGFR slope) when compared to untreated FD patients. Exploratory analyses from a randomized, placebo-controlled clinical trial also suggested a comparatively favorable clinical effect of Fabrazyme on the incidence of Fabry associated clinical events (renal, cardiac, cerebrovascular events, or death).

Galafold (migalastat) is an α-galactosidase A (α-Gal A) pharmacological chaperone that was approved under the accelerated approval regulations, 21 CFR 314.510 (subpart H) in 2018 in the United Stated and is indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase α gene (*GLA*) variant based on in-vitro assay data. It is given as an oral dose of 123 mg every other day. The phase 3 trial of Galafold included subjects with a diagnosis of FD with a *GLA* variant responsive to Galafold based on the clinical trial human embryonic kidney (HEK) assay. Treatment with Galafold resulted in a greater reduction in Gb-3 deposition in the KIC endothelial cells, as assessed by renal biopsy using the BLISS methodology, after 6 months of treatment, compared to placebo. The indication was approved under accelerated approval based on reduction in kidney interstitial capillary cell globotriaosylceramide (Gb-3) substrate.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Pegunigalsidase alfa is a pegylated, covalently cross-linked recombinant human protein α-galactosidase A (α-GAL-A) that is not currently marketed in the U.S (or elsewhere globally).

3.2. Summary of Presubmission/Submission Regulatory Activity

An original BLA (761161) application was submitted in May 2020 seeking accelerated approval. The primary evidence of efficacy was findings on renal histology in study F01/02. A complete response letter (CRL) was issued in April 2021. The two main deficiencies cited in the CRL were:

- Manufacturing site/other CMC issues
- Accelerated approval (AA) using a surrogate endpoint was no longer appropriate in context of Fabrazyme traditional approval prior to action date of the PRX-102 BLA. Therefore, PRX-102 was no longer eligible for AA unless the Applicant could demonstrate that PRX-102 was superior to Fabrazyme.

The Applicant submitted a Complete Response in November 2022 seeking traditional approval of PRX-102 based the findings of F20 study as primary support for efficacy.

A summary of the key regulatory history prior to the original BLA submission in May 2020 is described in the table below.

Table 1: Key regulatory history prior to original BLA submission

Date	Interaction	Topic
July 15, 2012	IND safety review	Placed on clinical hold because of insufficient nonclinical information
August 9, 2012	IND allowed to proceed	Clinical hold was removed after division accepted follow up information by the Applicant
November 3, 2015	End of Phase 2 meeting	The proposed phase 3 study (F20) would be adequate to support a BLA in a superiority study using Fabrazyme as a comparator
January 29, 2018	Fast Track Designation	Applicant was granted Fast Track Designation
February 27 2019	Type C meeting	The Agency agreed the Applicant can use the Accelerated approval Pathway based on histological reduction of Gb3 in kidney peritubular capillaries in treated subjects from study F01/02. The proposed confirmatory trial would be the ongoing F20 trial which assesses eGFR changes over 24 months in FD adult subjects treated with PRX-102 vs. Fabrazyme

October 15, 2019	Pre-BLA meeting	The Agency asked the Applicant to provide individual graphical patient profiles on the Gb3 scores over time and more details in the immunogenicity section of the BLA. Note: This submission included a draft SAP (dated Sept. 5, 2019) for study F20. For the primary endpoint of eGFR slope, the SAP stated that the primary analysis would be based on a linear mixed-effect model and a 2-stage method would be used as supportive analysis. The Agency recommended the 2-stage method as the primary analysis and the Sponsor's proposed primary analysis as a supportive analysis because the linear mixed-effect model assumes a specific covariance structure for the eGFR data.
January 29, 2020	Pediatric Study Plan	Agreed initial pediatric study plan (iPSP) was accepted

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Please see OSI memo dated 27-March-2023. Three sites were inspected. The data generated by these sites appeared acceptable to support the proposed indication.

4.2. Product Quality

No product quality issues impacting approvability were identified.

4.3. Clinical Microbiology

N/A

4.4. Devices and Companion Diagnostic Issues

N/A

5 Nonclinical Pharmacology/Toxicology

Refer to non-clinical review dated 8-May-2023 for additional details. No new non-clinical data have been submitted in this BLA re-submission. There were no approvability issues identified from a non-clinical perspective with the original submission.

6 Clinical Pharmacology

6.1. Executive Summary

Refer to Section 6 of the multi-disciplinary review dated 27-April-2021.

There are additional data and a new study (PB-102-F50) submitted in this BLA Complete Response [redacted] (b) (4).

[redacted] (b) (4)

Please refer to Clinical Pharmacology Review (Dr. Xiaohui (Michelle) Li dated 8-May-2023) for additional details.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Refer to Section 7.1 of the multi-disciplinary review dated 27-April-2021 for a listing of studies included in the original BLA review. The new clinical studies included in this Complete Response are studies PB-102-F20 and PB-102-F50.

PB-102-F20 study was ongoing and blinded at the time of the original BLA review. The study has since been completed and is the key study provided in support of the re-submission. This is the only multicenter, randomized, double-blind, active-controlled trial of PRX-102 for treatment of adults with confirmed FD. (Note: additional, uncontrolled studies do also contribute to the efficacy and safety database for PRX-102).

- The F20 study evaluated PRX-102 1 mg/kg IV every 2 weeks versus agalsidase beta 1 mg/kg IV every 2 weeks.
- The primary endpoint was the change in mean annualized eGFR slope comparing the 2 treatments. There were a number of secondary endpoints (see Section 8.1.1).
- The planned treatment duration was 2 years.
- A total of 78 subjects were randomized in a 2:1 ratio (PRX-102 to agalsidase beta).
- The study population included symptomatic Fabry adult (18 y/o to 60 y/o) who had received agalsidase beta 1 mg/kg for at least 1 year prior to enrollment.
- A total of 28 sites from 12 countries participated in the F20 study including Czech Republic, Finland, France, Hungary, Italy, Netherlands, Norway, Slovenia, Spain, Switzerland, UK, and US.

PB-102-F50 study evaluated a q4 weekly pegunigalsidase regimen. This was an open-label, single-arm study.

- The study evaluated pegunigalsidase alfa 2 mg/kg IV every 4 weeks
- The objectives were to evaluate safety and PK of a q4 weekly regimen
- The planned treatment duration was 52 weeks.
- The study population included FD subjects previously treated with either agalsidase alpha (Replagal) or beta (Fabrazyme).

7.2. Review Strategy

- This review covers the resubmission of this application. A detailed review of the effects of PRX-102 on reducing Gb3 deposition in kidney peritubular capillaries is documented in the original BLA review (April 2021) and is not repeated here.
- The resubmission includes the PB-102-F20 study and PB-102-F50 study which were not in the original submission.
- For several portions of the efficacy section of the F20 study, this clinical review cross references Dr. Yared Gurmu's primary statistical review.
- For safety, the focus of this review is on the F20 safety data with a secondary focus on the F50 study and integrated safety dataset. The F20 study is the only randomized, controlled dataset in the sponsor's re-submission. The F50 and ISS datasets do not include a comparator.
- For the F20 study, the safety review focuses on:
    - TEAE's, common AE's, and ADR's
    - A review of selected narratives for deaths, SAE's and AE's leading to drug discontinuation
    - Immunogenicity (e.g., development of ADA, Neutralizing Ab). Refer to Dr. Xiaohui Li's Clinical Pharmacology review for additional details.
    - Infusion related reactions, hypersensitivity reactions (including as a function of baseline ADA status)
- For the F50 study, the review focuses on TEAE's, common AE's, SAE's and AE's leading to drug discontinuation. This review does not rely on F50, a single-arm, uncontrolled study for conclusions on efficacy.

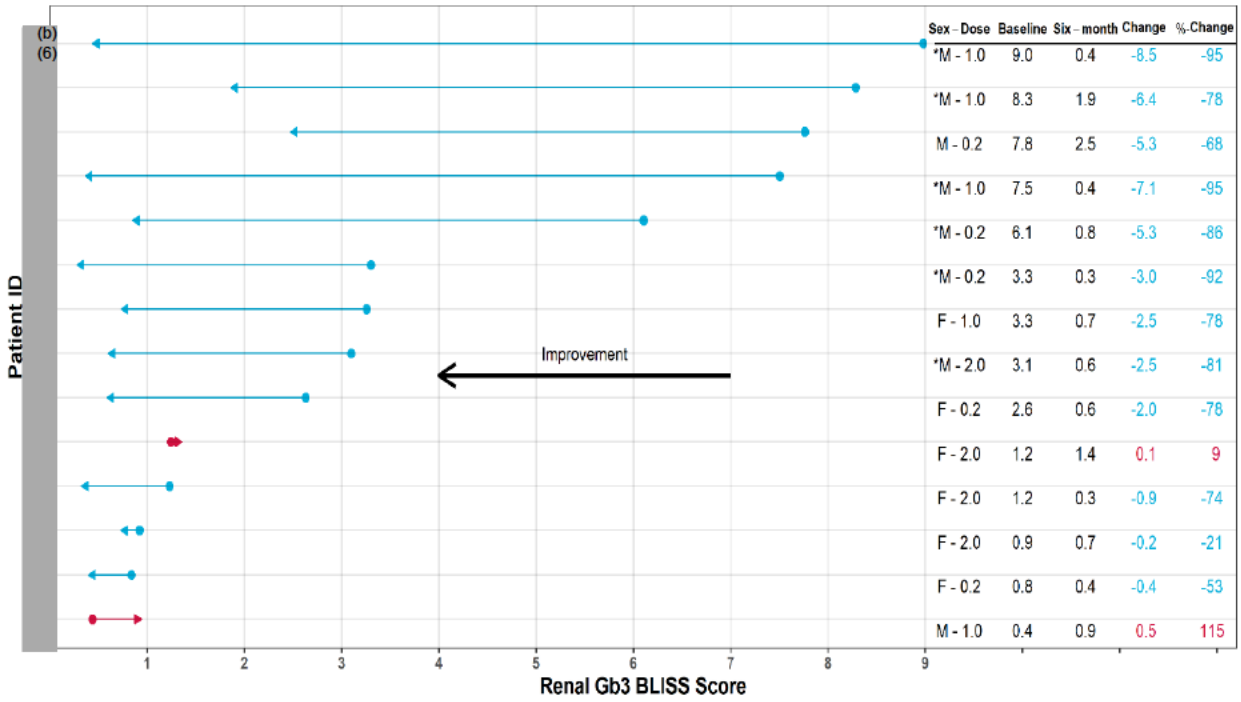
8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. PB-102-F01/02

PB-102-F01/02 was a single-arm (baseline control), dose-ranging (0.2, 1.0 or 2.0 mg/kg) study which evaluated the safety and efficacy of PRX-102 on histological decreases in accumulated Gb3 substrate in kidney peritubular capillaries (PTC) at 6 months assessed using Barisoni Lipid Inclusion Scoring System (BLISS). After 6 months of treatment with PRX-102, the observed median percent reduction compared to baseline in number of Gb3 inclusions per PTC was -78%; the absolute mean reduction compared to baseline was -3.1 (95% CI: -4.8, -1.4). Additional analyses performed at the subject level showed that 11 out of 14 subjects (with evaluable histology data) had at least a 50% reduction from baseline in the number of Gb3 inclusions. With respect to plasma lyso-Gb3, of the 16 evaluable subjects, all subjects showed at least some reduction in lyso-Gb3 levels. The reductions ranged from -5% to -79% at Month 12.

Figure 1: Changes in Renal Gb3 Bliss Score by Patient (Study F01/02)



Dots (●): Baseline BLISS score Arrow heads (◀): 6-Month BLISS score (*): Classic Fabry Disease
Increase in BLISS score from baseline to six month indicated in red while decrease in BLISS score is indicated in blue.
The biopsy data for 2 patients (out of the 16 patients enrolled in PB-102-F01/02) could not be used in the main efficacy analysis; 1 female patient had biopsy tissue that could not be scored at baseline as it was taken from the medulla of the kidney; 1 male patient had biopsy slides that were scanned out of focus and mislabeled, and subsequently could not be matched to correct visits (i.e. baseline versus six-month visit times could not be identified).

Despite the baseline control (a type of external control), the review team considers the F01/02 study to be adequate and well-controlled given published data indicating the absence of spontaneous reduction in Gb3 inclusions for untreated Fabry patients (see Section 1.2). The reductions in the BLISS score observed in the F01/02 study with PRX-102 are believed to be clinically relevant on the basis of the following:

- Available published literature collectively shows that accumulation of Gb3 is toxic to tissues
- Gb3 accumulates in tissues/organs which exhibit structural damage and functional impairment due to Fabry disease
- Gb3 accumulation in affected tissues correlates with tissue and end-organ damage and functional impairment.
- Confirmatory evidence from the PB-102-F20 study, discussed subsequently, that PRX-102 appears to have an effect on eGFR annualized slope that is comparable to agalsidase beta.

Reviewer comment: Despite the conclusions above, some uncertainties continue to exist including:

- *What magnitude of reduction in Gb3 deposition in affected tissues would translate into clinical events (e.g., delayed progression to renal failure, reduced incidence of MI/stroke, etc.)*
- *Does the magnitude of benefit on clinical events depend on the amount of pre-treatment Gb3 deposition (e.g., do subjects with larger amounts of deposition derive greater benefits)?*
- *What is the impact of timing of treatment initiation (e.g., pre- vs. post-onset of end organ damage) on clinical events?*
- *How similar or different is the pathophysiology of disease in Classic vs. non-Classic Fabry, male vs. female, etc.?*

Regarding this particular development program, it is notable that the observed treatment effect of PRX-102 on the reduction of Gb3 deposition in the kidney is large (approx. 70% in relative terms). In addition, as noted above, the findings from the F20 study provide confirmatory evidence in terms of the effects of PRX-102 on a clinical endpoint (eGFR slope).

8.1.2. PB-102-F20 (BALANCE, NCT02795676)

Trial Design

PB-102-F20 was a randomized, double-blind, active control study examining the safety and efficacy of PRX-102 (enzyme replacement therapy) in Fabry disease adult subjects with impaired renal function and on treatment with agalsidase-beta. Following screening, eligible subjects were randomized in a 2:1 ratio (PRX-102: agalsidase-beta) to either switch to PRX-102 or continue treatment with agalsidase-beta, with randomization stratified according to whether the urine protein to creatinine ratio (UPCR), a measure of kidney function, was above or below the threshold of 1gr/gr protein/creatinine. Subjects had to have been taking agalsidase beta (Fabrazyme®) for at least 1 year prior to study entry, and to have been on a stable dose for at least the last 6 months. It is important to note that the protocol did not require stratification based on sex.

Key Inclusion Criteria
Subjects had to meet all of the following inclusion criteria:
1. Symptomatic adult Fabry disease patients, age 18–60 years

2. Males:
Plasma and/or leucocyte alpha galactosidase activity (by activity assay) less than 30% mean normal levels and one or more of the characteristic features of Fabry disease:

i. neuropathic pain
ii. cornea verticillata (a whorl-like pattern of opacities in the corneal epithelium resulting from accumulation of glycosphingolipids)
iii. clustered angiokeratoma (a wart like lesion in the superficial layers of the skin)

3. Females:
a. historical genetic test results consistent with Fabry pathogenic mutation One or more of the described characteristic features of Fabry disease:

i. neuropathic pain,
ii. cornea verticillata,
iii. clustered angiokeratoma

b. or in the case of novel mutations a first-degree male family member with Fabry disease with the same mutation, and one or more of the characteristic features of Fabry disease

i. neuropathic pain
ii. cornea verticillata
iii. clustered angiokeratoma

4. Screening eGFR by CKD-EPI equation 40 to 120 mL/min/1.73 m^2
5. Linear slope of eGFR more negative than -2 mL/min/1.73 m^2, based on at least 3 serum creatinine values over approximately 1 year (range of 9 to 18 months, including the value obtained at the screening visit)
6. Treatment with a dose of 1 mg/kg agalsidase beta per infusion every 2 weeks for at least one year. Over the last 6 months, the dose had to have been stable and the patient had to have received at least 80% of the q2 weekly scheduled infusions.

Key Exclusion Criteria
The presence of any of the following criteria led to exclusion of a subject from study enrollment:

1. History of renal dialysis or transplantation
2. History of acute kidney injury in the 12 months prior to screening
3. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated or dose changed in the 4 weeks prior to screening
4. Patient with a screening eGFR value of 91-120 mL/min/1.73 m_2, having an historical eGFR value higher than 120 mL/min/1.73 m^2 (during 9 to 18 months before screening)
5. Urine protein to creatinine ratio (UPCR) > 0.5 gr/gr (0.5 mg/mg or 500 mg/g) and not treated with an ACE inhibitor or ARB
6. Cardiovascular event (myocardial infarction, unstable angina) in the 6-month period before randomization
7. Congestive heart failure NYHA Class IV
8. Cerebrovascular event (stroke, transient ischemic attack) in the 6-month period before

Randomization
9. History of anaphylaxis or Type 1 Hypersensitivity reaction to agalsidase beta.

Reviewer's Comment: The I/E criteria are generally acceptable. The population enrolled in the F20 study are entirely ERT (Fabrazyme) experienced subjects. In F20, the mean duration of agalsidase beta use prior to study entry was approximately 5.5 to 6.5 years. Inclusion criteria #5 above, led to enrollment of what appears to be a population experiencing an accelerated decline in renal function based on screening/baseline eGFR slope (see Table 3). However, the population was actually not experiencing as rapid a decline as the screening eGFR data would suggest. The baseline eGFR slope of – 8 mL/min/1.73 m2/year observed in the study is likely reflective of a regression to the mean and is not representative of the extent of renal co-morbidities of the population enrolled in F20. The limitations in how this baseline eGFR slope is calculated include: 1) the investigator discretion on which labs to use to qualify for study entry 2) no systematic collection of renal labs via a central laboratory.

Study Endpoints

The Primary endpoint was the comparison of the mean annualized change (slope) in estimated glomerular filtration rate (eGFR CKD-EPI) between treatment groups.

Secondary efficacy endpoints:
- Left Ventricular Mass Index (g/m2) by MRI
- Plasma Lyso-Gb3
- Plasma Gb3
- Urine Lyso-Gb3
- Protein/Creatinine ratio spot urine test
- Frequency of pain medication use
- Exercise tolerance (Stress Test)
- Short Form Brief Pain Inventory (BPI)
- Mainz Severity Score Index (MSSI)
- Quality of life EQ-5D-5L

Statistical Analysis Plan

Please refer to the Primary Statistical Review for details. The key elements are as follows:

- The primary efficacy analysis population was the Intent to Treat (ITT) population consisting of all randomized subjects who received at least one dose (including partial dose) of the study medication
- The Applicant's primary analysis (based on the latest version of the SAP) was based on a two-stage approach to estimate the median eGFR slope in each arm. In the first stage, patient-specific eGFR slope was estimated using a linear regression model for each

subject's eGFR data. In the second stage, the median eGFR slope is compared between the treatment arms using a quantile regression model that includes treatment arm indicator as a covariate

- Per the Applicant, non-inferiority will be demonstrated if the lower bound of the confidence interval for the treatment difference (PRX-102 minus agalsidase beta) is greater or equal to -3.0 mL/min/1.73 m^2/year.

Reviewer comment: The Division did not agree with the sponsor's proposed NI margin of -3 mL/min/1.73 m^2/year because it was based on an absolute change of the comparator in certain clinical experiences instead of preserving a minimum effect of the comparator compared to placebo. The sponsor provided data on the natural history of Fabry disease suggesting that eGFR declines by approximately 4 to 12 mL/min/1.73m2/year in untreated male Fabry disease subjects. However, such natural history data in untreated patients is of limited value if such data cannot be adjusted for population differences (e.g., sex, proteinuria, eGFR, etc.) relative to the F20 study. Such factors will have impact on the eGFR slope.

Protocol Amendments

Protocol amendments for the PB-102-F20 study are summarized below:

- Amendment 1 (April 2016): Number of subjects planned was changed to 78 instead of 69 and the assumption of a 15% dropout was added. This was subsequently reversed, for unclear reasons, during Amendment 4 (Sept 2016).
- Amendment 1 (April 2016): For regulatory purposes, demonstration of non-inferiority of PRX-102 compared to agalsidase beta at 12 months for submission of MAA to the European Medicines Agency and superiority at 24 months for FDA BLA submission will be considered trial success was added. (Note: Based on discussions with the Agency in Sept 2021 and Jan 2022, the analysis was changed from superiority to non-inferiority at Month 24).
- Amendment 4 (July 2017): No more than 50% of the subjects enrolled will be female was added.
- There were a number of other amendments (mostly local country) related to 1) ensuring safety of the enrolled study subjects and 2) administrative in nature

8.1.3. Study Results

Compliance with Good Clinical Practices

Section 5 of the PB-102-F20 CSR indicates that:

- An Institutional Review Board (IRB) or Independent Ethics Committee (IEC) reviewed and approved the study protocol and any amendments prior to their implementation. The IRB/IEC also reviewed the informed consent forms (ICFs) and any written materials given to subjects.

- This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, in compliance with the approved protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

Financial Disclosure

There was a sub-investigator (b) (6) at Site (b) (6) with a disclosable financial arrangement and/or interest. (b) (6) owns shares in the company >$45,000. Given that site (b) (6) randomized one subject and had one subject transfer from site (b) (6), it is unlikely that this financial arrangement/interest materially impacted the study results.

Patient Disposition

A total of 78 subjects were randomized into PB-102-F20 (53 on PRX-102 and 25 on agalsidase beta). There was 1 subject randomized but never received any study drug (PRX-102 arm). The analysis set consists of 77 subjects. Most of the analyses in this review focus on the safety analysis set (N=77). A total of 48 and 24 subjects in the PRX-102 and agalsidase-beta arms, respectively, completed the 24-month study period. A total of 5 subjects in the PRX-102 arm discontinued prematurely of which 2 were for adverse events and 3 were voluntary withdrawals. One subject in the agalsidase beta arm discontinued prematurely (voluntary withdrawal).

Protocol Violations/Deviations

A total of 55 (71%) of randomized subjects experienced at least one critical or major deviation with similar rates between the 2 treatment groups. The most common types of deviations were in the categories of study procedure criteria and lab assessment criteria. The protocol deviations don't appear to have impacted the efficacy and/or safety outcomes.

Baseline Demographic/Disease Characteristics

The baseline demographics, other than proportion of enrolled females, and disease characteristics were generally similar between the two treatment groups. There was a larger proportion of female subjects in the PRX-102 arm (44%) compared to the agalsidase beta arm (28%). Two-thirds of the overall population in the PB-102-F20 study were from the U.S.

Table 2: Baseline Demographic/Disease characteristics (PB-102-F20)

	PRX-102 (N = 52) n (%)	Agalsidase beta (N = 25) n (%)	Total (N = 77) n (%)
Sex			
Male	29 (56%)	18 (72%)	47 (61%)
Female	23 (44%)	7 (28%)	30 (39%)
Age			
Mean years (SD)	43.9	45.2	44.3
Median (years)	44	48	46
Min, max (years)	20, 60	18, 58	18, 60
Race			
White	49 (94%)	23 (92%)	72 (94%)
Black or African American	1 (2%)	2 (8%)	3 (4%)
Asian	2 (4%)	0	2 (3%)
Ethnicity			
Hispanic or Latino	0	2 (8%)	2 (3%)
Not Hispanic or Latino	52 (100%)	23 (92%)	75 (97%)
Region			
United States	33 (63%)	18 (72%)	51 (66%)
Rest of the World	19 (37%)	7 (28%)	26 (34%)
Type of Fabry disease			
Classic	27 (52%)	14 (56%)	41 (53%)
Non-classic	25 (48%)	11 (44%)	36 (47%)

(Note: Rest of World includes Czech Republic, Spain, Finland, France, Great Britain, Hungary, Italy, Netherlands, Norway, and Slovenia)
Source: Sponsor analyses Table 11.2 and Table 11.4

Additional baseline and disease characteristics are shown in the table below. Subjects in the PRX-102 arm had a relatively higher baseline mean and median urinary protein:creatinine ratio (UPCR) relative to the agalsidase beta arm. There was numerically greater ACEi/ARB use in the agalsidase beta arm compared to the PRX-102 arm. In addition, there was a numerically longer mean/median duration of agalsidase beta use prior to randomization in the agalsidase beta arm compared to the PRX-102 arm.

Although not shown in the table below, the mean plasma lyso-Gb3 levels in men and women respectively were 40.4 and 8.35 nanomolar respectively in the PRX-102 arm. The corresponding values in the agalsidase-beta arm were 42.4 and 5.69 nanomolar respectively. (Note: the conversion factor is 1 ng/mL = 1.27 nmol/L.).

Reviewer Comment: Even if agreement had been reached with the sponsor on the proposed non-inferiority margin, there are significant differences in the population between the F20 study and the Fabrazyme AGAL-008-00 study (a Randomized, double-blind, placebo-controlled study in Fabry disease evaluating the effects of Fabrazyme on a composite of renal, cardiovascular, cerebrovascular and mortality outcomes) which call into question the constancy assumption and preclude making conclusions on non-inferiority comparing PRX-102 versus Fabrazyme. The proportion of Classic Fabry subjects enrolled in F20 was 53% versus nearly 100% in the Fabrazyme AGAL-008-00 study. In addition, the proportion (30% to 40%) of females enrolled in the F20 study was significantly higher relative to the proportion (12%) of females in the Fabrazyme AGAL-008-00. The mean eGFR (74 mL/min/1.73m2) in the PB-102-F20 was significantly higher compared to the eGFR (53 mL/min/1.73m2) in the AGAL-008-00 study. Also, the mean UPCR was approximately 0.28 to 0.44 g/g versus 1.1 to 1.5 g/g in the PB-102-F20 study and AGAL-008-00 studies respectively. In general, the subjects enrolled in the F20 study could be considered as having less severe disease (or fewer comorbidities) relative to the AGAL-008-00 study. Finally, the subjects enrolled in F20 were an ERT experienced population unlike the AGAL-008-00 study where subjects were treatment naïve.

Table 3: Additional Baseline Disease characteristics PB-102-F20

	PRX-102 (N = 52)	AGALSIDASE BETA (N = 25)	Total (N = 77)
eGFR ($mL/min/1.73m^2$)			
Mean	73.46	74.16	73.69
Median	73.45	74.85	74.52
eGFR category ($mL/min/1.73m^2$)			

< 60	13 (25%)	8 (32%)	21 (27%)
60 to <= 90	28 (54%)	11 (44%)	39 (51%)
>90	11 (21%)	6 (24%)	17 (22%)
eGFR slope at baseline	-8.42	-7.79	-8.22
Mean UPCR at baseline (gr/gr)	0.441	0.284	
Median UPCR at baseline (gr/gr)	0.132	0.074	
UPCR Category (gr/gr)			
<=0.5	36 (69%)	20 (80%)	56 (73%)
>0.5 and < 1.0	9 (17%)	2 (8%)	11 (14%)
>= 1	7 (13%)	3 (12%)	10 (13%)
Treatment with ACEi or ARB			
Yes	26 (50%)	16 (64%)	42 (55%)
ADA status at Baseline			
Positive	18 (35%)	8 (32%)	
Negative	34 (65%)	17 (68%)	
Pre-Medication use for agalsidase beta infusion prior to enrollment			
Yes	20 (39%)	15 (60%)	35 (46%)
No	32 (62%)	10 (40%)	42 (55%)
Duration of Agalsidase beta Prior to enrollment (mean/median Months)	65/51	77/68	69/57

Source: Analyses based on Tables 11.3 and 11.4 of F20 CSR. The analyses of UPCR (mean and median) were by the Stats Reviewer.
UPCR = Urinary Protein: Creatinine Ratio
eGFR = estimated glomerular filtration rate

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Given the IV infusion nature of treatment, as expected, treatment compliance was high and comparable in the 2 treatment arms. See section 8.2.5 of this review regarding analyses related to infusion pre-medication to minimize the occurrence of infusion related reactions.

Efficacy Results – Primary Endpoint

Please refer to the Statistical Review by Dr. Yared Gurmu for additional details.

In summary, the applicant's SAP pre-defined primary analysis was a random intercept and random slope mixed effect model (RIRS) that compared the mean eGFR slope between PRX-102 and agalsidase arms adjusting for the randomization stratification factor of UPCR (UPCR <1 g/g; >=1 g/g).

The FDA Statistical team conducted a post-hoc, 2-stage ANCOVA adjusting for continuous UPCR as there were some baseline differences in UPCR in the two treatment arms of F20 and because it is known to be a predictor of eGFR decline. The FDA's statistical analysis of the primary endpoint is shown below.

- Stage 1: patient-level eGFR slopes are estimated by fitting a least-square line through each patient's eGFR profile
- Stage 2: mean eGFR slope across treatment arms are compared using ANCOVA after adjusting for binary UPCR (< 1 g/g vs. >= 1 g/g.

Table 4**:** FDA's Statistical analysis of the Primary endpoint

Adjusted for Baseline Proteinuria (<1 vs ≥ 1 g/g)

	PRX-102 (N=51)	Fabrazyme (N=25)
Mean Slope (95% CI)	-2.3 (-4.1, -0.5)	-2.4 (-3.7, -1.3)
Difference (95% CI) in Mean Slopes	0.1 (-2.0, 2.2)	
Median Slope (95% CI)	-1.8 (-3.1, -0.5)	-2.2 (-3.9, -0.5)
Difference (95% CI) in Median Slopes	0.4 (-1.7, 2.4)	

The 95% CIs were obtained using bootstrap methods.

Adjusted for Baseline Proteinuria (continuous)

	PRX-102 (N=51)	Fabrazyme (N=25)
Mean Slope (95% CI)	-2.0 (-3.6, -0.4)	-3.1 (-4.6, -1.7)
Difference (95% CI) in Mean Slopes	1.1 (-0.8, 3.1)	
Median Slope (95% CI)	-2.5 (-3.8, -1.3)	-2.6 (-4.2, -1.3)
Difference (95% CI) in Median Slopes	0.1 (-1.9, 2.0)	

The 95% CIs were obtained using bootstrap methods.

The results of the FDA Statistical analysis were comparable to the Sponsor's primary analysis.

Based on the Applicant's primary analysis adjusted for the binary baseline proteinuria (< 1 vs ≥ 1 gr/gr), the estimated mean eGFR slope between the two arms were comparable (-2.4 for PRX-102 and -2.3 for agalsidase beta), and the estimated treatment difference was -0.1 (95% CI: -2.3, 2.1) mL/min/1.73 m^2/year. These comparable results were supported by the review team's post-hoc analyses, including an analysis adjusted for the continuous baseline proteinuria. This analysis yielded the estimated mean eGFR slopes of -2.0 and -3.1 mL/min/1.73 m^2/year in the PRX-102 and agalsidase beta arms, respectively, and the treatment difference of 1.1 (95% CI: -0.8, 3.1) mL/min/1.73 m^2/year.

Reviewer comments: Conclusions regarding non-inferiority between PRX-102 and agalsidase beta in the F20 study would need to rely on a well characterized effect of the active comparator (agalsidase beta) compared to placebo. Unfortunately, there is lack of previous data to determine the treatment effect of agalsidase beta compared to placebo for the patient population studied in F20. Although there are data on the effects of agalsidase beta versus placebo from a randomized, placebo-controlled, Fabrazyme study (AGAL-008-00), the population in that study was different (i.e., more advanced disease) relative to the F20 study (see prior Reviewer comment). This limitation precludes any conclusion regarding non-inferiority of PRX-102 to agalsidase beta. However, to aid in the interpretation of the comparable results of the eGFR slope between PRX-102 and agalsidase beta observed in the F20 study, eGFR slope data external (i.e., observational study) to the F20 study in a healthier population leads the review team to conclude that the comparable results on eGFR slope between PRX-102 and agalsidase beta are comparable and can serve as confirmatory evidence in favor of approval (see Statistical review for additional details).

Data Quality and Integrity

There are no concerns about data quality and integrity. The datasets were accessible with analytic tools. The adverse event coding appeared reasonable.

There was no single site that dominated enrollment into the study. There was a total of 28 sites that enrolled subjects in the study with each site enrolling no more than 1 or 2 subjects each.

Efficacy Results – Secondary and other relevant endpoints

In general, changes in biomarkers from baseline (e.g., plasma lyso-Gb3, plasma Gb3, etc.) over the 104-week study duration were numerically worse on PRX-102 compared to agalsidase beta. However, the clinical relevance of these trends is unclear. Please refer to the Clinical Pharmacology Review by Dr. Xiaohui (Michelle) Li for analyses on the biomarker endpoints.

Clinical events that are known to be associated with Fabry disease were evaluated as a secondary endpoint. This secondary endpoint was added to the Statistical analysis plan after the trial started but prior to unblinding. Fabry clinical events were evaluated by the sponsor's medical monitor in a blinded manner. Such events were classified into four categories:

- 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
- Cerebrovascular events: hemorrhagic or ischemic stroke or transient ischemic attack
- Non-cardiac-related death Fabry clinical events were assessed by the sponsor medical monitor in a blinded manner.

- Renal events: First occurrence of either initiation or chronic dialysis (>40 days), or renal transplantation

The decision as to whether an event met the criteria for inclusion in Table 5 below was made by the sponsor's medical monitor, blinded to treatment assignment, based on a review of reported AE terms and additional clinical information included in the database. The sponsor's summary of subjects experiencing a FCE is shown below. Of the 9 subjects in the PRX-102 arm experiencing a FCE event, 1 experienced a serious adverse event (Subject (b) (6) and 1 experienced an event that led to study drug discontinuation (Subject (b) (6). Narratives of these two subjects are located in Section 8.2.4 of this Review. Of the 2 subjects in the agalsidase beta arm experiencing a FCE event, both subjects (Subjects (b) (6) experienced an adverse event classified as serious by the investigator. The decision as to whether or not an event met the criteria for inclusion in Table 5 below was made by the blinded sponsor medical monitor, based on a review of reported AE terms and additional clinical information included in the database. The sponsor's summary of subjects experiencing a FCE is shown below. Of the 9 subjects in the PRX-102 arm experiencing a FCE event, 1 experienced a serious adverse event (Subject (b) (6) and 1 experienced an event that led to study drug discontinuation (Subject (b) (6). Narratives of these two subjects are located in Section 8.2.4 of this Review. Of the 2 subjects in the agalsidase beta arm experiencing a FCE event, both subjects (Subjects (b) (6) experienced an adverse event classified as serious by the investigator.

Table 5: Sponsor's analysis of Fabry Clinical Events (PB-102-F20)

	PRX-102		Agalsidase beta	
Fabry clinical events categories	Number (%) of Patients N=52	Number of Events (Rate)	Number (%) of Patients N=25	Number of Events (Rate)
Overall	9 (17.3%)	11 (11.2)	2 (8.0%)	2 (4.0)
Cardiac events	6 (11.5%)	7 (7.1)	2 (8.0%)	2 (4.0)
Cerebrovascular events	3 (5.8%)	3 (3.1)	0	0
Renal events	1 (1.9%)	1 (1.0)	0	0
Non-cardiac related death	0	0	0	0

[1] Rate of events adjusted to 100 years of exposure

Source: Sponsor analysis; Table 11.24 of PB-102-F20 CSR

The clinical reviewer conducted an independent analysis of the sponsor's adverse event database selecting terms suggestive of cardiovascular and/or cerebrovascular pathology. There were additional events identified in the independent analysis below. There were two subjects (Subject (b) (6) with a PT of "Cerebral Infarction" in the agalsidase beta arm not confirmed as FCE by the sponsor's medical monitor. In the February 14, 2023, response to an Information Request, the Applicant indicated their medical monitor did not consider silent infarcts and transient neurologic deficits lasting less than 24 hours to be FCE's. The sponsor's

analysis should not be discounted or dismissed given that the analysis of FCE event was pre-specified and done in a blinded manner.

Table 6: Clinical Reviewer Analysis of Potential FCE (PB-102-F20)

	PRX-102 (N = 52)	AGALSIDASE BETA (N = 25)
Subjects with at least 1 reported cardiovascular or cerebrovascular AE	10 (19%)	4 (16%)
Atrial Fibrillation	4	1
Cerebral Infarction	0	2
Transient Ischemic attack	2	0
Atrial flutter	1	0
Cardiac flutter	1	0
Cerebrovascular accident	1	0
Myocardial Ischemia	1	0
Ventricular tachycardia	0	1

The apparent numeric imbalance in FCE in the PRX-102 arm (based on the analysis described in Table 11.24 of F20 CSR) does not appear to be explained by imbalances in cardiovascular, cerebrovascular and/or renal disease medical history as summarized in the table below. The proportion of subjects with a cardiac disorder, nervous system disorder or vascular disorder System Organ class medical history was numerically higher on the agalsidase beta arm. A similar analysis from the sponsor (Table 14.1.7 of the CSR) based on Cardiac disorders, Nervous system disorders and vascular disorders medical history SOC terms demonstrated a higher proportion of affected subjects in the agalsidase beta arm compared to PRX-102.

Table 7: Medical history of Selected Cardiovascular, Cerebrovascular and Renal Disease Terms (PB-102-F20)

	PRX-102 (N = 52)	AGALSIDASE BETA (N = 25)
TOTAL	26(50%)	16 (64%)
Arrhythmia	2	0
Atrial fibrillation	3	1
Atrial thrombosis	1	0
Atrioventricular block first degree	2	1
Atrioventricular block second degree	1	1
Basal ganglia infarction	1	0
Cardiac failure	0	1
Cardiac failure congestive	0	1
Cardiac septal hypertrophy	1	0

	PRX-102 (N = 52)	AGALSIDASE BETA (N = 25)
Cardiomyopathy	0	1
Cerebellar infarction	1	0
Cerebral infarction	0	1
Cerebrovascular accident	5	4
Chronic kidney disease	7	4
Coronary artery disease	0	1
Deep vein thrombosis	1	1
Hemiparesis	1	1
Lacunar infarction	0	1
Left ventricular hypertrophy	4	3
Microalbuminuria	0	2
Myocardial fibrosis	0	1
Myocardial infarction	0	1
Proteinuria	11	7
Restrictive cardiomyopathy	0	1
Right ventricular hypertrophy	0	1
Thalamic infarction	1	0
Thrombosis	1	0
Transient ischemic attack	4	2
Ventricular tachycardia	1	0

Reviewer comments: The sponsor's FCE analysis was pre-specified (per the SAP) and done in a blinded manner suggests a numeric imbalance in events not favoring PRX-102. This imbalance is not explained by baseline differences in cardiovascular or cerebrovascular medical history. The FDA reviewer's independent analysis (albeit post-hoc and unblinded) suggests less of a numeric imbalance. One possibility is that PRX-102 could be relatively less effective in preventing cardiovascular/cerebrovascular events relative to agalsidase beta. Another possibility is that this is a chance finding due to absence of a systematic ascertainment and adjudication of events by the sponsor medical monitor. The reviewer believes the latter possibility is slightly more likely. However, the former possibility cannot be definitely excluded absent a larger dataset with more events.

Dose/Dose Response

Not applicable

Durability of Response

Not evaluated.

Persistence of Effect

Not evaluated.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not reviewed.

Additional Analyses Conducted on the Individual Trial

Not conducted except as noted throughout this review.

Integrated Review of Effectiveness

8.1.4. Assessment of Efficacy Across Trials

Not applicable

8.1.5. Integrated Assessment of Effectiveness

Not applicable

8.2. Review of Safety

8.2.1. Safety Review Approach

The focus of the safety review will primarily be on PB-102-F20 since it is the largest and longest duration randomized, double-blind dataset within BLA761161. The other studies submitted within this BLA do not have a comparator arm. An integrated safety analysis that pools data from the PRX-102 arm from the uncontrolled studies as well as the PRX-102 arm from F20 is described in Section 8.2.1.1. A focused review of the safety results from the F50 study are also included in this review. Safety results from the F01/02 were reviewed in detail in the original April 2021 BLA review. Those results are not repeated in this review but are briefly summarized towards the end of this section.

The safety review, based on PB-102-F20, focused on:

- TEAE's, common AE's
- Review of narratives for deaths, SAE's and AE's leading to drug discontinuation
- Review of safety as a function of baseline ADA status
- Immunogenicity (e.g., development of ADA, Neutralizing Ab). For a more detailed discussion on immunogenicity, please refer to Dr. Xiaohui Li's (Clinical Pharmacology) review,
- Infusion reactions, Hypersensitivity reactions, Pre-medication Usage, and Infusion Durations

The safety review, based on PB-102-F50, focused on:

- TEAE's, common AE's (including hypersensitivity and infusion reactions)

- Review of narratives for deaths, SAE's and AE's leading to drug discontinuation

In the F01/02 study, a treatment-naïve or pseudo-naïve population was enrolled. A total of 3 doses were evaluated (0.2 mg/kg IV q2 weeks, 1.0 mg/kg IV q2 weeks, and 2.0 mg/kg IV q2 weeks). The scheduled treatment duration was 12 months. A total of 6, 8 and 4 subjects were enrolled into the 3 dose groups respectively.

- Although the size of the F01/02 study is quite limited, there was not a suggestion of any dose-related adverse events
- The more frequently reported adverse events were similar between the F01/02 study and the F20 study. This included adverse event terms of nasopharyngitis, nausea, vomiting, fatigue, respiratory tract infection and rash.
- Two subjects in the 1.0 mg/kg group discontinued from treatment. One subject (b) (6) discontinued due to an anaphylaxis event following exposure to the first dose (see Section 8.2.11 for a narrative description). A second subject was discontinued by the investigator due to non-compliance and also withdrew consent.
- Two serious adverse events were reported (both in the 1 mg/kg dose group). Subject (b) (6) with anaphylaxis and subject (b) (6) who experienced a renal hematoma event secondary to the renal biopsy.

8.2.2. Review of the Safety Database

Overall Exposure (F20)

A total of 78 subjects were randomized into the PB-102-F20 study of which 77 subjects received at least 1 dose of study drug. A summary of cumulative (patient*months) exposure by randomized treatment arm is shown in table below. Exposures were generally comparable on PRX-102 and agalsidase beta. Please see Section 8.1.2 for a tabular summary of baseline demographic and disease characteristics in the F20 study.

Table 8: Study drug Exposure PB-102-F20

	PRX-102 N=52	**Agalsidase Beta N=25**
Cumulative Exposure (Months)	1176.2	596.4
Exposure (Months):		
Mean (SE)	22.62 (0.72)	23.86 (0.27)
Median (Min; Max)	23.95 (0.9 ; 27.4)	23.95 (17.7 ; 26.0)

Source: Sponsor's Analysis F20 CSR, Table 12.1

Overall Exposure (F50)

A total of 30 subjects were enrolled and treated in the F50 study. The median (range) exposure was 12 (0.03 to 13.8) months, and the mean exposure was 11.7 months.

In terms of the baseline demographic and disease characteristics, the mean age of subjects enrolled was 40.5 years. Twenty percent were female. Seventy-seven percent had received prior agalsidase beta treatment prior to study entry while twenty-three percent received agalsidase alfa prior to study entry. The mean/median eGFR was 99.89 and 102.25 mL/min/1.73m^2 respectively. Fifty three percent were Classic phenotype while forty-seven percent were of the non-classic phenotype.

Adequacy of the safety database:

The submitted safety database appears reasonable in terms of exposure and number of subjects particularly given the rarity of the condition being evaluated. Amongst the studies included in BLA761161, the PB-102-F20 study is most informative from a safety perspective, given its randomized, double-blind design. Other studies included in the BLA (including the F50 study) are relatively less interpretable given their single-arm, uncontrolled design. The bulk of the safety data come from studies which enrolled treatment-experienced (i.e., agalsidase beta or agalsidase alpha) subjects. The studies included both male and female subjects.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Safety assessments in the PB-102-F20 study included collection of adverse events, clinical laboratory measurements, physical exam, electrocardiography, vital signs, anti-drug antibodies, brain magnetic resonance imaging, and chest X-ray. A comparable set of assessments were done in the F50 study.

In the F20 study, events of hypersensitivity were considered events of "particular interest". In addition, events of acute kidney injury (AKI), defined as a >= 1.5-fold increase in serum creatinine from the immediately previous laboratory value, were considered to be an "important event" to be reported as an adverse event.

Regarding safety data collection, there do not appear to be issues with data integrity or quality.

Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) versions 19.0 was used to code adverse events in PB-102-F20 and F50. Coding quality appeared acceptable.

Routine Clinical Tests

Biochemistry assessments and hematology assessments were performed at baseline and approximately every 3 months during the study in F20 and F50.

8.2.4. Safety Results

Deaths

There were no deaths reported in either treatment arm during the 104-week duration of the PB-102-F20 study.

There were no deaths reported during the 1-year duration of the F50 study.

Serious Adverse Events

PB-102-F20
A total of 8 (15.4%) subjects in the PRX-102 arm experienced a serious adverse event during PB-102-F20. A total of 6 (24%) subjects in the agalsidase beta arm experienced a serious adverse event. A brief description of the SAEs in the PRX-102 arm are detailed below. The sources for the data below are 1) Sponsor's narrative and 2) Additional text details provided in JMP ADAE ADAM dataset.

USUBJID	SEX	RACE	COUN	TRTSDT	TRTA	AEDECOD	AREL	AESTD	AEOUT	AEACN
(b) (6)	F	WHITE	USA	(b) (6)	PRX-102	Aortic stenosis	N	365	RECOVERE	DOSE NOT CHANGED
	M	WHITE	USA		PRX-102	Bronchitis	N	516	RECOVERE	DOSE NOT CHANGED
	M	WHITE	USA		PRX-102	Acute kidney injury	N	113	RECOVERE	DOSE NOT CHANGED
	M	WHITE	USA		PRX-102	Dehydration	N	129	RECOVERE	DOSE NOT CHANGED
	M	WHITE	NLD		PRX-102	Nephrectomy	N	507	RECOVERE	DOSE NOT CHANGED
	M	WHITE	NLD		PRX-102	Atrioventricular block second degree	N	260	RECOVERE	DOSE NOT CHANGED
	M	WHITE	NLD		PRX-102	Venous thrombosis limb	N	301	RECOVERE	DOSE NOT CHANGED
	M	WHITE	NLD		PRX-102	Hepatic enzyme increased	N	309	RECOVERE	DOSE NOT CHANGED
	M	WHITE	NLD		PRX-102	Hypothermia	N	367	RECOVERE	DOSE NOT CHANGED
	M	WHITE	NLD		PRX-102	Protein-losing gastroenteropathy	N	397	NOT RECC	DOSE NOT CHANGED
	M	WHITE	SVN		PRX-102	Medical device battery replacement	N	137	RECOVERE	DOSE NOT CHANGED
	M	WHITE	SVN		PRX-102	Contusion	N	390	RECOVERE	DOSE NOT CHANGED
	M	WHITE	FRA		PRX-102	Hypersensitivity	Y	1	RECOVERE	DRUG INTERRUPTED
	M	WHITE	FRA		PRX-102	Femur fracture	N	434	RECOVERE	DOSE NOT CHANGED
	M	WHITE	USA		AGALSIDA	Tachycardia	N	413	RECOVERE	DOSE NOT CHANGED
	M	WHITE	USA		AGALSIDA	Acute respiratory failure	N	354	RECOVERE	DOSE NOT CHANGED
	M	WHITE	USA		AGALSIDA	Altered state of consciousness	N	354	RECOVERE	DOSE NOT CHANGED
	M	WHITE	USA		AGALSIDA	Chest pain	N	9	RECOVERE	DOSE NOT CHANGED
	M	WHITE	USA		AGALSIDA	Pneumonia	N	726	RECOVERE	DOSE NOT CHANGED
	M	WHITE	USA		AGALSIDA	Sepsis	N	729	NOT RECC	DOSE NOT CHANGED
	M	WHITE	HUN		AGALSIDA	Ventricular tachycardia	N	496	RECOVERE	DOSE NOT CHANGED
	M	WHITE	HUN		AGALSIDA	Suicidal ideation	N	674	RECOVERE	DOSE NOT CHANGED
	M	WHITE	USA		AGALSIDA	Atrial fibrillation	N	71	RECOVERE	DOSE NOT CHANGED
	M	BLACK (	USA		AGALSIDA	Chronic obstructive pulmonary disease	N	693	RECOVERE	DOSE NOT CHANGED
	M	BLACK (	USA		AGALSIDA	Chest pain	N	707	RECOVERE	DOSE NOT CHANGED

PB-102-F50

There were 2 SAEs reported in 2 subjects in the F50 study. One was a subject that experienced

a motor vehicle accident 8 days following the first infusion and was considered unrelated to the infusion. The subject withdrew from the study. The second SAE was a case of carbamazepine overdose approximately 8.5 months after study drug initiation.

Dropouts and/or Discontinuations Due to Adverse Effects

PB-102-F20
Three subjects, both in the PRX-102 arm, experienced TEAEs that led to withdrawal from treatment and the study (see the bullets that immediately follow for a listing of these subjects). No subjects in the agalsidase beta arm experienced a TEAE that led to withdrawal from treatment.

- Subject (b) (6) See section 8.2.11 for a detailed anaphylaxis narrative
- Subject A 27 y/o male from US completed 28 weeks of treatment with PRX-102 before withdrawing from the study due to end stage renal disease which was classified as a Fabry's clinical event (FCE). The subject was known to have severely deteriorated kidney function prior to enrollment in the F20 study. The subject ultimately required a kidney transplant.
- Subject (b) (6): See below "Significant Adverse Events" (note: the sponsor's study report identifies 2 subjects that discontinued due to an adverse event which excluded this subject. This subject was noted as having "interrupted" study drug approximately 2.5 months prior to the scheduled end of the study and never appeared to have resumed treatment.

PB-102-F50

There were no subjects that experienced a TEAE that led to withdrawal from treatment and/or the study.

Significant Adverse Events

Please see above sections describing serious adverse events and discontinuations due to adverse events.

Subject (b) (6) was a 41 y/o White male from the US who experienced an event of membranoproliferative glomerulonephritis that was considered severe and related to study drug. The event was initially suspected due to an increase in urinary protein to creatinine ratio (1.8 g/g (b) (6), 4.1 g/g (b) (6), 3.0 g/g (b) (6), 2.4 g/g (b) (6) The diagnosis was made by performing a kidney biopsy on (b) (6) which confirmed the suspected diagnosis of MPGN. The event was not considered serious because it did not result in hospitalization. The event led to interruption of treatment. Although the onset day was reported as Day 647 (b) (6) per the table below, there was an increase in serum creatinine and proteinuria observed starting in (b) (6). The last dose date of study drug, per the ADAE dataset, is (b) (6). The outcome is reported as recovering/resolving.

Table 9: Selected renal laboratory values over time for subject (b) (6)

Visit	Date	Serum Creatinine (mg/dL)	$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	UPCR (mg/mg)	Plasma Gb3 (nM)	Plasma Lyso-Gb3 (nM)
SCREENING	(b) (6)	1.11	82.04	1.095		
VISIT 1 / BASELINE (WEEK 0)		1.15	78.60	0.874	7240	65.20
VISIT 14 (WEEK 26)		1.21	73.91	0.831	8299	80.30
VISIT 27 (WEEK 52)		1.21	73.40	0.739		64.20
VISIT 40 (WEEK 78)		1.66	50.08	1.824	7698	73.50
VISIT 47 (WEEK 92)		1.79	45.40	2.477		
VISIT 49 (WEEK 96)		1.74	46.98			
UNSCHEDULED VISIT 7		1.69	48.66	2.196		
VISIT 51 (WEEK 100)		1.66	49.73			
UNSCHEDULED VISIT 9		1.98	40.18	3.163		
VISIT 53 (WEEK 104)		1.55	54.03	1.554	9067	97.90

Source: Table from F20 CSR containing this subject's narrative description

Please refer to Section 8.2.11 (Integrated Assessment of Safety) for a detailed review of Anaphylaxis events across the PRX-102 program.

Treatment Emergent Adverse Events and Adverse Reactions

A total of 47 (90%) and 24 (96%) of subjects in the PRX-102 and agalsidase beta arms respectively experienced at least 1 treatment emergent adverse event.

The following table lists treatment emergent adverse events with an incidence of at least 5% in the PRX-102 arm of the PB-102-F20 study. The terms that occurred with an incidence of greater than 5% on PRX-102 and occurred more frequently on PRX-102 (PRX-102 - Agalsidase Beta Incidence Difference >=5%) included nasopharyngitis, nausea, abdominal pain, proteinuria, neuralgia, upper respiratory tract infection, peripheral neuropathy, sciatica, infusion site extravasation, urine protein:creatinine ratio increase, and hematuria. These may potentially be adverse reactions of PRX-102.

Table 10: Summary of the most commonly reported adverse events >=5% in PRX-102 arm (PB-102-F20)

Dictionary-Derived Term	PRX-102 (N = 52)	(%)	AGALSIDASE BETA (N = 25)	(%)
Nasopharyngitis	11	21%	4	16%
Headache	11	21%	5	20%
Diarrhea	10	19%	6	24%
Nausea	9	17%	3	12%
Fatigue	9	17%	4	16%
Sinusitis	8	15%	3	12%
Back pain	8	15%	5	20%
Pain in extremity	8	15%	4	16%
Upper respiratory tract infection	6	12%	4	16%
Urinary tract infection	6	12%	3	12%
Vomiting	6	12%	3	12%
Abdominal pain	6	12%		
Dizziness	6	12%	2	8%
Cough	6	12%	5	20%
Proteinuria	6	12%		
Bronchitis	5	10%	5	20%
Pyrexia	5	10%	3	12%
Muscle spasms	5	10%	3	12%
Rash	5	10%	2	8%
Neuralgia	4	8%		
Oedema peripheral	4	8%	3	12%
Arthralgia	4	8%	2	8%
Upper respiratory tract congestion	4	8%		
Atrial fibrillation	4	8%	1	4%
Seasonal allergy	4	8%	1	4%

Anemia	4	8%	2	8%
Viral infection	3	6%	3	12%
Respiratory tract infection	3	6%	1	4%
Gastroesophageal reflux disease	3	6%	1	4%
Neuropathy peripheral	3	6%		
Sciatica	3	6%		
Infusion site extravasation	3	6%		
Musculoskeletal pain	3	6%	2	8%
Oropharyngeal pain	3	6%	3	12%
Nasal congestion	3	6%	1	4%
Urine protein/creatinine ratio increased	3	6%		
Palpitations	3	6%	2	8%
Hematuria	3	6%		
Vertigo	3	6%	1	4%
Hypertension	3	6%	1	4%

In the F50 study, the most commonly reported TEAE's were:

- Nasopharyngitis: 6 (20%) subjects
- Fatigue: 5 (17%) subjects
- Infusion related reaction: 5 (17%) subjects
- Cough: 4 (13%) subjects
- Nausea: 4 (13%) subjects
- Diarrhea: 3 (10%) subjects
- Headache: 3 (10%) subjects
- Oropharyngeal pain: 3 (10%) subjects
- Pain: 3 (10%) subjects
- Pain in Extremity: 3 (10%) subjects
- Paresthesias: 3 (10%) subjects
- Sinusitis: 3 (10%) subjects
- Viral Infection: 3 (10%) subjects

With respect to the infusion related reactions, none were SAEs. The majority were mild or moderate in severity.

Laboratory Findings

Biochemistry assessments and Hematology assessments were performed at baseline and every 3 months during the study. There is no clear difference in the 2 treatment arms with respect to changes in biochemistry assessments (including liver enzymes) and hematology assessments during the study.

Vital Signs

Vital sign assessments were performed pre-dose, 30, 60, 120, 180, 240, 300, and 360 minutes after the start of infusion, and at the end of the observation period. Changes in Systolic blood pressure, diastolic blood pressure and pulse appear comparable between PRX-102 and agalsidase beta. A summary of subjects in the PB-102-F20 study experiencing at least 1 occurrence of SBP, DBP or Pulse measurement above or below the listed threshold, at any time during the study, is presented in the table below.

Table 11: Vital sign outliers PB-102-F20

		PRX-102 (N= 52)	AGALSIDASE BETA (N = 25)
Sys BP (mm Hg)	>160	11 (21%)	5 (20%)
	<100	42 (81%)	21 (84%)
Dias BP (mm Hg)	>100	10 (19%)	3 (12%)
	<60	49 (94%)	23 (92%)
Pulse	>100	12 (23%)	5 (20%)
	<50	27 (52%)	11 (44%)

Electrocardiograms (ECGs)

Electrocardiographic assessments were done approximately every 3 months during the study. The table below summarizes the incidence of Atrial fibrillation and atrial flutter prior to treatment initiation (i.e., screening/baseline) and anytime post randomization. The incidence of atrial fibrillation and atrial flutter detected by electrocardiography during scheduled or unscheduled visits was small. In general, the pattern of abnormalities was similar in the two treatment groups. Although there were numerically more post-randomization atrial fibrillation and atrial flutter events in the PRX-102 arm, the numbers are quite small to draw any definitive conclusions.

Table 12: Incidence of Atrial fibrillation and Atrial flutter as assessed by ECGs at baseline and post-randomization (PB-102-F20)

		PRX-102 (N= 52)	AGALSIDASE BETA (N = 25)
Atrial Fibrillation	Screening/Baseline	1 (2%)	1 (4%)
	Post-Randomization	4 (7.7%)	1 (4%)
Atrial Flutter	Screening/Baseline	0	0
	Post Randomization	3 (5.8%)	0

Immunogenicity

In PB-102-F20, at baseline, 34.6% and 32% of subjects in the PRX-102 arm and agalsidase beta arms respectively tested positive for IgG anti-drug antibodies. The presence of anti-drug antibodies at baseline in the agalsidase beta arm is expected given the population enrolled (i.e., subjects that had been on agalsidase beta for at least a year or more prior to study entry). The presence of anti-drug antibodies prior to PRX-102 exposure is explained by cross-reactivity to components of PRX-102 that are shared with agalsidase beta. Amongst the subjects that tested positive for IgG anti-drug antibodies at baseline, all but one subject in each treatment group also tested positive for neutralizing antibodies.

The occurrence of treatment-emergent anti-drug antibodies post-baseline was also evaluated. This analysis evaluated the occurrence of subjects that tested anti-drug antibody positive at baseline AND subsequently had a titer increase of at least 4-fold at a subsequent timepoint OR those who were anti-drug antibody negative at baseline AND subsequently tested positive at a later timepoint. A total of 6 (11.5%) and 5 (20%) met this treatment-emergent ADA positivity criteria in the PRX-102 and agalsidase beta arms respectively.

8.2.5. Analysis of Submission-Specific Safety Issues

Hypersensitivity, Infusion Reactions and Related events

Treatment-emergent Hypersensitivity and Infusion related reactions (both serious and non-serious) were analyzed using FDA Medical Queries (FMQ) narrow and broad. No meaningful difference (albeit slightly numerically higher on PRX-102 vs. agalsidase beta) exists in the incidence rate on PRX-102 versus Agalsidase beta as shown in the summary table below.

Table 13: Summary of Hypersensitivity FMQ, Infusion Reactions and other related FMQ's (PB-102-F20)

FDA Medical Query	Scope	PRX-102 (N = 52)	AGALSIDASE BETA (N = 25)
Any of the Broad FMQ Terms from list below		21 (40%)	8 (32%)
Hypersensitivity	Broad	16 (30.8%)	8 (32%)
Local Administration Reaction	Broad	7 (13.5%)	2 (8%)
Anaphylactic Reaction	Broad	2 (3.8%)	2 (8%)
Bronchospasm	Broad	2 (3.8%)	1 (4%)
Angioedema	Broad	2 (3.8%)	0 (0%)
Dyspnea	Broad	2 (3.8%)	0 (0%)
Erythema	Broad	2 (3.8%)	2 (8%)
Any Broad FMQ Terms from the list below (within 2 hours of infusion onset)		8 (15%)	3 (12%)
Any Broad FMQ Terms from the list below (within 24 hours of infusion onset)		9 (17%)	4 (16%)
Any Narrow FMQ Terms from list below		12 (23%)	4 (16%)
Hypersensitivity	Narrow	2 (3.8%)	2 (8%)
Local Administration Reaction	Narrow	7 (13.5%)	2 (8%)
Bronchospasm	Narrow	0 (0%)	1 (4%)
Dyspnea	Narrow	2 (3.8%)	0 (0%)
Erythema	Narrow	2 (3.8%)	2 (8%)
Any Narrow FMQ Terms from the list below (within 2 hours of infusion onset)		7 (14%)	2 (8%)
Any Narrow FMQ Terms from the list below (within 24 hours of infusion onset		8 (15%)	3 (12%)

Hypersensitivity:

- Narrow PT's: Hypersensitivity, Drug hypersensitivity, Epidermolysis
- Broad PT's: Above narrow PTs plus Rash, Erythema, Infusion related reactions, Pruritus, Rash pruritic, Urticaria, Asthma, Dermatitis allergic, Flushing, Gingival swelling, Oedema, Rash macular, Rash maculo-papular, Swelling face, Toxic skin eruption

Local administration reaction:

- Narrow PT's: Infusion related reaction, Infusion site extravasation, Catheter site pain, Infusion site pain, Vaccination site pain
- Broad PT's: Above narrow terms only (nothing additional)

Bronchospasm:

- Narrow PT's: Asthma
- Broad PT's: Above narrow term plus Dyspnea

Anaphylactic Reaction:

- Narrow PT's: None that hit
- Broad PT's: Hypersensitivity and Drug Hypersensitivity

Angioedema:

- Narrow PT's: None that hit

- Broad PT's: Drug hypersensitivity, Swelling face

Dyspnea:

- Narrow PT's: Dyspnea
- Broad PT's: Above narrow term only (nothing additional)

Erythema:

- Narrow PT's: Erythema, Flushing
- Broad PT's: No additional terms that hit from Broad PT list

The following two tables are an analysis of select FDA medical queries (FMQ's) as a function of ADA status at baseline (ADA positivity: first of 2 tables below and ADA negativity: 2nd of 2 tables below). A total of 26 subjects in the two treatment groups combined were positive for ADA at baseline and 51 subjects were negative for ADA.

The overall number of subjects with an event is small but it doesn't appear that the incidence of various event categories listed in the table below are meaningfully different between the subset of subjects that are ADA positive or ADA negative at baseline in the PRX-102 treatment arm. In the agalsidase beta arm, there appears to be a higher incidence of events in ADA positive (versus negative) subjects.

Table 14: FMQ's in ADA positive subjects

FDA Medical Query	Scope	PRX-102 (N = 18)	AGALSIDASE BETA (N = 8)
Hypersensitivity	Broad	5 (27.8%)	4 (50%)
Anaphylactic Reaction	Broad	1 (5.6%)	2 (25%)
Erythema	Broad	1 (5.6%)	1 (12.5%)
Local Administration Reaction	Broad	0 (0%)	2 (25%)
Angioedema	Broad	1 (5.6%)	0 (0%)
Bronchospasm	Broad	0 (0%)	1 (12.5%)
Hypersensitivity	Narrow	1 (5.6%)	2 (25%)
Pruritus	Narrow	1 (5.6%)	2 (25%)
Erythema	Narrow	1 (5.6%)	1 (12.5%)
Local Administration Reaction	Narrow	0 (0%)	2 (25%)
Bronchospasm	Narrow	0 (0%)	1 (12.5%)

Table 15: FMQ's in ADA negative subjects

FDA Medical Query	Scope	PRX-102 (N = 34)	AGALSIDASE BETA (N = 17)
Hypersensitivity	Broad	11 (32.4%)	4 (23.5%)
Local Administration Reaction	Broad	7 (20.6%)	0 (0%)
Bronchospasm	Broad	2 (5.9%)	0 (0%)
Erythema	Broad	1 (2.9%)	1 (5.9%)
Anaphylactic Reaction	Broad	1 (2.9%)	0 (0%)
Angioedema	Broad	1 (2.9%)	0 (0%)
Local Administration Reaction	Narrow	7 (20.6%)	0 (0%)
Erythema	Narrow	1 (2.9%)	1 (5.9%)

FDA Medical Query	Scope	PRX-102 (N = 34)	AGALSIDASE BETA (N = 17)
Hypersensitivity	Narrow	1 (2.9%)	0 (0%)

There was only 1 subject that experienced a treatment-emergent serious adverse event of hypersensitivity (Subject (b) (6) A detailed narrative of the hypersensitivity adverse event is described in Section 8.2.4. There were no subjects in the Agalsidase beta arm that experienced a treatment emergent serious adverse event of hypersensitivity or infusion related reaction.

The sponsor defined infusion-related reactions (IRR) as treatment-emergent adverse events that occurred during an infusion or within 2 hours after its completion and whose causality was assessed as definitely, probably, or possibly related to study treatment. IRR's excluded injection site reactions (ISR's). Some of the more common MedDRA preferred terms included in the analysis below were Chills, Hypersensitivity, Infusion related reactions, Fatigue, Nausea and Vomiting. Nearly all the IRR's included in the table below were mild or moderate in severity. The only serious one was subject (b) (6) discussed above.

Table 16: Infusion Related Reaction (sponsor's analysis) PB-102-F20

	PRX-102 (N= 52)	Agalsidase beta (N = 25)
Infusion-related reaction (up to 2 hours post infusion)	11 (21%)	6 (24%)
Infusion-related reaction (up to 24 hours post infusion)	17 (33%)	8 (32%)

Source: Sponsor's analysis Table 12.14 and 12.18

Per the protocol, pre-medication to prevent infusion related adverse reactions was not required in all subjects. At the time of randomization, if pre-medication was used for the agalsidase beta infusions prior to study entry, it was to be continued in the PB-102-F20 study and gradually tapered, if tolerated, at the investigator's discretion during the first 3 months of the study. For subjects not initially receiving premedication, it could be considered during subsequent infusions, at the discretion of the investigator, for subjects experiencing early clinical signs of hypersensitivity or rash/urticaria that responds promptly to oral antihistamine administration. As an alternative to pre-medication (or in addition), the infusion rate (IR) could also be adjusted according to individual subject symptoms and signs.

Table 17: Use of Infusion Pre-medication

			PRX-102	AGALSIDASE BETA
Baseline	No		31/52 (59.6%)	9/25 (36.0%)
	Yes		21/52 (40.4%)	16/25 (64.0%)
		Before infusion	20/52 (38.5%)	15/25 (60%)
		During Infusion	0	0
		Before and During Infusion	1/52 (1.9%)	1/25 (4.0%)
Week 104	No		44/47 (93.6%)	21/24 (87.5%)

	PRX-102	AGALSIDASE BETA
Yes	3/47 (6.4%)	3/24 (12.5%)
Before infusion	3/47 (6.4%)	3/24 (12.5%)
During infusion	0	0
Before and During Infusion	0	0

Sponsor analysis: Table 14.3.9.3

Infusion Duration

At baseline, the duration of infusion was 3.08 and 2.96 hours on PRX-102 and Agalsidase beta respectively. At week 104, the duration of infusions was reduced in both treatment arms to a duration of 1.56 and 1.71 hours respectively.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable

8.2.7. Safety Analyses by Demographic Subgroups

The size of the PB-102-F20 study is too small to perform any meaningful subgroup analyses for safety. There were no subjects aged 65 years or older enrolled in F20 to evaluate whether the safety and tolerability of PRX-102 is different in older vs. younger.

In the PRX-102 arm, 33 (100%) and 14 (74%) subjects from the US and ex-US sites respectively experienced at least 1 TEAE. In the agalsidase beta arm, 17 (94%) and 7 (100%) from the US and ex-US sites respectively experienced at least 1 TEAE. The numbers are too limited to draw conclusions on differences in the incidence of TEAE by region.

8.2.8. Specific Safety Studies/Clinical Trials

The PB-102-F20 study is the only randomized, controlled trial allowing for a safety assessment.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

There were no reported serious adverse events of malignancy in the PB-102-F20 study. One subject (b) (6) randomized to PRX-102 experienced a non-serious event of Clear cell renal cell carcinoma on Day 449. This was an incidental finding discovered during follow-up evaluation of renal cysts. The diameter of the carcinoma was approximately 3cm. The subject was treated via a partial nephrectomy.

Human Reproduction and Pregnancy

In the PB-102-F20 study, there were no treatment-emergent pregnancies reported. One pregnancy was reported in study PB-102-F03. The patient had normal ultrasound findings at week 13 of gestation but decided to terminate the pregnancy at week 14 for personal reasons.

Data are limited to make a conclusion regarding the effects of pegunigalsidase alfa usage on pregnancy outcomes, potential effects on a developing fetus and/or growth and development of a newborn exposed to pegunigalsidase alfa during pregnancy.

Pediatrics and Assessment of Effects on Growth

The youngest subject enrolled into the PRX-102 arm of the PB-102-F20 study was 20 years. Thus, no conclusion can be made regarding the safe and effective use of PRX-102 in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There have been no reports of overdose with pegunigalsidase alfa. The sponsor has not observed any evidence of withdrawal or rebound with PRX-102.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

Not applicable.

8.2.11. Integrated Assessment of Safety

An integrated assessment of safety (i.e., Cohort 3) pooled data across multiple studies and included a total of 142 subjects. The studies that contributed to this integrated safety dataset were: PB-102-F01/02/03, PB-102-F20, PB-102-F30, PB-102-F50/51, PB-102-F60.

The mean age of this integrated safety dataset was 42.5 years (range 17 to 60 years). Two-thirds of the integrated safety dataset were male. 133 (94%) of this integrated safety dataset were white. This integrated safety dataset contains 4875 subject-months of exposure. The mean exposure time was 34.3 months with a maximum exposure duration of 91 months (approximately 7.5 years).

Amongst the 142 PRX-102 subjects:

- 11 (7.7%) were exposed for less than 6 months
- 7 (4.9%) were exposed for at least 6 months but less than 12 months
- 25 (17.6%) were exposed for at least 12 months but less than 24 months
- 99 (69.7%) were exposed for at least 24 months

This section describes (based on the Integrated dataset Cohort 3):

- Most frequently reported adverse events
- Hypersensitivity events (Including Anaphylaxis narratives) and Infusion related reactions
- Death event narratives
- Cardio and Cerebrovascular events

The most frequently reported (incidence >=10%) adverse events in the ISS dataset are summarized in the table below. Given the absence of a comparator arm, it is difficult to assign causality to the events.

Table 18: Most frequently reported adverse events (ISS dataset)

	PRX-102 (N = 142)	
AEDECOD	# of subjects with event	%
Nasopharyngitis	35	24.6
Fatigue	30	21.1
Headache	28	19.7
Back pain	27	19.0
Cough	25	17.6
Diarrhea	25	17.6
Pain in extremity	23	16.2
Nausea	22	15.5
Upper respiratory tract infection	21	14.8
Vomiting	21	14.8
Arthralgia	19	13.4
Pyrexia	18	12.7
Abdominal pain	17	12.0
Sinusitis	16	11.3
Dizziness	15	10.6
Oropharyngeal pain	15	10.6
Rash	15	10.6

Hypersensitivity (Including Anaphylaxis Narratives) and Infusion related reactions

The reviewer conducted an independent review and analysis of the Integrated dataset (Cohort 3) using both broad and narrow FMQ terms. The reviewer conducted a review of line listings of events captured by these FMQ's evaluating the investigator's verbatim reported term,

additional case report form comments entered by the investigator, whether the event was deemed serious/non-serious, event severity, and action taken with study medication (e.g., treatment interruption, treatment discontinuation, slowing rate of infusion)

The following table in a summary of the incidence of hypersensitivity and infusion related reaction terms based on broad and narrow FMQ's based on the Integrated dataset. The vast majority of subjects that experienced an event that fell into one of the FMQ's in the table below experienced events that were not serious, events that were primarily mild to moderate in severity and that recovered/resolved with treatment continued

Table 19: Summary of Hypersensitivity FMQ, Infusion Reactions and other related FMQ's (Integrated dataset)

FDA Medical Query	Scope	PRX-102 (N = 142)
Hypersensitivity	Broad	54 (38%)
Local Administration Reaction	Broad	23 (16.2%)
Bronchospasm	Broad	17 (12%)
Dyspnea	Broad	11 (7.7%)
Anaphylactic Reaction	Broad	9 (6.3%)
Pruritus	Broad	8 (5.6%)
Erythema	Broad	7 (4 9%)
Angioedema	Broad	6 (4 2%)
Local Administration Reaction	Narrow	23 (16.2%)
Dyspnea	Narrow	11 (7.7%)
Hypersensitivity	Narrow	10 (7%)
Pruritus	Narrow	8 (5.6%)
Erythema	Narrow	7 (4 9%)
Bronchospasm	Narrow	5 (3.5%)

A total of 5 subjects experienced a serious infusion related reaction on pegunigalsidase alfa detailed below; 4 of these 5 were considered anaphylaxis.

The first of the 5 events was not deemed to be a case of anaphylaxis.

- Subject (b) (6) (SAE of chills): 52 y/o Black male enrolled into the F20 study in (b) (6) during which he was randomized to the agalsidase beta arm. He completed the F20 study. He consented to the F60, long-term extension study and was enrolled in (b) (6). On Day 186 of the F60 study, the subject experienced SAEs of chills that started approximately 10 minutes after the completion of a 1-hour infusion of PRX-102. The subject did not have a fever. The patient received treatment with methylprednisolone, diphenhydramine, meperidine, and oxygen. The subject's chills improved, however, he was admitted for observation and placed on antibiotics for suspicion of infection. The infectious work-up was negative, the antibiotics were stopped after 2 days, and the subject recovered completely. The subject had not received any pre-medication prior to this infusion as the subject never previously

needed pre-medication with prior infusions. Subsequently, the subject received pre-medication with future PRX-102 infusions without further occurrences of chills.

Anaphylaxis Narratives

Four of these serious infusion related reactions occurred during the very first infusion of PRX-102 and met Sampson's criteria[5] for anaphylaxis. Anaphylaxis is a known risk with enzyme replacement therapies. The labeling will include a Boxed warning for the risk of hypersensitivity including anaphylaxis providing guidance for health care providers on risk mitigation and patient management.

- Subject (b) (6) 1 mg/kg (SAE of bronchospasm): 52 y/o White male with a history of Fabry disease, treatment-naive, and was assigned to receive PRX-102 1 mg/kg. The subject experienced Grade 3 bronchospasm approximately 40 minutes post infusion initiation. This was the subject's very first infusion and no pre-medication was administered. The infusion was interrupted, the subject was hospitalized and recovered the following day. Treatment with PRX-102 was permanently discontinued. The subject was noted to be positive for anti-pegunigalsidase IgE and IgG.
- Subject (b) (6) (SAE coded term of Hypersensitivity, verbatim term: "allergic reaction"). A 39 y/o male from (b) (6) ADA positive at baseline, experienced a SAE of severe allergic reaction. Prior the initiating the first infusion of PRX-102, the subject was premedicated with paracetamol and desloratadine. The infusion was initiated at a rate of 85 mL/hour. After approximately 30 minutes, an allergic reaction occurred, and the infusion was stopped. The subject experience symptoms and signs of urticaria, upper airway obstruction, macroglossia, lip edema and low blood pressure. The patient required treatment with oral cetirizine, albuterol inhalation, methylprednisolone IV 20 mg, Oxygen, and terbutaline inhalation. The study drug was re-challenged approximately 1 month later at a slower infusion rate (30 mL/hour). However, the subject again experienced an allergic reaction, and the study medication was stopped, and the subject was withdrawn from the study.
- Subject (b) (6), 1 mg/kg (SAE coded term Type 1 Hypersensitivity; Verbatim Immediate hypersensitivity reaction). This is a 29 y/o White male with Fabry disease who had been treated with Replagal for more than 8 years prior to study entry. The subject experienced a Type 1 hypersensitivity reaction after the very first infusion. Symptoms and signs included nausea, itchy eyes, vomiting, shortness of breath, throat tightness, facial edema, hives, blanching rash over trunk and tachycardia. No infusion pre-medication was administered. The infusion was interrupted after approximately 18 minutes. The subject was treated with epinephrine, cetirizine, hydrocortisone,

[5] Sampson et. al. J Allergy Clin Immunol 2006

prednisolone and was admitted to a short stay unit for overnight observation. The subject was noted to have anti-drug IgE antibodies but was negative for anti-drug IgG antibodies. Study drug was permanently discontinued. ADA status at baseline was negative.

- Subject (b) (6) 1 mg/kg (SAE coded term Type 1 Hypersensitivity; Verbatim Immediate hypersensitivity reaction). This is a 24 y/o White male with Fabry disease who had been treated with Replagal for more than 12 years prior to study entry. The subject experienced a Type 1 hypersensitivity reaction after the very first infusion. Symptoms include nausea, headache, agitation, edema of hands, periorbital area and tongue, rigor, and chills. Blood pressure had decreased to 84/45 from 134/81. No infusion pre-medication was administered. The infusion was interrupted after approximately 5 minutes. The subject was treated with methylprednisolone, clemastine, and sodium chloride IV infusion. The subject recovered the same day without sequelae. Study drug was permanently discontinued. The subject was found to have anti-drug IgE antibodies but negative for anti-drug IgG antibodies. ADA status at baseline was negative.

Narratives of Death Events

A total of 4 subject that experienced treatment-emergent deaths on pegunigalsidase alfa based on ISS dataset (Cohort 3). There does not appear to be a causal association between PRX-102 treatment and the death events described below. The cases appear to be more likely secondary to progression of underlying disease. The size of the database makes it challenging to assign causality with certainty.

- PB-102- (b) (6): Death secondary to chronic obstructive pulmonary disease after an exposure of approximately 38 months.
- PB-102- (b) (6): The subject was a 60 y/o male enrolled into the F20 study in (b) (6) during which he was randomized to the agalsidase beta arm. He completed the F20 study. He consented to the F60, long-term extension study and was enrolled in (b) (6) and began receiving PRX-102. On day 391 of the F60 study, the subject had an SAE of obstructive airway disorder and was hospitalized. According to the subject, he vomited on Day 390 possibly from something he ate and woke up on Day 391 with a swollen throat and trouble breathing. Per the hospital record, the subject was noted to have a swollen uvula and narrowed glottic airway. The subject was treated with methylprednisolone 125 mg and diphenhydramine 25 mg. The event resolved and subject was discharged the next day. The subject received the next scheduled dose of PRX-102 approximately 8 days later and continued in the study. After approximately 20 months (Day 623) of treatment with PRX-102 in the F60 study, the subject experienced sudden death. The subject had some additional SAEs during participation during the F60 study but were thought to be unrelated to treatment.
- PB-102- (b) (6) The subject was a 60 y/o male enrolled into the F20 study in (b) (6) during which he was randomized to agalsidase beta arm. He completed

the F20 study. He consented to the F60, long-term extension study and was enrolled in [redacted] and began receiving PRX-102. The subject experienced an SAE of pneumonia on Day 24 following PRX-102 initiation which was thought to be unrelated to treatment. On Day 60, the subject experienced a non-serious adverse event of atrial fibrillation. On Day 527 (approximately 1.44 years after PRX-102 initiation), the subject experienced a stroke and died.

- PB-102-[redacted] The subject was a 61 y/o male enrolled into the F30 study in [redacted] during which he received PRX-102. The consented to the F60, long-term extension study and was enrolled in [redacted]. On Day 551 of the F60 study, the subject experienced an SAE of worsening heart failure. Despite treatment with diuretics and inotropes, the subject deteriorated and died on Day 560. The subject experienced an SAE loss of consciousness on Day 365 which was thought to be unrelated to study drug.

Listing of Cardiovascular Events

The following is a listing of subjects that experienced a cardiovascular serious adverse event. These events could have occurred during the original study at which the subject entered the PRX-102 development program or during the long-term extension (e.g., PB-102-F60).

As noted in the PB-102-F20, a randomized trial, there was a numerical imbalance in the incidence of Fabry clinical events that did not favor PRX-102. The following is a listing of cardiovascular events that were reported in the Integrated dataset. Given that there is no concurrent control group, it is not possible to determine whether the events below are treatment related or secondary to underlying disease.

Table 20: Cardiovascular and Cerebrovascular adverse events (Integrated dataset)

Subject ID #	Reported Serious AE	Relative Day
PB-102-[redacted]	CARDIAC EVENT	2150
PB-102-[redacted]	STROKE	872
PB-102-[redacted]	STROKE	1037
PB-102-[redacted]	STROKE	527
PB-102-[redacted]	NON-ST ELEVATED MYOCARDIAL INFARCTION	15
PB-102-[redacted]	STROKE-LEFT SIDED	1471
PB-102-[redacted]	NSTEMI (NON ST ELEVATED MYOCARDIAL INFARCTION	259
PB-102-[redacted]	ST ELEVATED MYOCARDIAL INFARCTION	489
PB-102-[redacted]	ATRIAL FIBRILLATION	817
PB-102-[redacted]	ATRIAL FLUTTER	481
PB-102-[redacted]	IMPLANTATION ICD/PACEMAKER. INDICATION: 2ND DEGREE AV BLOCK AND NON-SUSTAINED VTS ON HOLTER EVALUATION	260
PB-102-[redacted]	VENOUS THROMBOSIS L ARM	301

PB-102-	CONGESTIVE CARDIAC FAILURE	430
PB-102-	PLANNED HOSPITALISATION DUE TO IMPLANTED CARDIAC DEFIBRILATOR (ICD) BATTERY CHANGE	137
PB-102-	ICD (IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR) INSERTED	1102
PB-102-	ANGINA PECTORIS	568
PB-102-	ISCHEMIC HEART DISEASE	804
PB-102-	WORSENING HEART FAILURE	929

(b) (6)

8.3. Statistical Issues

Please refer to the Primary Statistical Review by Dr. Yared Gurmu

8.4. Conclusions and Recommendations

The determination for traditional approval of Elfabrio (pegunigalsidase-alfa) is based on the following:

- Single adequate and well-controlled study: Results from the F01/02 demonstrated statistically significant effects of PRX-102 in lowering Gb3 deposition in the peritubular cells of the kidney assessed via renal biopsy (BLISS methodology). A single arm study is considered appropriate to draw this conclusion given that Gb3 deposition in the PTC of the kidney do not spontaneously resolve (see discussion in Section 1.2). Published in-vivo and in-vitro studies demonstrating that the Gb3 substrate is toxic to tissue, causing damage to organ systems. The degree of accumulation of the substrate appears to correlate with the degree of damage in renal tissue, providing a strong biological rationale that a reduction in Gb3 accumulation would be expected to modify the pathophysiology of FD, which is further supported in this development program by the PB-102-F20 study.
- Confirmatory Evidence:
    - Results from the PB-102-F20 study, a randomized, double-blind, active comparator study versus Fabrazyme, an approved ERT for treatment of Fabry disease, suggesting a comparable eGFR slope over a 2-year treatment period.
    - Additional confirmatory evidence includes the effects of PRX-102 on reducing plasma lyso-Gb3 levels as observed in the F01/02 study in enzyme replacement therapy naïve subjects. The changes in plasma lyso-Gb3 showed statistical correlation with renal Gb3 inclusion changes in F01/02.
    - Confirmatory evidence also includes strong mechanistic support. The well-established etiology of the disease as a monogenic inborn error of glycosphingolipid metabolism from a single enzymatic deficiency. The targeted mechanism of action of PRX102 as an exogenous enzyme replacement for the deficient/absent endogenous enzyme.

Non-clinical efficacy data on Gb3 reductions following a single 0.1 or 1 mg/kg dose in αGAL KO mice are not considered adequate for use as confirmatory evidence. Although the data suggested the possibility of reductions in Gb3 in liver, spleen, kidney, and heart on Days 3 and 14 post-dose, a major limitation was that the assay method used in the study does not actually quantify Gb3 but instead stains for lipids.

Taken together, the review team concludes that substantial evidence of effectiveness of PRX-102 for the treatment of Fabry disease has been demonstrated.

The safety profile of PRX-102 is generally consistent with that of other enzyme replacement therapies. The main safety concern is the risks of severe hypersensitivity reactions, including anaphylaxis, and infusion-associated reactions. One subject receiving PRX-102 in the PRX-102 program experienced an adverse reaction of membranoproliferative glomerulonephritis due to immune-mediated complexes to PRX confirmed by biopsy. Although there were numerically a higher percentage of Fabry Clinical Events (FCE) in the PRX-102 arm compared to the agalsidase beta arm, the number of events was small and the process of identifying and evaluating potential FCE events was not robust. The observed numeric imbalance could potentially be a chance finding.

Based on a careful review of the submitted evidence as a whole, this BLA package demonstrates that the benefits of PRX-102 outweigh risks and appears sufficient to support validation of the previously used renal histologic surrogate endpoint in this specific clinical development program and to support approval of Elfabrio.

(b) (6) the approval of the 1 mg/kg q2 weekly regimen is recommended (b) (6)

(b) (6)

9 Advisory Committee Meeting and Other External Consultations

An advisory committee was not necessary and was not held for this application.

10 Pediatrics

The granted indication is for only adult patients with Fabry disease. Pegunigalsidase alfa does not have orphan designation which therefore triggers PREA regulations. The application previously submitted an initial pediatric study plan (iPSP). The Agency has agreed to the sponsor's proposal for a partial waiver of pediatric studies in a Fabry disease subpopulation of 0 to 23 months. The sponsor has proposed (b) (4) trial to evaluate the safety, efficacy, PK and PD effects of pegunigalsidase alfa in pediatric patients with confirmed Fabry's. The sponsor's proposed pediatric clinical study should include an assessment of Gb3 deposition assessed via skin biopsy. The approval letter will note a post-marketing requirement, with required milestones, that will require the sponsor to submit a full protocol for a pediatric study for the Agency to review and agree upon prior to commencing the study.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

See agreed upon final labeling

12 Risk Evaluation and Mitigation Strategies (REMS)

The risks are typical of those seen with enzyme replacement therapies and do not warrant mitigation approaches beyond labeling.

13 Postmarketing Requirements and Commitment

PMR/PMC's will be outlined in the final approval letter (e.g., clinical pharmacology and non-clinical PMC's). There is a PREA PMR to evaluate the safety, efficacy, PK and PD of PRX-102 in pediatric patients aged 2 to <18 years of age with confirmed Fabry disease. There is additionally a post-marketing registry study to assess the effects of PRX-102 on pregnancy and maternal complications, adverse effects on developing fetus and neonate and adverse effects on the infant. There are also additional PMR's related to development of various assays (Neutralizing antibody, anti-drug antibody (e.g., IgG, IgM, IgE, etc.)

14 Appendices

14.1. References

References included as footnotes on the particular page where reference cited.

14.2. Financial Disclosure

There were multiple investigators and sub-investigators involved in the conduct of various studies in the Clinical development program of PRX-102. Many of these individuals overlap between the various studies. A unique number of investigators is challenging to determine.

The focus of this review is on the PB-102-F20 study. Please see original BLA review for a review of the financial disclosures evaluated at the time of the original BLA submission.

Covered Clinical Study (Name and/or Number): PB-102-F20

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 88		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☒	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.3. Nonclinical Pharmacology/Toxicology

Not applicable

14.1. OCP Appendices (Technical documents supporting OCP recommendations)

Not applicable

14.2. Additional Clinical Outcome Assessment Analyses

Not applicable

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MEHUL G DESAI
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Office of Clinical Pharmacology Review

BLA Number	BLA 761161
Link to EDR	\\CDSESUB1\evsprod\BLA761161\0058
Submission Date	November 9, 2022
Submission Type	BLA Class 2 resubmission
Brand Name	ELFABRIO
Generic Name	Pegunigalsidase alfa-iwxj
Dosage Form and Strength	Injection: 20 mg/10 mL (2 mg/mL) solution in a single-dose vial.
Route of Administration	Intravenous infusion
Proposed Dosing Regimen	1 mg/kg every 2 weeks (recommended); (b) (4)
Proposed Indication	Treatment of adults with confirmed Fabry disease
Applicant	Chiesi Farmaceutici S.p.A
OCP Review Team	Xiaohui Li, Hongshan Li, Jiang Liu, and Jie Wang
OCP Final Signatory	Michael Pacanowski

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1. EXECUTIVE SUMMARY

Pegunigalsidase alfa (also referred to as PRX-102) is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme. Pegunigalsidase alfa is a PEGylated, covalently cross-linked recombinant human α-galactosidase-A enzyme that is produced by genetically modified Bright Yellow 2 (*Nicotiana tabacum*) plant cells. The proposed drug product ELFABRIO injection is a 20 mg/10 mL (2 mg/mL) solution in a single-dose vial for intravenous infusion after dilution.

In the initial submission for the original BLA, the Applicant submitted results from studies PB-102-F01/F02 and PB-102-F03 in enzyme replacement therapy (ERT)-naive patients and from study PB-102-F30 in patients previously treated with Replagal (agalsidase alfa) to support the proposed indication and dosing regimen of pegunigalsidase alfa in adults with Fabry disease. The proposed dosing regimen of pegunigalsidase alfa was 1 mg/kg administered every 2 weeks (Q2W) by intravenous (IV) infusion. ERT-naïve patients were defined as patients who had never received ERT or had not received ERT in the past 6 months and had a negative test for anti-pegunigalsidase alfa antibodies at screening. The Applicant intended to pursue accelerated approval based on the effect of pegunigalsidase alfa treatment on reduction of globotriaosylceramide (Gb3) inclusions in the kidney peritubular capillary in biopsied renal samples. The original BLA received a Complete Response letter on April 27, 2021, because of manufacturing deficiencies and because the application could not use the accelerated approval pathway due to the full approval of Fabrazyme (agalsidase beta) in March 2021.

The Applicant submitted the current Class 2 resubmission for BLA 761161 to pursue a full approval of pegunigalsidase alfa for the treatment adults with Fabry disease. The Applicant provided results from two additional clinical studies in ERT-experienced patients: (1) study PB-102-F20 that evaluated the effect of pegunigalsidase alfa treatment on annualized rate of change in eGFR (eGFR slope) in patients previously treated with Fabrazyme; and (2) study PB-102-F50 that evaluated the 2 mg/kg administered every 4 weeks (Q4W) dosage regimen in patients previously treated with Fabrazyme or Replagal. (b) (6)

Pharmacokinetics (PK) of pegunigalsidase alfa were evaluated in studies PB-102-F01/F02, PB-102-F20, and PB-102-F50. Pharmacodynamic (PD) effects of pegunigalsidase alfa on plasma globotriaosylceramide (Gb3) and globotriaosylsphingosine (Lyso-Gb3, a metabolite of Gb3) were assessed in all completed clinical studies included in the resubmission. In addition, immunogenicity and its impact on PK, PD, efficacy, and safety of pegunigalsidase alfa treatment were assessed in the completed studies. The review of the current BLA resubmission focused on the new information provided in the resubmission. Refer to the Multi-Disciplinary Review and Evaluation for the original BLA application (Document ID: 4786588, by SMPOKOU, PATROULA I, dated 04/27/2021).

The key review findings with specific recommendations and comments are summarized in **Table 1**.

Table 1 Summary of Clinical Pharmacology Findings

Review Issues	Recommendations and Comments
Substantial evidence of effectiveness	Substantial evidence of effectiveness of pegunigalsidase alfa in adult patients with Fabry disease was established with one adequate and well-controlled (A&WC) trial with confirmatory evidence. <u>One A&WC trial:</u> • Treatment with pegunigalsidase alfa reduced Renal Biopsy Bliss Score of Gb3 inclusions in kidney peritubular capillary (PTC) cells in ERT-naïve patients in study PB-102-F01/F02. Of note, study PB-102-F01/F02 was an open-label dose-ranging study by design. See Clinical review for the justification for considering this study as an A&WC trial. <u>Confirmatory evidence</u>: • Effect on eGFR: Switching treatment to pegunigalsidase alfa in patients previously treated with Fabrazyme resulted in comparable eGFR slope as patients who continued treatment with Fabrazyme (Study PB-102-F20). Fabrazyme is an approved ERT in U.S. for the treatment of patients with Fabry disease. • PD biomarkers: Plasma Gb3 and globotriaosylsphingosine (lyso-Gb3, a metabolite of Gb3) concentrations are elevated in patients with Fabry disease. Treatment with pegunigalsidase alfa resulted in reductions of plasma Gb3 and lyso-Gb3 concentrations by Week 52 compared to baseline in ERT-naïve patients (studies PB-102-F01/02 and PB-102-03). The PD effect on reductions of plasma Gb3 and lyso-Gb3 demonstrated pharmacological activity of pegunigalsidase alfa in patients. Furthermore, lyso-Gb3 reductions showed statistical correlation with the renal Gb3 inclusion changes from baseline. Although the PD biomarker data were from the same A&WC trial as the primary efficacy results based on kidney Gb3 inclusion, the PD effects are a distinct measurement and reflect the drug effect on multiple tissues whereas the kidney Gb3 inclusion directly measures drug effect in one organ or tissue. • Well-established etiology of the disease and the mechanism of action of pegunigalsidase alfa: Fabry disease is caused by deficiency of the lysosomal enzyme alpha-galactosidase A and pegunigalsidase alfa provides an exogenous source of alpha-galactosidase A.

General dosing instructions	• The proposed dosing regimen of 1 mg/kg Q2W was studied in both ERT-naïve (studies PB-102-F01/02 and PB-102-03) and ERT-experienced patients (study PB-102-F20) and is supported by the overall efficacy and safety results. The proposed dosing regimen of 1 mg/kg Q2W is the recommended dosing regimen for pegunigalsidase alfa in adults with Fabry disease. (b) (4)
Dosing in patient subgroups (intrinsic and extrinsic factors)	• The recommended dosage regimen, 1 mg/kg Q2W, for pegunigalsidase alfa in adult patients with Fabry disease is based on individual patient's actual body weight. The currently available data do not support a recommendation for further dose adjustment based on other intrinsic or extrinsic factors. • Anti-pegunigalsidase alfa IgG antibodies (ADA) had a significant effect on the PK of pegunigalsidase alfa. Patients who developed ADA had lower plasma pegunigalsidase alfa concentrations compared to ADA negative patients. However, dose adjustment based on subject ADA status is not recommended because the impact of ADA on efficacy of pegunigalsidase alfa and the exposure-response relationship between plasma pegunigalsidase alfa concentrations and efficacy have not been fully characterized.

Immunogenicity	• Immunogenicity incidences are summarized in section 3.2.5. • Immunogenicity effect on PK: ADA, including pre-existing ADA, significantly decreased pegunigalsidase alfa exposures (AUC and Cmax), which was associated with ADA IgG titers. Patients with higher ADA titers had lower drug concentrations compared to patients with lower ADA titers. In the PK subgroup (N=17) in study PB-102-F20 in ERT-experienced patients, 3 patients had pre-existing ADA at baseline and remained ADA positive following treatment with pegunigalsidase alfa. Among these three patients, 1 patient with the highest ADA titer had plasma pegunigalsidase alfa concentrations that were below the limit of quantification of the assay throughout the study and the other 2 patients had low plasma pegunigalsidase alfa concentrations with AUC approximately 5% of the expected AUC for ADA-negative patients. • Immunogenicity effect on PD: Plasma lyso-Gb3 levels at baseline and post-treatment were higher in ADA-positive patients compared with ADA-negative patients regardless of prior ERT treatment; this immunogenicity effect was observed only in male patients. The ADA-positive patient who had drug concentrations below the limit of quantification of the assay had the highest plasma lyso-Gb3 levels among the patients. • Immunogenicity effect on efficacy: The effect of ADA on efficacy based on kidney Gb3 inclusions was not fully characterized. The kidney biopsy data were not collected in study PB-102-F20; therefore, it is not feasible to assess whether there is an impact of ADA on kidney Gb3 inclusions in those ADA positive patients who had significantly lower drug exposure and reduced PD response due to high titer ADA. • Immunogenicity effect on safety: The association between IgE ADA and events of hypersensitivity reactions was not fully characterized. Other infusion associated reactions (IARs) occurred more frequently in patients who were ADA-positive compared to those who were ADA-negative.
Bridge between the to-be-marketed and clinical trial formulations	• The to-be-marketed formulation of pegunigalsidase alfa was used in clinical trials; therefore, there is no need to bridge between the to-be-marketed formulation to the clinical trial formulation.

1.1 Recommendation

From a clinical pharmacology standpoint, the BLA resubmission is acceptable to support approval of pegunigalsidase alfa for the treatment of adults with Fabry disease.

1.2 Post-Marketing Requirements and Commitments

The OCP review team recommends that the Applicant conduct a post-marketing study to evaluate neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa in clinical samples from studies PB-102-F01/02 and PB-102-F20. We also agree with the Office of Biotechnology Products review team's recommendations for the Applicant to conduct post-marketing studies to develop new or improve the current immunogenicity assays. The recommended post-marketing studies and rationale are summarized in **Table 2**.

Table 2 Post-Marketing Requirements and Commitments

PMR or PMC	Recommended studies and key issues to be addressed	Rationale and key considerations
PMR xxxx-3	Develop and validate an assay for detection of neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa.	Pegunigalsidase alfa is a lysosomal ERT that requires cellular internalization for achieving pharmacological activity. Antibodies inhibiting the cellular uptake of pegunigalsidase alfa are expected to reduce the drug effect and should be considered as neutralizing antibodies (NAb). The Applicant did not evaluate NAb inhibiting cellular uptake of pegunigalsidase alfa in the BLA because the assay was not available. Therefore, to adequately assess this risk, the Applicant is required to develop and validate an assay for detection of NAb that inhibit the cellular uptake of pegunigalsidase alfa. Additionally, as a separate PMR (PMR xxxx-7), the Applicant in required to assess the NAb using banked clinical samples from studies PB-102-F01/02 and PB-102-F20.
PMR xxxx-4	Develop and validate an anti-PEG IgE assay.	An assay that is able to detect anti-PEG IgE antibodies was not developed in the BLA. Therefore, to adequately assess the immunogenicity risk, the Applicant is required to develop and validate an assay that specifically detects anti-PEG IgE antibodies.
PMR xxxx-5	Improve the current anti-pegunigalsidase alfa IgG antibody assay or develop a new assay to improve the drug tolerance. Validate the assay.	The current ADA assay used in the BLA can tolerate pegunigalsidase alfa concentrations up to 500 ng/mL for detection of low ADA concentrations (250 ng/mL) and can tolerate pegunigalsidase alfa concentrations up to 4000 ng/mL for detection of high ADA concentrations (2000 ng/mL). The PK data in ERT-naïve patients indicate that plasma pegunigalsidase alfa concentrations at 2

		mg/kg could interfere with the detection of low ADA concentrations (250 ng/mL). Pegunigalsidase alfa in plasma could also interfere with some immunogenicity samples at 1 mg/kg, especially at later timepoints (e.g., Month 12). The PK data in ERT-experienced patients indicates that pegunigalsidase alfa in plasma at 1 mg/kg Q2W could also interfere with the detection of low ADA concentrations (250 ng/mL).
PMR xxxx-6	Revise and re-validate the anti-pegunigalsidase alfa IgM antibody assay with anti-pegunigalsidase alfa IgM antibodies to be used as positive controls.	The anti-drug IgM assay validation in the BLA was not adequate because the positive control used in the method validation was not appropriate.
PMR xxxx-7	Evaluate neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa in clinical samples from studies PB-102-F01/02, PB-102-F03, and PB-102-F20, using the assay developed and validated under PMR XXXX-3. Assess the impact of cellular uptake neutralizing antibodies on the pharmacokinetics, pharmacodynamics, efficacy, and safety of pegunigalsidase alfa in a representative sample of patients with Fabry disease treated with the product in clinical trials.	See PMR xxxx-3.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

Pegunigalsidase alfa provides an exogenous source of alpha-galactosidase A (α-GAL-A). Pegunigalsidase alfa is internalized and transported into lysosomes where it is thought to exert enzymatic activity and reduce accumulated globotriaosylceramide (Gb3). Fabry disease is caused by deficiency of α-GAL-A.

Pharmacodynamics

In ERT-naïve patients in study PB-102-F01/02, pegunigalsidase alfa treatment resulted in approximately -43% (Week 4), -57% (Week 26), -68% (Week 52), and -84% (Week 104) reductions in median plasma lyso-Gb3 concentrations compared to baseline in male patients and approximately -3% (Week 4), -19% (Week 26), -32% (Week 52), and -75% (Week 104) median reductions in female patients. In ERT-experienced patients in study F20, switching to pegunigalsidase alfa treatment resulted in approximately 11% (Week 6), 15% (Week 26), and 18% (Week 104) increase in median plasma lyso-Gb3 concentrations in male patients and no significant changes in female patients.

Pharmacokinetics

The pharmacokinetics (PK) of pegunigalsidase alfa in plasma following IV infusion of pegunigalsidase alfa 1 mg/kg every other week (Q2W) in ERT-naïve patients with Fabry disease in study F01/02 are summarized in **Table 3**. The exposure of pegunigalsidase alfa increased with dose in a more than dose-proportional manner. The maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) of pegunigalsidase alfa increased with longer duration of treatment following multiple dose administrations through Month 12. The PK of pegunigalsidase alfa in plasma following IV infusion of pegunigalsidase alfa 1 mg/kg Q2W and 2 mg/kg Q4W in ERT-experienced patients with Fabry disease in studies F20 and F50 are summarized in **Table 4** and **Table 5**, respectively.

Table 3 Pharmacokinetics of Pegunigalsidase Alfa in Adult Patients with Fabry Disease Following Intravenous Infusion of Pegunigalsidase Alfa 1 mg/kg Every Other Week in ERT-Naïve Patients (Study PB-102-F01/F02)

PK Parameters	Pegunigalsidase Alfa			
	Day 1	Month 3	Month 6	Month 12
	N=6	N=6	N=6	N=6
Mean Body Weight (kg)	73.7	74.6	75.3	76.6
Mean Infusion Duration (h)	5.5	4.4	3.9	3.3
PK Parameters (Mean[±SD])				
Tmax (h) [b]	5.3 (4.1, 8.7)	5.0 (2.1, 7.0)	4.4 (2.0, 6.5)	4.3 (1.7, 6.5)
C_{max} (µg/mL)	11.1±2.4	11.9±2.4	13.3±3.0	17.3±6.1
AUC0-2wk (µg·h/mL) [a]	374±126	479±163	692±196	1217±729
Vz (mL/kg) [a]	321±71	271±89	226±116	186±91
C_{last} (µg/mL) [a, b]	0.1 (0.06, 0.3)	0.2 (0.04, 0.5)	0.4 (0.09, 0.6)	0.3 (0.3- 0.4)
$t_{1/2}$ (h) [a]	78.9±10.3	85.7±28.4	96.5±31.4	121±22
CL (mL/h/kg) [a]	2.9±0.7	2.3±0.8	1.6±0.6	1.1±0.7

C_{max}=maximum maximum plasma concentration; Clast=last measurable concentration in the dosing interval; AUC=area under the plasma concentration-time curve; Vz=volume of distribution; t1/2=elimination half-life; CL=clearance.
[a] At Month 12, N=5 for AUC, Vz, t1/2 and CL, and N=2 for Clast.
[b] Median (min, max) for Tmax and Clast
Source of data: Table 23 in Module 2.7.2; PB-102-F01 Data Listing 6 and PB-102-F02 Data Listing 6 (Appendix 16.2.4).

Table 4 Pharmacokinetics of Pegunigalsidase Alfa in Adult Patients with Fabry Disease Following Intravenous Infusion of Pegunigalsidase Alfa 1 mg/kg Every Other Week in ERT-experienced Patients (Study PB-102-F20)

PK Parameters	Pegunigalsidase Alfa			
	Day 1	Month 6	Month 12	Month 24
	N=16	N=16	N=14	N=15
Dose (mg)	81.4	81.9	78.8	80.4
Mean Infusion Duration (h)	3.0	1.9	1.6	1.6
PK Parameters (Mean[±SD])				
Tmax (h) [c]	3.2 (0, 4.0)	2.0 (0, 5.5)	1.5 (0, 3.6)	1.6 (1.5, 3.6)
C_{max} (µg/mL)	21.2±9.9	23.3±12.1	22.9±9.5	21.9±10.2
AUC0-2wk (µg·h/mL)	958±624	1020±583	1074±547	972±425
C_{last} (µg/mL) [a]	0.8 (0.03, 4.0)	0.7 (0.03,8.3)	0.9 (0.05, 5.7)	0.7 (0.02, 3.8)
Vz (L) [b]	9.1±3.8	9.9±7.0	13.4±16.4	10.1±4.3
$t_{1/2}$ (h) [b]	82.6±40.9	84.5±36.6	93.8±39.6	97.0±37.4
CL (mL/h) [b]	557±1170 57 (38, 3604)	354±805 54 (33, 2848)	518±1322 54 (40, 3791)	193.4±488.7 60 (43, 1891)

C_{max}=maximum plasma concentration; Clast=last measurable concentration in the dosing interval; AUC=area under the plasma concentration-time curve; Vz=volume of distribution; $t_{1/2}$=elimination half-life; CL=clearance.
[a] Median (min, max) for C_{last}, with N=15, 15 and 13 for Day 1, Month 6, and Month 12, respectively.
[b] For Vz, $t_{1/2}$ and CL, N=11, 14, 8, and 13 for Day 1, Month 6, Month 12, and Month 24, respectively. In addition to mean (±SD), median (min, max) values are also provided for CL.
[c] Median (min, max) for Tmax
Source of data: Table 11-4 in PB-102-F20 PK Report ICX-B166.

Table 5 Pharmacokinetics of Pegunigalsidase Alfa in Adult Patients with Fabry Disease Following Intravenous Infusion of Pegunigalsidase Alfa 2 mg/kg Every 4 Weeks in ERT-experienced Patients (Study PB-102-F50)

PK Parameters	Pegunigalsidase Alfa			
	Day 1	Month 6	Month 10	Month 12
	N=30	N=11	N=14	N=28
Dose (mg)	164.59	163.58	161.93	162.44
Mean Infusion Duration (hr)	4.79	2.27	2.37	2.23
PK Parameters (Mean[±SD])				
Tmax (hr) [d]	4.6 (1.5, 14.1)	2.0 (0, 4.0)	2.2 (1.0, 6.0)	2.0 (1.0, 12.9)
C_{max} (mcg/mL)	35.9±11.9	43.3± 20.0	36.3±17.8	46.8±27.9
Clast (mcg/mL) [a]	0.2 (0.03, 2.1)	2.1 (0.07, 0.4)	0.3 (0.02,1.4)	0.3 (0.04, 48.0)
AUC0-4wk (mcg•hr/mL) [b]	1783± 783	2179± 463	1658±1036	2652±3253
Vz (L) [c]	12.5±6.5	14.6± 4.5	14.9±6.2	15.1±5.0
$t_{1/2}$ (hr) [c]	100.1±58.3	132.7±28.0	106.1±78.3	133.7±47.8
CL (mL/hr) [c]	290.9±868.6 84 (41, 4808)	77.1±19.1 72 (53, 114)	854.7±1757.3 87 (51, 4870)	217.0±595.1 77 (33, 3028)

C_{max}=maximum plasma concentration; Clast=last measurable concentration; AUC=area under the plasma concentration-time curve; Vz=volume of distribution; $t_{1/2}$=elimination half-life; CL=clearance.
[a] Median (range) for Clast.
[b] For AUC at Month 6, N=10.
[c] For Vz, $t_{1/2}$ and CL, N=10, 13 and 26 at Month 6, Month 10, and Month 12, respectively. In addition to mean (±SD), median (min, max) values are also provided for CL.
[d] Median (min, max) for Tmax
Source of data: Table 9-3 in PB-102-F50 PK Report ICX-B165.

Immunogenicity

See summary of immunogenicity findings in **Table 1**.

2.2 Dosing and Therapeutic Individualization

General Dosing
The efficacy and safety results in clinical studies in ERT-naïve and ERT-experienced patients with Fabry disease overall support that the proposed pegunigalsidase alfa dosing regimen of 1 mg/kg administered IV every 2 weeks is acceptable.

Therapeutic Individualization
The recommended dosage regimen 1 mg/kg Q2W of pegunigalsidase alfa in patients with Fabry disease is based on body weight, which is the approach used in the clinical trials. The currently available data do not support a recommendation for further dose adjustment based on other intrinsic or extrinsic factors.

2.3 Outstanding Issues

There are no outstanding issues that would preclude the approval of pegunigalsidase alfa from a clinical pharmacology perspective.

The OBP and OCP review teams identified a few review issues related to the limitation of the immunogenicity assays used in the BLA. We recommend PMR studies to address the outstanding issues. See **Table 2** for detailed discussion of the review issues and PMR recommendations.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends inclusion of the following information in the final product labeling for ELFABRIO:

- Patients that received prior enzyme-replacement therapy (ERT) are more likely to have pre-existing anti-drug antibodies (ADA) to pegunigalsidase alfa which could be due to the ADA cross-reactivity to pegunigalsidase alfa by prior ERT. When switching from other ERT to ELFABRIO, pre-existing ADA may reduce the plasma pegunigalsidase alfa concentrations, which may reduce ELFABRIO efficacy. The risk of ELFABRIO-related hypersensitivity and infusion-associated reactions may be increased in certain patients with pre-existing ADA from prior ERT. Consider monitoring clinical or pharmacodynamic responses (e.g., plasma lyso-Gb3 levels) when switching from Fabrazyme to ELFABRIO, in patients with pre-existing ADA.

3. Comprehensive Clinical Pharmacology Review

3.1 General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology aspects of pegunigalsidase alfa that are relevant to the interpretation of benefit and risk are summarized in **Table 6**.

Table 6. Summary of Clinical Pharmacology for Pegunigalsidase Alfa

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Pegunigalsidase alfa is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme.
Mechanism of action	Fabry disease is caused by deficiency of the lysosomal enzyme alpha-galactosidase A (α-GAL-A). Pegunigalsidase alfa provides an exogenous source of α-GAL-A. Pegunigalsidase alfa is internalized and transported into lysosomes where it is thought to exert enzymatic activity and reduce accumulated globotriaosylceramide (Gb3).
Active moieties	The active moiety is pegunigalsidase alfa. Pegunigalsidase alfa is a PEGylated, covalently cross-linked, recombinant human α-Gal A that is produced by genetically modified Bright Yellow 2 (Nicotiana tabacum) plant cells.
	General Information
Bioanalysis	An enzyme-linked immunosorbent assay (ELISA) was used to quantify pegunigalsidase alfa concentrations in human plasma in PK samples collected in clinical trials. The performance of the bioanalytical method was acceptable.
Healthy subjects vs patients	Pegunigalsidase alfa has not been studied in healthy subjects.
Drug exposure at steady state following the therapeutic dosing regimen	The PK of pegunigalsidase alfa in patients with Fabry disease following IV infusion at the recommended dosage regimen 1 mg/kg every other week (Q2W) in ERT-naïve patients and ERT-experienced patients are summarized in **Table 3** and **Table 4**, respectively.
Range of effective dosage(s) or exposure	The recommended dosage of pegunigalsidase alfa is 1 mg/kg Q2W IV. (b) (4) [redacted]
Accumulation	Following pegunigalsidase alfa IV infusion 1 mg/kg Q2W for 12 months in ERT-naïve patients, the mean accumulation ratio for AUCtau was 3.3. Following pegunigalsidase alfa IV infusion 1 mg/kg Q2W for 24 months in ERT-experienced patients, no significant accumulation was observed.
Time to achieve steady-state	In ERT-naïve patients, AUC and Cmax of pegunigalsidase alfa increased from Day 1 to Month 12 following 1 mg/kg Q2W IV administration; therefore, the minimum time to achieve steady-state in ERT-naïve patients is 12 months. In ERT-experienced patients, AUC and Cmax of pegunigalsidase alfa appeared to be stabilized by Month 6 following 1 mg/kg Q2W IV administration.

Characteristic	Drug Information
Bridge between to-be-marketed and clinical trial formulations	The to-be-marketed formulation of pegunigalsidase alfa was used in clinical trials; therefore, there is no need to bridge the to-be-marketed formulation to the clinical trial formulation.
	Absorption
Bioavailability	100% since pegunigalsidase alfa is administered via IV infusion.
T_{max}	T_{max} is expected to be achieved at the end of IV infusion.
	Distribution
Volume of distribution	Refer to **Table 3** and **Table 4.**
	Elimination
Clearance	Pegunigalsidase alfa exhibited nonlinear PK with the clearance decreasing as the dose increased from 0.2 mg/kg to 2 mg/kg following Q2W administration in ERT-naïve patients. Refer to **Table 3** and **Table 4.**
Half-life	Refer to **Table 3** and **Table 4.**
Metabolic pathway(s)	The metabolic pathway of pegunigalsidase alfa has not been characterized. As a lysosomal neutral glycosphingolipid-specific enzyme, pegunigalsidase alfa is expected to be metabolized into small peptides by catabolic pathways.
Primary excretion pathways (% dosage)	The excretion pathways of pegunigalsidase alfa have not been characterized.
	Intrinsic Factors and Specific Populations
Body weight	The population PK analysis results did not identify body weight as a significant covariate affecting the PK of pegunigalsidase alfa. At the same body weight-based dose level (e.g., 1 mg/kg), the population PK model predicted that the exposure of pegunigalsidase alfa increased with increasing body weight, which is not considered clinically meaningful considering the currently proposed indication in adults and based on the current understanding of the exposure-response relationship for pegunigalsidase alfa.
Antibodies development	The presence of IgG antibodies to pegunigalsidase alfa including pre-existing ADA significantly decreased the exposures of pegunigalsidase alfa. In addition, patients with higher ADA titers had lower pegunigalsidase alfa concentrations compared to those with lower ADA titers.
Age and sex	Based on population PK analysis, age or sex did not significantly affect the PK of pegunigalsidase alfa.
Renal impairment	No formal trial was conducted to evaluate the effect of renal impairment on the PK of pegunigalsidase alfa. Intact pegunigalsidase alfa (molecular weight of approximately 116 kDa) is unlikely to be filtered by kidney or excreted in urine.
Hepatic impairment	No formal trial was conducted to evaluate the effect of hepatic impairment on the PK of pegunigalsidase alfa. Metabolism by CYP enzymes or secretion into bile is generally not a significant contributor to the elimination of therapeutic proteins such as pegunigalsidase alfa.

Characteristic	Drug Information
	Pharmacodynamics
Biomarker	The concentrations of lyso-Gb3 in plasma were reduced from baseline in ERT-naïve patients after treatment with pegunigalsidase alfa at doses of 0.2, 1 and 2 mg/kg Q2W and in agalsidase alfa-experienced patients after the treatment with pegunigalsidase alfa at 1 mg/kg Q2W. However, in patients who were previously treated with Fabrazyme, the median plasma lyso-Gb3 increased approximately 11% (Week 6), 15% (Week 26), and 18% (Week 104) in male patients, while plasma Lyso-Gb3 levels were reduced by approximately 13% in patients who continued with their previous Fabrazyme treatment. Compared to male patients, female patients had lower baseline lyso-Gb3 levels and maintained the low levels after the PRX-102 treatment in both ERT-naïve and ERT-experienced patients.
	Immunogenicity
Bioanalysis	The following bioanalytical methods for immunogenicity assessment were used in the BLA: • ELISA for detecting anti-pegunigalsidase alfa IgG antibodies • ELISA for detecting anti-pegunigalsidase alfa IgM antibodies • ELISA for detecting anti-pegunigalsidase alfa IgE antibodies • Enzymatic activity assay for detecting neutralizing antibodies specific to pegunigalsidase alfa • Assay for detecting antibodies specific for plant glycan motifs in pegunigalsidase alfa • ELISA for detecting antibodies to PEG crosslinker on pegunigalsidase alfa • ELISA for detecting antibodies to unpegylated enzyme moiety (BCL) Specific issues related to the limitation of the immunogenicity assays were identified by the OCP and Office of Biological Products (OBP) review teams. See **Table 2** for detailed discussion of the review issues and PMR recommendations to address these issues.
Incidence	Refer to *Section 3.2.5.*
Clinical impact	Refer to **Table 1**.

3.2 Clinical Pharmacology Questions

3.2.1 Does the clinical pharmacology program provide supportive evidence effectiveness?

Yes. The pharmacodynamic effect on reduction of plasma Gb3 and lyso-Gb3 levels in ERT-naïve patients demonstrated the pharmacological activity of pegunigalsidase alfa in patients with Fabry disease. The reduction of plasma lyso-Gb3 also showed statistical correlation with the reduction of renal Gb3 inclusions from baseline (Refer to Section 8, Multi-disciplinary review and evaluation for the original BLA application, Document ID: 4786588, by SMPOKOU, PATROULA I, dated 04/27/2021). Therefore, the PD effect of pegunigalsidase alfa in ERT-naïve patients provides confirmatory evidence of effectiveness of pegunigalsidase alfa for the treatment of Fabry disease.

Pharmacodynamic effect on reduction of plasma lyso-Gb3 in ERT-Naïve Patients

All patients had reductions in plasma lyso-Gb3 concentrations from baseline following treatment with pegunigalsidase alfa for 12 months and/or 24 months in study PB-102-F01/F02 in ERT-naïve patients. Individual patient plasma lyso-Gb3 concentrations, absolute changes from baseline, and percentage (%) changes from baseline following treatment with pegunigalsidase alfa are summarized **Table 7**. Male patients had higher plasma lyso-Gb3 concentrations at baseline than female patients. The individual percentage change from baseline ranged from -5% to -79% at Month 12 across all patients. Based on the data from the patients who had plasma lyso-Gb3 assessment at both Month 12 and 24, there is a trend for decreasing plasma lyso-Gb3 over time. Overall, greater mean percentage reductions from baseline were observed in male patients compared to those in female patients.

Table 7. Individual Plasma Lyso-Gb3 Levels in Studies PB102-F01/F02 and F03

			Plasma Lyso-Gb3 (ng/mL)				%Change from baseline	
Subject ID	PRX-102 dose (mg/kg)	Sex	Study PB-102-F01/F02			Study PB-102-F03	Month 12	Month 24
			Baseline	Month 6	Month 12	Month 24		
(b) (6)	0.2	F	19.2	NA	17.7	NA	-7.8%	NA
	1	M	5.1	2.9	2.8	NA	-45.1%	NA
	1	F	14.4	NA	7.1	NA	-50.7%	NA
	1	M	193.4	NA	46.7	9.2	-75.9%	-95.2%
	1	M	123.0	24.5	35.6	13.7	-71.0%	-88.9%
	2	M	61.8	NA	30.8	11.2	-50.2%	-81.9%
	0.2	M	66.5	6.7	25.2	10.7	-62.1%	-83.9%
	1	M	80.8	34.7	17.2	NA	-78.7%	NA
	1	F	6.8	5.5	4.2	NA	-38.2%	NA
	0.2	M	112.5	NA	40.0	20.7	-64.5%	-81.6%
	2	F	3.4	NA	2.6	1.0	-23.5%	-70.6%
	2	F	5.0	NA	2.2	1.0	-55.6%	-80.0%
	0.2	M	272.9	142.3	69.5	10.3	-74.5%	-96.2%
	2	F	10.8	6.6	7.3	1.9	-32.4%	-82.4%
	0.2	M	84.7	44.5	45.7	21.1	-46.0%	-75.1%
	0.2	F	7.5	16.2	7.1	3.3	-5.3%	-56.0%

Normal range of plasma lyso-Gb3 is < 1.89 ng/mL.
ERT-naïve patients were randomized to receive pegunigalsidase alfa 0.2, 1 and 2 mg/kg Q2W treatment for 12 months, then transitioned to receive 1 mg/kg Q2W in study PB-102-F03 up to 60 months. Treatment naïve patients were defined as patients with FD who had either never received ERT or who had not received ERT in the preceding 6 months and had a negative anti-pegunigalsidase alfa antibody test before enrollment into study PB-102-F01/F02.
a. This patient did not enroll into Study PB-102-F03.
b. Subjects (b) (6) were ADA positive.
Source of data: Table 2, Summary of Clinical Pharmacology Studies; Listing 7.4.1, CSR for Study PB-102-F03

Pharmacodynamic effect on plasma lyso-Gb3 in ERT-experienced patients

In Fabrazyme-experienced patients in study PB-102-F20, at baseline (randomization), the median plasma lyso-Gb3 concentration was 15.2 nM (12 ng/mL) in the pegunigalsidase alfa treatment group and 17.6 nM (14 ng/mL) in the Fabrazyme treatment group. The plasma lyso-Gb3 levels in female patients were lower than in male patients (**Table 8**). After treatment for 24 months in male patients, the median plasma Lyso-Gb3 concentrations increased slightly by 18% in the pegunigalsidase alfa group, compared to approximately 13% decrease in the Fabrazyme group (**Table 8** and **Figure 1**). Female patients did not show significant change in

plasma lyso-Gb3 concentrations, with median change of 0.1 nM in the pegunigalsidase alfa group and -0.3 nM in the Fabrazyme group. Of note, none of the patients in the two treatment groups achieved plasma lyso-Gb3 levels within the normal range (<2.4 nM) by Month 24, except for one female patient in the Fabrazyme group (b) (6) ADA-negative) who had plasma lyso-Gb3 levels of 2.1 nM at baseline and 1.5 nM at Month 24.

In ERT (agalsidase alfa)-experienced patients in study PB-102-F30, the median plasma lyso-Gb3 concentration at baseline was 42.4 nM (33.4 ng/mL) in males and 13.8 nM (10.9 ng/mL) in females. After the 12-month pegunigalsidase alfa treatment, the median plasma Lyso-Gb3 concentrations were reduced by 36% and 23% in males and females, respectively (**Table 9**).

The PD results from studies PB-102-F20 and PB-102-F30 indicated that the type of ERTs (agalsidase beta vs agalsidase alfa) previously received in ERT-experienced patients before switching to pegunigalsidase alfa might have an impact on the magnitude of PD response of pegunigalsidase alfa. In ERT-experienced patients who previously received Fabrazyme, switching to pegunigalsidase alfa resulted in a 10% increase in plasma lyso-Gb3 at month 24, comparing to a 34% decrease at month 12 in ERT-experienced patients who previously received Replagal (**Table 8** and **Table 9**). Of note, the different baseline plasma lyso-Gb3 levels prior to switching may also have contributed to the differences in PD response of pegunigalsidase alfa between the two ERT-experienced patient populations.

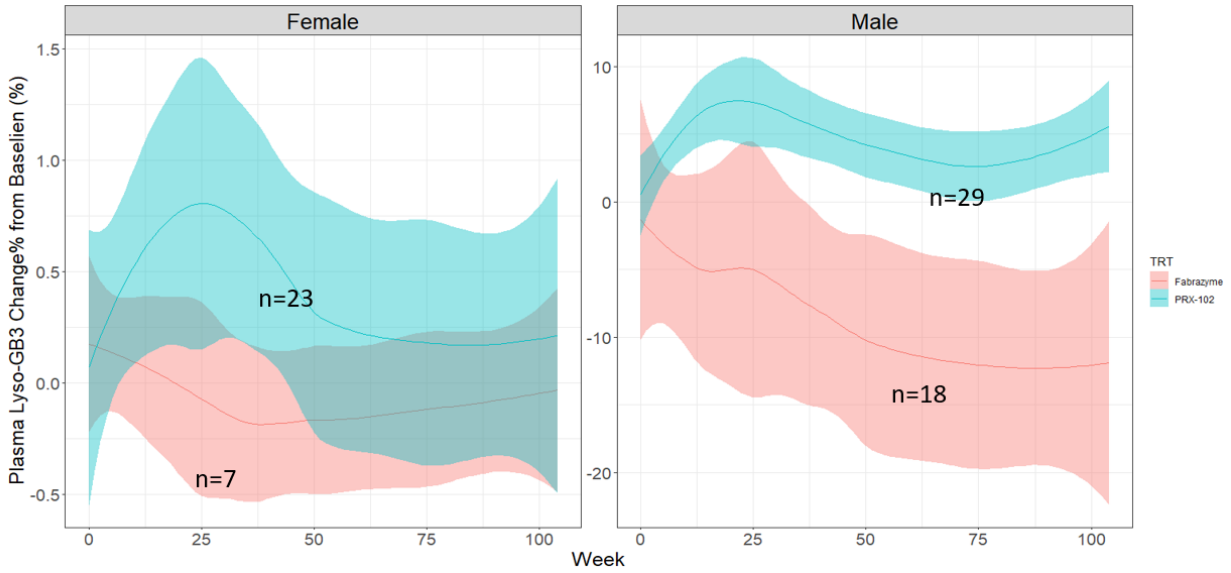
Table 8. Summary of Plasma Lyso-Gb3 Levels (Study PB102-F20)

			Plasma Lyso-Gb3 (nM)			Change from baseline	%Change from baseline
			Baseline	Month 12	Month 24	Month 24	Month 24
Pegunigalsidase Alfa	All	N	52	47	46	46	46
		Mean (SD)	26.2 (27.3)	28.1 (27.6)	29.2 (30.4)	3.30 (9.4)	10.3 (25.8)
		Median (range)	15.2 (0.8; 143.9)	16.2 (2.3; 123.9)	18.8 (2.4; 139.4)	1.15 (-32.2;32.7)	10.0 (-47.2; 73.0)
	M	N	29	25	25	25	25
		Mean (SD)	40.4 (29.6)	45.4 (28.0)	46.9 (31.7)	5.9 (12.1)	19.3 (25.3)
		Median (range)	30.7 (0.8; 143.9)	35.5 (3.4; 123.9)	34.4 (3.2; 139.4)	5.3 (-32.2;32.7)	18.1 (-38.5; 73.0)
	F	N	23	22	21	21	21
		Mean (SD)	8.4 (3.2)	8.5 (3.8)	8.1 (4.4)	0.2 (2.12)	-0.3 (22.5)
		Median (range)	8.40 (2.8; 16.2)	8.05 (2.3; 19.3)	8.9 (2.4; 22.0)	0.1 (-4; 5.8)	2.4 (-47.2; 35.8)
Agalsidase Beta	All	N	25	24	22	22	22
		Mean (SD)	32.1 (35.4)	25.0 (23.0)	19.7 (16.9)	-8.74 (22.7)	-12.7 (21.6)
		Median (range)	17.6 (2.1; 142.0)	18.8 (1.5; 95.5)	15.3 (1.5; 71.2)	-1.5 (-102.3 2.4)	-11.4 (-72.0; 22.5)
	M	N	18	17	15	15	15
		Mean (SD)	42.4 (36.9)	33.0 (22.9)	26.2 (16.8)	-12.8 (26.8)	-18.1 (21.5)
		Median (range)	23.7 (8.9; 142.0)	24.8 (6.6; 95.5)	20.5 (6.2; 71.2)	-2.4 (-102.3;2.4)	-13.3 (-72.0; 19.4)
	F	N	7	7	7	7	7
		Mean (SD)	5.7 (2.9)	5.6 (2.9)	5.7 (2.8)	-0.03 (0.7)	-1.1 (18.0)
		Median	4.40	5.0	4.9	-0.3	-3.6

		(range)	(2.1; 10.4)	(1.5; 9.7)	(1.5; 9.7)	(-0.7; 0.9)	(-28.6; 22.5)

Normal range of plasma lyso-Gb3 is < 2.4 nM.
The conversion factor for plasma Lyso-Gb3 is 1.27, i.e., 1 ng/mL=1.27 nM.
Patients who had been receiving Fabrazyme treatment for at least one year prior to enrollment and stayed on Fabrazyme during the screening period were randomized in study PB-102-F20 to either switch to pegunigalsidase alfa 1 mg/kg Q2W treatment or continue with the Fabrazyme treatment. M=Male; F=Female
Source of data: Table 14.2.3.1, CSR for Study PB-102-F20

Figure 1. %Change from Baseline in Plasma Lyso-Gb3 Concentration (Study PB-102-F20)



Source of data: FDA Reviewer's analysis

Table 9. Plasma Lyso-Gb3 Concentrations (Study PB-102-F30)

Population		Plasma Lyso-Gb3 (nM)			Change from baseline	%Change from baseline
		Baseline	Month 6	Month 12	Month 12	Month 12
All	N	20	20	20	20	20
	Mean (SD)	38.51 (43.31)	29.56 (29.11)	24.20 (22.80)	-14.31 (22.95)	-31.46 (15.53)
	Median (range)	22.10 (1.2; 189.4)	19.15 (1.1; 122.4)	13.35 (0.9; 90)	-6.55 (-99.4; 3.9)	-34.45 (-52.5; 9.2)
Male	N	13	13	13	13	13
	Mean (SD)	51.81 (49.03)	38.88 (32.63)	32.25 (24.86)	-19.55 (27.24)	-32.35 (17.38)
	Median (range)	42.4 (1.2; 189.4)	26.8 (1.1; 122.4)	29 (0.9; 90)	-8.2 (-99.4; 3.9)	-36.05 (-52.5; 9.2)
Female	N	7	7	7	7	7
	Mean (SD)	13.81 (6.11)	12.23 (3.94)	9.24 (2.86)	-4.57 (3.76)	-29.81 (12.41)
	Median (range)	12.9 (7.4; 23.2)	13.10 (7.2; 17.4)	10.6 (4.7; 12.6)	-2.7 (-10.6; -1.4)	-23.3 (-45.7; -17.3)

Normal range of plasma Lyso-Gb3 is < 2.4 nM.
The conversion factor for plasma Lyso-Gb3 is 1.27, i.e., 1 ng/mL=1.27 nM.
Patients who had received agalsidase alfa treatment for at least two years prior to enrollment and stayed on agalsidase alfa during the screening period then were switched to pegunigalsidase alfa 1 mg/kg Q2W,
Source of data: Table 14.2.2.1.1.1, Final CSR for Study PB-102-F30

Pharmacodynamic effect on reduction of plasma Gb3 in ERT-Naïve Patients

Reductions in plasma Gb3 concentrations from baseline were observed across the dose groups following treatment with pegunigalsidase alfa for 12 months in ERT-naïve patients in study PB-102-F01/F02 (**Table 10**). Similar to plasma lyso-Gb3, male patients had higher plasma Gb3 concentrations at baseline and greater percentage reductions from baseline than female patients. Because the Applicant provided very limited assay validation information of the bioanalytical methods used for assessing plasma Gb3, the PD data on plasma Gb3 is not recommended for labeling and further E-R analysis based on plasma Gb3 was not conducted.

Table 10. Effect of Pegunigalsidase Alfa on Plasma Gb3 Concentrations in ERT-Naïve Patients (Study PB-102-F01/02).

		0.2 mg/kg		1.0 mg/kg		2.0 mg/kg	
		Male	**Female**	**Male**	**Female**	**Male**	**Female**
Day 0 (baseline)	N	3	2	4	2	1	3
	Mean±SD	14.0±4.5	5.8±2.5	13.3±8.4	6.5±0.7	12.7	5.8±0.5
	Median	13.3	5.8	12.4	6.5	12.7	6.0
Week 52	N	4	2	4	2	1	3
	Mean±SD	10.6±1.5	5.5±2.5	6.3±2.3	6.2±2.2	6.3	5.5±0.8
	Median	10.9	5.5	6.7	6.2	6.3	5.1
	%Change from baseline (mean)	-23.8%	-6.4%	-42.7%	-6.7%	-50.2%	-4.9%
	%Change from baseline (median)	-35.7%	-6.4%	-46.6%	-6.7%	-50.2%	-1.0%

ERT-naïve patients were randomized to receive pegunigalsidase alfa 0.2, 1 and 2 mg/kg Q2W treatment for 12 months.
Source: Table 9, CSR for study PB-102-F01/02

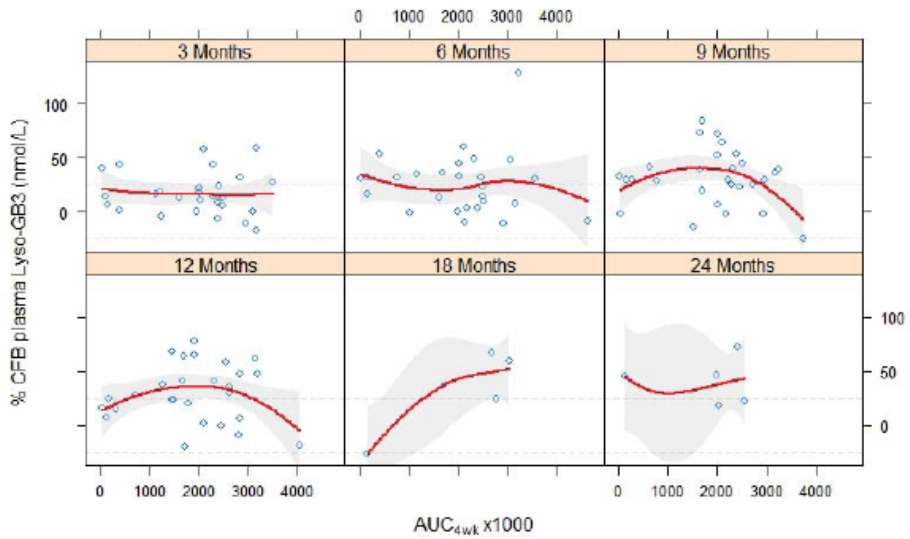
Exposure-response for Plasma lyso-Gb3

The overall exposure-response (E-R) relationship for plasma lyso-Gb3 is not clearly established in ERT-naïve or ERT-experienced patients.

For ERT-naïve patients, the overall E-R relationship for plasma lyso-Gb3 based on the data from Studies PB-102-F01/02 is considered inconclusive. Although greater reduction in plasma lyso-Gb3 was observed with increasing pegunigalsidase alfa exposure (e.g., AUCtau) in male patients, the E-R analysis had multiple limitations such as small number of subjects and pooled lyso-Gb3 data over time from the same subjects, confounded by factors including varying baseline values of lyso-Gb3 across dose levels and imbalanced distribution in sex. Further E-R analysis based on the percent change from baseline of plasma lyso-Gb3 did not show a clear E-R relationship in male or female patients; however, this observation may also be confounded by imbalanced baseline values and FD phenotypes across dose groups (Refer to Section 15.3.2, Multi-disciplinary review and evaluation for the original BLA application, Document ID: 4786588, by SMPOKOU, PATROULA I, dated 04/27/2021).

Similar to the inconclusive E-R relationship in ERT-naïve patients, there is no clear E-R relationship for plasma lyso-Gb3 in ERT-experienced patients. The percent change from baseline of plasma lyso-Gb3 also did not show a clear E-R relationship **(Figure 2**). See Section 4.2 for more details.

Figure 2. Relationship Between AUC4week of Pegunigalsidase Alfa and Percent Change from Baseline in Plasma Lyso-Gb3 Stratified by Study Visit for Male Patients in Studies PB-102-F20 and PB-102-F50



Red line: smooth, shaded region: se at 0.90 significance level, circles: observed data; Dotted lines are 25% increase and decrease in plasma Lyso-Gb3 that Applicant selected as clinically significant change.
Source: Figure 12-16, PKPD report ICX-B173 MSAR2

3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

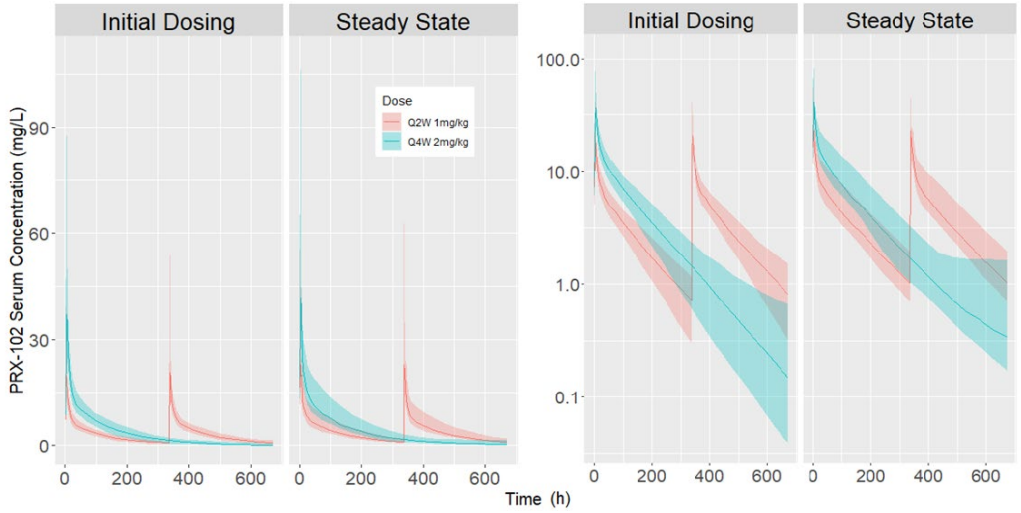
(b) (6)

The 1 mg/kg Q2W dosing regimen has been studied in ERT-naïve and ERT-experienced patients in studies PB-102-F01/F02, PB-102-F20, and PB-102-F30 and is supported by the overall efficacy and safety results (Refer to clinical review for details). The 1 mg/kg Q2W dosing regimen is appropriate for the general adult patients with Fabry disease.

(b) (4)

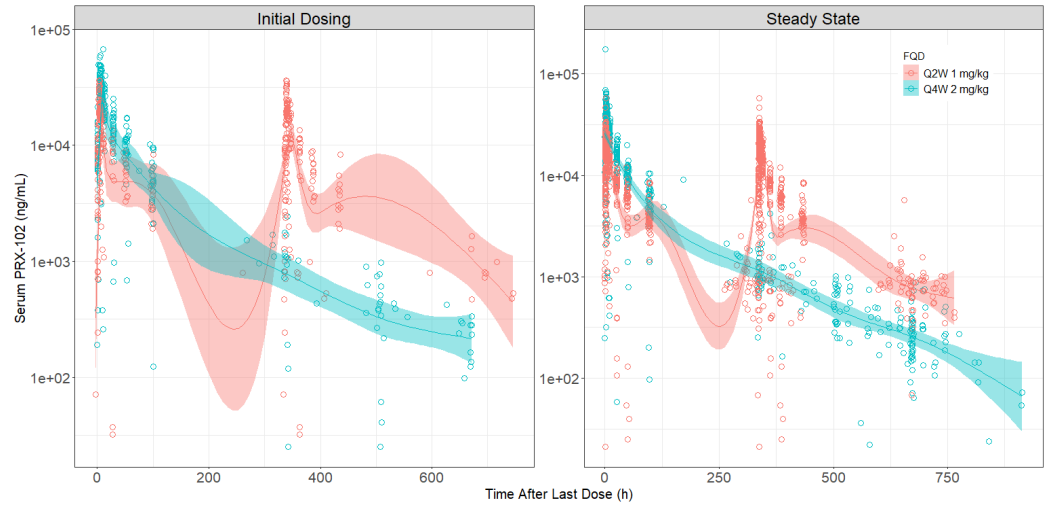
(b) (4)

Figure 3. Predicted Exposure Comparison Between Pegunigalsidase Alfa 1 mg/kg Q2W and 2 mg/kg Q4W Dosing Regimens



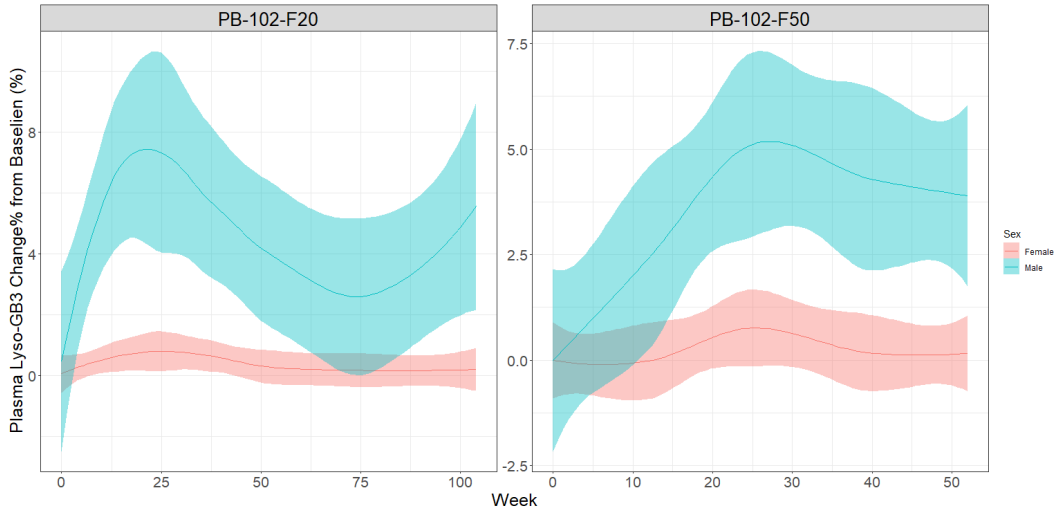
The line is for median prediction and the polygon covers 5th and 95th percentiles of the prediction. ADA negative patients from Studies F20 and F50 were used for simulation. See next figure for the reason why patients from Studies F01/F02 were excluded.
Source: Reviewer's analysis based on PK parameters of ADA negative patients.

Figure 4. Comparison of Observed PK Between 1 mg/kg Q2W (Study PB-102-F20) and 2 mg/kg Q4W (Study PB-102-F50)



The line is for mean prediction and the polygon covers 2.5th and 97.5th of the loess smooth.
Source: Reviewer's analysis

Figure 5 Comparison of Plasma Lyso-Gb3 Change% from Baseline: 1 mg/kg Q2W (Study PB-102-F20) vs 2 mg/kg Q4W (Study PB-102-F50)



Note: The line is for mean prediction and the polygon covers 2.5th and 97.5th of the loess smooth.
Source: *Reviewer's analysis*

Table 11. Summary of Plasma Lyso-Gb3 Levels (Study PB102-F50 and its extension study PB102-F51)

		Plasma Lyso-Gb3 (nM)			Change from baseline	%Change from baseline
		Baseline	**Month 12**	**Month 24**	**Month 24**	**Month 24**
All	N	29	28	25	25	25
	Mean (SD)	19.4 (18.1)	22.2 (19.1)	23.0 (18.6)	3.4 (6.5)	26.5 (35.8)
	Median (range)	14.5 (0.5; 75.1)	19.2 (0.6; 80.8)	20.4 (0.7; 68.2)	1.3 (-9.9; 15.4)	18.5 (-15.8; 127.3)
Male	N	23	22	20	20	20
	Mean (SD)	23.3 (18.3)	27.1 (18.8)	27.30 (18.4)	4.0 (7.1)	29.6 (37.4)
	Median (range)	17.2 (0.5; 17.2)	22.3 (0.6; 80.8)	23.5 (0.7; 68.2)	4.5 (-9.9; 15.4)	22.7 (-15.8; 127.3)
Female	N	6	6	5	5	5
	Mean (SD)	4.4 (2.5)	4.5 (2.7)	5.7 (2.4)	0.7 (1.8)	14.2 (28.7)
	Median (range)	4.4 (0.7; 7.8)	4.2 (0.6; 7.7)	5.4 (3.4; 9.4)	0.5 (-1.2; 3.5)	14.9 (-15.4; 59.3)

Normal range of plasma Lyso-Gb3 is < 2.4 nM.
The conversion factor for plasma Lyso-Gb3 is 1.27, i.e., 1 ng/mL=1.27 nM.
Source of data: Table 14.2.2.1.1, CSR for Study PB-102-F50 and Study PB-102-F51

Dose-/exposure-response for efficacy

Kidney biopsy for Gb3 inclusions in renal peritubular capillaries was performed at baseline in study PB-102-F01/F02 and following a total of 6 months of treatment with pegunigalsidase alfa. The average number of Gb3 inclusions in renal peritubular capillaries was assessed as the primary efficacy endpoint. No clear dose-response relationship was identified when comparing the change from baseline in renal Gb3 inclusions across the three doses (0.2 mg/kg, 1 mg/kg, and 2 mg/kg Q2W), which may be due to the small number of subjects per dose group, confounding factors (e.g., sex), and the lack of randomization in the study design.

See pharmacometrics review in appendix for more details on exposure-response relationships for efficacy and safety.

3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No, an alternative dosing regimen or management strategy is not necessary for subpopulations based on intrinsic factors. The intrinsic factor identified to have an impact on PK of pegunigalsidase alfa was the presence of IgG ADA, which was associated with decreased plasma pegunigalsidase alfa concentrations. However, the currently available data in the BLA do not support a dose adjustment based on a subject's immunogenicity status and dose adjustment based on ADA has not been a general practice for ERT treatments.

3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interaction is unlikely for pegunigalsidase alfa because pegunigalsidase alfa is administered by IV infusion.

Metabolism-mediated or transporter-mediated drug-drug interaction studies have not been studied with pegunigalsidase alfa. The enzyme portion of pegunigalsidase alfa is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous proteins. To our knowledge, cytochrome P450 (CYP) enzymes do not play a considerable role in PEG elimination, although the exact route of elimination of the PEG portion of pegunigalsidase alfa has not been characterized. Direct drug interactions between pegunigalsidase alfa and small molecule drugs that are metabolized by CYP enzymes are unlikely.

3.2.5 What are the immunogenicity incidences and what are the impact of immunogenicity on PK, PD, efficacy, and safety of pegunigalsidase alfa?

Anti-pegunigalsidase alfa IgG antibodies (anti-drug antibodies or ADA) were assessed in all clinical studies with pegunigalsidase alfa treatment. The ADA positive samples were further assessed for ADA titers and neutralizing antibodies (NAb) that inhibit enzyme activity; however, NAb that inhibit cellular uptake of pegunigalsidase alfa have not been assessed. In addition, the positive anti-pegunigalsidase alfa IgG antibody samples were characterized for ADA specific to the enzyme moiety on pegunigalsidase alfa, ADA specific to the PEG moieties on pegunigalsidase alfa, and ADA specific to the plant glycan motifs on pegunigalsidase alfa. In the event of serious hypersensitivity reactions, IgE antibodies were assessed post-event and at screen/baseline retrospectively. For patients who were treated with other ERTs previously, ADA to other ERTs was also assessed at baseline.

Immunogenicity incidences

In study PB-102-F03, ERT-naïve patients from studies PB-102-F01/F02 who received pegunigalsidase alfa treatment at 0.2, 1, or 2 mg/kg Q2W 12 months transitioned to 1 mg/kg Q2W for up to 60 months. Pre-existing anti-pegunigalsidase alfa IgG antibodies were detected

at baseline (at the beginning of studies PB-102-F01/F02) in 11.1% (2/18) of patients, and 31.3% (5/16) patients were IgG ADA positive post-baseline (**Table 12**). Among the patients with positive anti-pegunigalsidase alfa IgG antibodies, antibody specificity was predominantly directed against the non-PEGylated enzyme moiety (anti-BCL) of pegunigalsidase alfa.

Table 12 Immunogenicity Incidences of Anti-pegunigalsidase Alfa Antibodies in Studies PB-102-F01/F02/F03

Antibody % (n/N)	**At Baseline**	**Post-treatment** [d]
IgG ADA	11.1% (2F/18)	31.3% (5M/16)
Treatment emergent	--	31.3% (5/16; 1 boosted+4 induced)
Of those Positive for ADA:	N=2	N=5
Persistent ADA [a]	--	80% (4/5)
NAb	0 (0/2)	60% (3/5)
Anti-enzyme (BCL)	100% (2/2)	80% (4/5)
Anti-Glycan [b]	100% (2/2)	40% (2/5)
Anti-PEG	0% (0/2)	20% (1/5)
IgM ADA	0% (0/18)	0% (0/16)
IgE ADA [c]	1/1 positive	NA [d]

a. Defined as a positive result in the ADA assay remained positive through Month 12, regardless of any missing sample.
b. One was discontinued and 1 became ADA negative during treatment.
c. IgE test was only performed on patients with serious hypersensitivity reactions and available samples.
d. One patients (b) (6) terminated treatment after the first visit and was excluded from post-Baseline assessments (was detected positive for anti-enzyme, anti-glycans IgG, and IgE ADA at the post infusion test).
Source of data: Tables 33 and 34, Immunogenicity Summary.

In study PB-102-F20, patients were previously treated with agalsidase beta and randomly assigned to receive pegunigalsidase alfa treatment (N=52) or agalsidase beta treatment (N=25). At baseline (randomization), pre-existing anti-pegunigalsidase alfa IgG antibodies were detected in 34.6% (20/52) of patients in the pegunigalsidase alfa group before initiating the pegunigalsidase alfa treatment, and 32% (8/25) patients in the agalsidasebeta group were positive for agalsidase beta IgG antibodies (**Table 13**). After 24-month pegunigalsidase treatment, 20 (38.5%) patients were ADA positive to pegunigalsidase alfa.

Table 13 Summary of Antibody Responses and Characteristics (Study PB-102-F20)

	Pegunigalsidase alfa (N=52)		**Agalsidasebeta (N=25)**	
Antibody Specificity [a] % (n/N)	**At Baseline**	**Post-treatment**	**At Baseline**	**Post-treatment** [d]
IgG ADA	34.6% (18/52)	38.5% (20/52)	32% (8/25)	44.4% (11/25)
Treatment emergent	--	11.5% (6/52; 3 boosted+3 induced)	--	20% (5/25; 2 boosted+3 induced)
Of those Positive for ADA:	N=18	N=20	N=8	N=11
NAb	94.4% (17/18)	75% (15/20)	7.5% (7/8)	81.8% (9/11)
Anti-enzyme (BCL)	100% (18 /18)	90% (18/20)	NA	NA

Anti-Glycan	0	0	NA	NA
Anti-PEG	11.1% (2 /18)	15.0% (3/20)	NA	NA
IgE ADA [b]	50% (1/2)	100% (2/2)	66.7% (2/3)	0 (0/2)

a nAb and titer tested only for IgG positive samples; anti-BCL, anti-PEG, anti-plant glycan ant bodies tested only for IgG anti-pegunigalsidase alfa positive samples.
b IgE only performed on patients with serious hypersensitivity reactions and available samples. IgE ADA was tested in both the screening/baseline visit (stored samples) and post event samples; 1 patient treated with pegunigalsidase alfa with hypersensitivity did not have IgE testing conducted; 1 patient treated with agalsidase beta was tested and positive for IgE but did not have a hypersensitivity reaction.
Source of data: Tables 48, 49, 50, Immunogenicity Summary

In addition, sex differences in antibody response were observed in both arms of study F20, i.e., anti-pegunigalsidase alfa antibody incidences were higher in male patients than in female patients (**Table 14**). All patients who had pre-existing ADA (n=18) were male, all patients who had induced ADA (n=3) were female, and all patients who had boosted ADA (n=3) were male.

Table 14 Summary of Antibody Responses by Sex (Study PB-102-F20)

	Pegunigalsidase alfa (N=52)		**Agalsidase beta (N=25)**	
Timepoint % (n/N)	**Male (N=29)**	**Female (N=23)**	**Male (N=18)**	**Female (N=7)**
IgG ADA				
Baseline	62.1% (18/29)	0 (0/23)	44.4% (8/18)	0 (0/7)
Post-Treatment	58.6% (17/29)	13% (3/23)	44.4% (8/18)	42.8% (3/7)

Source of data: Table 14.1.5.1, CSR of study PB-102-F20.

In study PB-102-F50 which evaluated pegunigalsidase alfa 2 mg/kg Q4W in agalsidase beta- or agalsidase alfa- experienced patients (N=30), 10 patients (all males, 33.3%) had pre-existing anti-pegunigalsidase alfa IgG antibodies prior to initiating the pegunigalsidase alfa treatment. All patients with pre-existing anti-pegunigalsidase alfa IgG antibodies had been previously treated with agalsidasebeta and were also positive for antibodies against agalsidase beta (**Table 15**). After pegunigalsidase alfa treatment for up to 12 months, 8 (27.6%) patients (all males) were ADA positive to pegunigalsidase alfa, including 1 patient who was treatment-boosted. Among those 8 ADA-positive patients, 87.5% (7/8) were positive for NAb and anti-BCL ADA and none had antibodies to plant glycans or PEG.

Table 15 Immunogenicity Incidences of Anti-pegunigalsidase alfa in Study PB-102-F50

Antibody Specificity % (n/N)	**At Baseline (N=30)**	**Post-treatment (N=29)**
IgG anti- agalsidase alfa [a]	0 (0/6)	--
IgG anti-agalsidase beta [a]	45.8% (11/24)	--
IgG anti-pegunigalsidase alfa	33.3% (10M/30) [a]	27.6% (8/29) Male 33.3% (8/24) Female 0 (0/5)
Treatment emergent	--	3.4% (1/29; 1 boosted; 0 induced)
Of those positive for IgG anti-pegunigalsidase alfa:	N=10	N=8

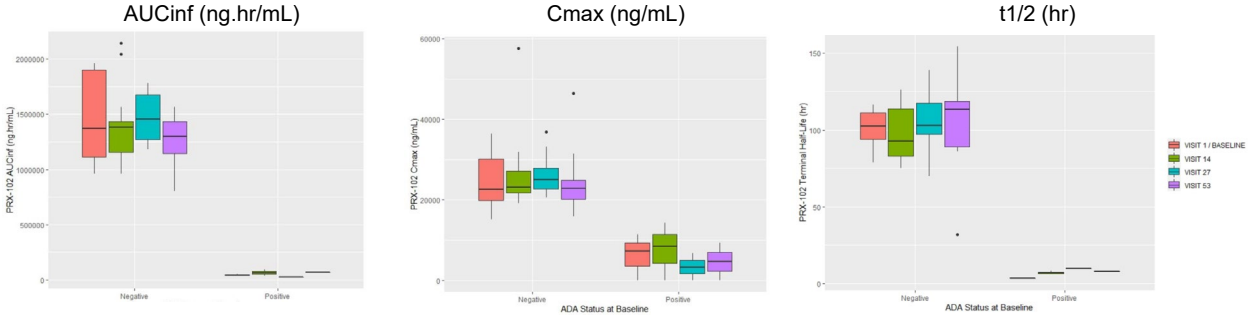
NAb	100% (10/10)	87.5% (7/8)
Anti-enzyme (BCL)	90% (9/10)	87.5% (7/8)
Anti-Glycan	0 (0/10)	0 (0/8)
Anti-PEG	0 (0/10)	0 (0/8)
IgE ADA [b]	4/4 positive	3/4

a. Test results only provided for ERT (agalsidase alfa or agalsidase beta) that patients had last taken prior to their study entry.
b IgE only performed on patients with serious hypersensitivity reactions, therefore prevalence not determined. 4/4 patients had detectable IgE at screening and 3/4 had detectable IgE in the sample collected after the suspected event.
Source of data: Table 77, Immunogenicity summary.

Impact of immunogenicity on PK

In the PB-102-F20 Study, PK were assessed in a subset of pegunigalsidase alfa treated patients (N=17), in which 3 patients (b) (6) were ADA positive (peak titers: (b) (4) at baseline and during the treatment. AUCinf, Cmax, and t1/2 were >18-fold, >3.6-fold, and >13-fold greater, respectively, in the patients who were ADA-negative than those in the patients who were ADA-positive (**Figure 6**).

Figure 6. Comparison of PK Parameters of Pegunigalsidase alfa Between ADA Positive and Negative Patients in Study PB-102-F20



N=2 for ADA positive patients. Patient (b) (6) is not included in the plot because the subject had BLQ values for PRX-102 at all visits (Visits 1, 14, 27 and 53).
Source: Figure 22, Immunogenicity summary

Impact of immunogenicity on PD

In Study PB-102-F20, plasma lyso-Gb3 levels at baseline and post-treatment appeared to be higher in ADA-positive patients compared to ADA negative patients; and this was only observed in male patients (**Table 16**). The one ADA-positive patient who had plasma pegunigalsidase alfa concentrations below the limit of quantification of the assay throughout the study had the highest plasma lyso-Gb3 levels than other patients. For female patients, ADA-positive and ADA-negative patients had similar plasma Lyso-Gb3 levels at baseline and post-treatment.

Table 16 Summary of Plasma Lyso-Gb3 Levels in ADA-Positive and ADA-Negative Patients and by Sex (Study PB-102-F20)

		Male		Female	
		ADA+	**ADA-**	**ADA+**	**ADA-**
		N=18 [a]	N=11 [b]	N=3 [c]	N=20 [b]
Plasma lyso-Gb3					
At Baseline (nM)	Mean (SD)	54.6 (28.6)	17.2 (10.5)	6.8 (2.6)	8.6 (3.3)

	Median (min, max)	51.8 (24.7, 143.9)	20.3 (0.8, 32)	8.1 (3.8, 8.4)	9.2 (2.8, 16.2)
At Month 24 (nM)	Mean (SD)	62.5 (31.0)	23.5 (13.1)	8.0 (3.9)	8.2 (4.6)
	Median (min, max)	66.6 (29, 139.4)	26.1 (3.2, 46.2)	9.5 (3.6, 11.0)	8.2 (2.4, 22.0)
Change from Baseline (nM)	Mean (SD)	6.7 (14.8)	4.7 (6.9)	1.3 (1.56)	0.01 (2.18)
	Median (min, max)	5.8 (-32.2, 32.7)	3.1 (-4.2, 19.5)	1.1 (-0.2, 2.9)	0.1 (-4, 5.8)
%Change from Baseline	Mean (SD)	17 (25)	23 (26)	14.5 (20.6)	-3 (22.3)
	Median (min, max)	13 (-39, 51)	19 (-13%, 73%)	13 (-5.3, 35.8)	-0.4 (-47, 36)

[a] Subjects were ADA-positive at baseline or positive in at least one post-baseline visit (ADA+ at baseline only (N=1), ADA+ at both baseline and post-baseline (N=17)). Lyso-Gb3 results at Month 24 were available in 15 subjects.
[b] Subjects who were ADA-negative at baseline and remained ADA-negative at all post-baseline visit. Lyso-Gb3 results at Month 24 were available in 10 male subjects and 18 female subjects.
[c] Subjects who were ADA-negative at baseline but became ADA-positive in at least one post-treatment (b) (4) (Female), (b) (4) (Female), (b) (4) (Female)), (b) (4)
Note: Normal plasma lyso-Gb3 <2.4 nM.
Source of data: Listing 16.2.2.2, CSR F20; TABLE 14.2.3.1_new2 in IR (dated April 11, 2023)

Impact of immunogenicity on efficacy

The effect of anti-pegunigalsidase alfa antibody responses on efficacy of pegunigalsidase alfa treatment has not been fully characterized. Based on the limited data from 2 ADA-positive patients who had kidney Gb3 score results available in Study PB-102-F01/02, it appeared that ADA had no apparent effect on kidney Gb3 inclusion in ERT-naive patients; however, the ADA effect on kidney Gb3 inclusion is unknown in ERT-experienced patients because the kidney biopsy data were not collected in Study PB-102-F20.

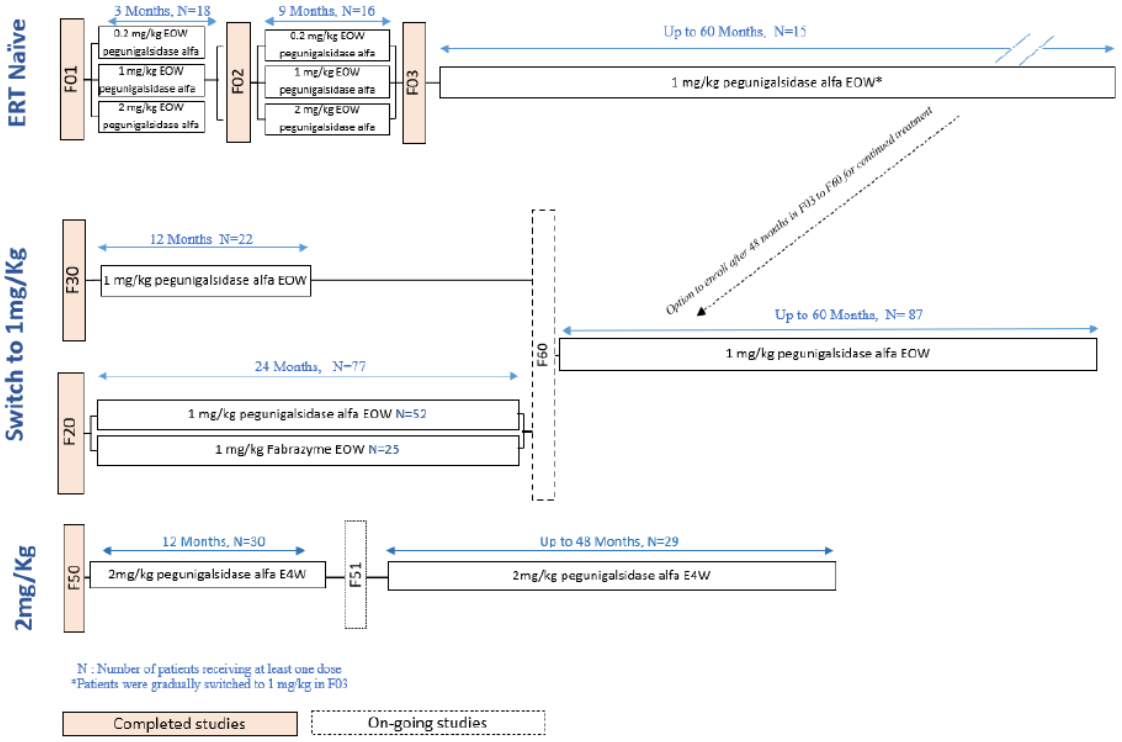
Impact of immunogenicity on safety

The effect of ADA on hypersensitivity reaction of pegunigalsidase alfa treatment has not been fully characterized. In pegunigalsidase alfa clinical trials, 4 patients (1 ERT-naïve and 3 ERT-experienced patients) experienced anaphylaxis during the initial infusion and were IgE ADA positive. Other IARs occurred more frequently in IgG ADA positive patients compared to IgG ADA negative patients.

4 OCP Appendices

The overall clinical studies of pegunigalsidase alfa submitted in the original BLA and BLA resubmission are presented in **Figure 7**. See Multi-Disciplinary Review and Evaluation for the original BLA application (Document ID: 4786588, by SMPOKOU, PATROULA I, dated 04/27/2021) for additional technical data supporting OCP recommendations.

Figure 7. Schematic Presentation of Clinical Development Program



*Overall enrolled patients in PB-102-F60: N=97

Cut-off date for ongoing study PB-102-F51: 08 August 2021; for ongoing study PB-102-F60: 15 July 2021.
EOW: every other week; E4W: every 4 weeks; ERT: Enzyme replacement therapies
Source: Figure 1, Module 2.5 Clinical Overview

4.1 Individual Study Summary

4.1.1 Study PB-102-F20

PB-102-F20 is a randomized (2:1 ratio), double-blind, active control study of the safety and efficacy of pegunigalsidase alfa 1 mg/kg Q2W compared to agalsidase beta in adult patients with Fabry disease. Patients enrolled in this study were previously treated with agalsidase beta for at least 1 year and on a stable dose for at least 6 months prior to screening, with a documented renal decline defined as a linear negative slope of ≤-2 mL/min/1.73 m^2/year based on at least 3 serum creatinine values over approximately one year. A total of 78 patients were randomized (2:1), 77 patients were treated (52 for pegunigalsidase alfa and 25 for agalsidase beta), and 72 patients completed the 24-month treatment period.

Pharmacokinetics

PK of pegunigalsidase alfa was evaluated in a subset of 17 patients (10 females and 7 males) at different treatment times (Day 1, Month 6, Month 12, and Month 24, corresponding to Visits 1, 14, 27 and 53) in study PB-102-F20 following IV infusions of 1 mg/kg Q2W. At each PK assessment, blood samples were collected at pre-infusion, 0.5 and 1 hour after the beginning of infusion, at the end of infusion, and at 0.5, 1, 2, 4, 8, 24, 48, 72, 96 hours and 2 weeks post-infusion. The PK parameters of pegunigalsidase alfa are summarized in **Table 17**.

Table 17. PK Parameters of Pegunigalsidase Alfa in Agalsidase beta-Experienced Patients (Study PB-102-F20)

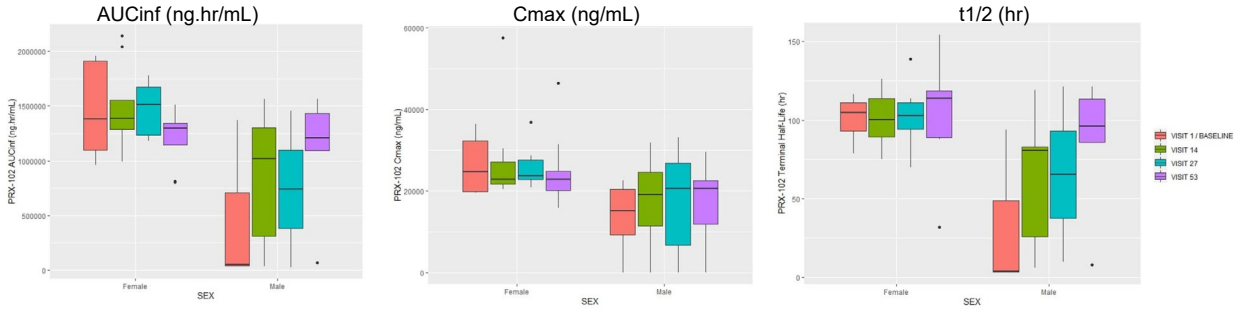
Variable	Unit	Timepoint	N	Mean	SD	CV%	Min	Median	Max	Geometric Mean	Geometric CV%
AUC_{all}	hr*ng/mL	V1 (Baseline)	16	958205.06	623718.78	65.09	0.00	991875.38	1900741.66		
		V14 (Week 26)	16	1019833.87	582557.45	57.12	0.00	1153667.72	2042486.18		
		V27 (Week 52)	14	1073565.30	546993.23	50.95	0.00	1164620.21	1693017.40		
		V53 (Week 104)	15	971985.69	424614.16	43.69	10.50	1106343.84	1410917.43	423462.67	9613.58
AUC_{last}	hr*ng/mL	V1 (Baseline)	15	1022030.51	589044.04	57.63	36828.10	992156.10	1900741.66	699481.07	182.24
		V14 (Week 26)	15	1087720.06	533477.24	49.05	35561.12	1208603.10	2042486.18	800342.98	157.05
		V27 (Week 52)	13	1156046.45	470051.43	40.66	26298.30	1223284.06	1693017.40	896764.31	152.96
		V53 (Week 104)	15	971775.39	425092.20	43.74	5.25	1106343.84	1410917.43	403139.38	16607.15
C_{last}	ng/mL	V1 (Baseline)	15	1108.00	1015.78	91.68	32.00	799.00	4040.00	654.30	223.12
		V14 (Week 26)	15	1167.60	1999.78	171.27	25.00	732.00	8270.00	555.92	234.35
		V27 (Week 52)	13	2036.85	2117.45	103.96	54.00	910.00	5730.00	1171.44	190.01
		V53 (Week 104)	15	881.73	866.38	98.26	21.00	721.00	3770.00	575.14	168.60
C_{max}	ng/mL	V1 (Baseline)	16	21163.75	9862.25	46.60	0.00	20400.00	36500.00		
		V14 (Week 26)	16	23314.38	12129.15	52.02	0.00	22650.00	57600.00		
		V27 (Week 52)	14	22860.71	9526.44	41.67	0.00	23700.00	36800.00		
		V53 (Week 104)	15	21918.73	10200.54	46.54	21.00	22300.00	46400.00	13923.68	524.79
T_{last}	hours	V1 (Baseline)	15	259.39	144.62	55.75	26.92	335.55	409.75	193.42	122.86
		V14 (Week 26)	15	292.37	121.74	41.64	50.45	336.28	411.12	247.35	82.34
		V27 (Week 52)	13	276.17	119.01	43.09	47.30	319.50	407.83	236.51	76.29
		V53 (Week 104)	15	289.58	130.49	45.06	1.50	335.73	407.22	195.24	275.91
T_{max}	hours	V1 (Baseline)	16	3.18	0.93	29.13	0.00	3.24	4.00		
		V14 (Week 26)	16	2.10	1.14	54.11	0.00	2.00	5.50		
		V27 (Week 52)	14	1.74	0.84	48.26	0.00	1.52	3.58		
		V53 (Week 104)	15	1.82	0.57	31.45	1.50	1.57	3.60	1.76	25.53

AUClast = Area under the concentration-time curve from time zero to last measurable concentration; Clast = last measurable concentration; Cmax = maximum observed drug concentration; CV = coefficient of variation; max = maximum; min = minimum; N = number of patients; SD = standard deviation; Tlast = time to last measurable concentration; Tmax = time to maximum concentration; V = Visit.

Source: Table 24, Summary of Clinical pharmacology studies.

The AUC, Cmax, and half-life values of pegunigalsidase alfa by sex and study visits are shown in **Figure 8**. The results showed that males had lower AUC and shorter terminal half-lives than females at earlier visits (baseline, visit 14, and visit 27). There was a trend of increasing AUC and half-lives in males from baseline to Visit 53, and the AUC between males and females appeared to be similar at Visit 53. Of note, 3 ADA positive patients [redacted] (b) (6) in study F20 were all males and lower drug concentrations (BLQ for patient [redacted] (b) (6) were observed in these 3 patients.

Figure 8. AUC, Cmax, and Half-Life of Pegunigalsidase Alfa by Sex and Study Visit



Source: Figures 11-6, 11-7, 11-8, PB-102-F20 PK Report.

Pharmacodynamics

Plasma Lyso-Gb3 levels were measured at Baseline, Month 1.5 (Visit 4), every 3 months up to 12 months, and then every 6 months up to 24 months (104 weeks). At baseline, the mean plasma lyso-Gb3 concentrations were 26 nM and 32 nM in the pegunigalsidase alfa and agalsidase beta treatment groups, respectively (**Table 18**). At Week 104, a 10% increase of percent
change from baseline was observed in the pegunigalsidase alfa treatment group compared to a 13% increase from baseline in the agalsidase beta group.

Table 18 Plasma Lyso-Gb3 Concentrations in Patients with Fabry Disease Following Treatment with PRX-102 or Agalsidase beta (Study PB-102-F20)

	Pegunigalsidase alfa N=52	Fabrazyme N=25
Plasma Lyso-Gb3 Concentration (nM)		
Baseline		
n	52	25
Mean (SE)	26.22 (3.78)	32.14 (7.08)
Change from Baseline at Week 104 (nM)		
n	46	22
Mean (SE)	3.30 (1.38)	-8.74 (4.85)
Percent Change From Baseline At Week 104		
Mean (SE)	10.34 (3.80)	-12.69 (4.60)

Fabrazyme (agalsidase beta)

Source: Table 14, Clinical Pharmacology summary

Immunogenicity

Incidences of pre-existing ADA at baseline and post-treatment ADA through Week 104 are summarized in **Table 19**. All the patients with pre-existing ADA were males for both groups. For the PRX-102 group, most patients maintained the same ADA status at baseline and post-treatment, except for one male patient who had pre-existing ADA became ADA negative post-treatment and 3 female patients who were ADA negative at baseline became ADA positive.

Table 19 ADA Incidences in Study PB-102-F20

Treated	Pegunigalsidase alfa N=52	Fabrazyme N=25
Positive IgG ADA at one or more time points post-treatment [a]	20 (38.5%)	11 (44.0%)
Treatment emergent ADA:	**6 (11.5%)**	**5 (20.0%)**
Titer boosted response	3 (50%)	2 (40%)
Induced response	3 (50%) (2 Transient + 1 Persistent)	3 (60%) (3 Transient)
Positive for ADA at baseline:	**18 (34.6%)**	**8 (32.0%)**
Negative for ADA at baseline	**34 (65.4%)**	**17 (68.0%)**
Positive at baseline and Positive in at least one post-baseline visit	17 (94.4%)	8 (100.0%)
Positive at baseline and remained Negative all post-baseline visits	1 (5.6%)	0
Negative at baseline and became Positive in at least one post-baseline visit	3 (8.8%)	3 (17.6%)
Negative at baseline and remained Negative all post-baseline visits	31 (91.2%)	14 (82.4%)

Source: Table 48, Immunogenicity summary

Sex differences in ADA incidences were observed in both treatment groups (**Table 14**). All patients who had treatment-induced ADA (n=3 pegunigalsidase alfa and n=3 agalsidase beta) were females and all patients who had boosted antibody response (n=3 pegunigalsidase alfa and n=2 agalsidase beta) were males. In the female patients who had treatment-induced ADA, the titers were generally low (with the peak titer ranging from 180 to 1778 for the PRX-102 arm) and ADA appeared to be transient with 4 females (2 in each treatment arm) showing positive ADA at a single time point and 2 females (1 in each treatment arm) showing positive ADA at two time points.

Impact of Immunogenicity

In the PB-102-F20 Study, PK were assessed in a subset of pegunigalsidase alfa treated patients (N=17), in which 3 patients (b) (6) were ADA positive (peak titers: (b) (6) at baseline and during the treatment. AUCinf, Cmax, and t1/2 were >18-fold, >3.6-fold, and >13-fold greater, respectively, in the patients who were ADA-negative than those in the patients who were ADA-positive (**Figure 6**).

Overall, mean plasma Lyso-Gb3 levels at baseline and post-treatment were higher in ADA-positive patients than in ADA-negative patients for both treatment groups (**Table 20**). The ADA effect on plasma Lyso-Gb3 for the PRX-102 treatment group was only observed in male patients, not in female patients (**Table 16**). For female patients, ADA-positive and ADA-negative patients had similar plasma Lyso-Gb3 levels at baseline and post-treatment. For male patients, the mean plasma Lyso-Gb3 levels were higher in ADA positive patients (N=17) than in ADA negative patients (N=11). In addition, among the male ADA positive patients, there was a trend of higher Lyso-Gb3 levels in patients with higher ADA titer (**Table 21**). Of note, the 3 ADA+

patients in the PK subset of this study had higher plasma Lyso-Gb3 levels and low drug concentrations; one patient who had plasma concentrations below the limit of quantification of the assay had the highest plasma Lyso-Gb3 levels.

Table 20 Summary of Plasma Lys-Gb3 by ADA Status a (Study PB-102-F20)

	Pegunigalsidase alfa		Fabrazyme	
ADA Status	**Negative**	**Positive**	**Negative**	**Positive**
# of Patients (n)	**34**	**18**	**17**	**8**
Mean (SE) Baseline Plasma Lyso-Gb3 concentration (nM) [Min; Max]	11.20 (1.30) [0.8; 32.0]	54.59 (6.73) [24.7; 143.9]	14.59 (2.53) [2.1; 38.3]	69.44 (14.60) [17.6; 142.0]
# of Patients (n), W104	31	15	16	6
Mean (SE) Week 104 Plasma Lyso-Gb3 concentration (nM) [Min; Max]	13.14 (1.94) [2.4; 46.2]	62.45 (8.01) [29.0; 139.4]	12.67 (2.14) [1.5; 30.5]	38.25 (8.24) [16.7; 71.2]
Mean (SE) change from baseline nM	1.65 (0.84) [-4.2; 19.5]	6.69 (3.81) [-32.2; 32.7]	-1.54 (0.90) [-14.0; 2.4]	-27.93 (15.94) [-102.3; -0.9]
Mean (SE) % change from Baseline [Min; Max] to Week 104	7.20 (4.64) [-47.2; 73.0]	16.83 (6.51) [-38.5; 51.0]	-6.71 (4.29) [-36.6; 22.5]	-28.62 (10.45) [-72.0; -5.1]

a ADA status at baseline
Source: Table 53, Immunogenicity summary

Table 21 Summary of Plasma Lyso-Gb3 by ADA Titer Category (Study PB-102-F20)

	ADA+ Male			ADA+ Female		
	Low titer	**Medium titer**	**High titer**	**Low titer**	**Medium titer**	**High titer**
	N=4	N=9	N=3	N=2	N=1	N=0
At Baseline (nM)	38.8 (9.9)	49.1 (22.6)	77.1 (37.7)	6.0 (3.0)	8.4	-
At Month 24 (nM)	30.9 (2.7)	55.2 (21.5)	94.5 (32.6)	7.3 (5.2)	9.5	-
Change from Baseline (nM)	0.25 (7.9)	6.1 (15.6)	11.3 (16.0)	1.4 (2.2)	1.1	-
%Change from Baseline	3 (26)	19 (28)	19 (24)	15 (29)	13	-

Plasma lyso-Gb3 levels are reported as mean (SD).
Titer categorization is based on the highest titer level on/after Baseline. Values lower than the 25% Quartile (900) are categorized as low. Values higher than the 75% Quartile (20900) are categorized as high. Values between these limits are categorized as medium.
Source of data: Table 14.2.3.1_new4 in IR response (dated April 11, 2023)

Overall, ADA did not show significant effect on eGFR slope. At baseline and following 104-week treatment, the eGFR slopes were comparable in ADA positive patients and ADA negative patients (**Table 22**). Additional analyses by sex showed that there was no clear ADA effect on eGFR slope in female patients, while the male ADA- patients had a more negative slope than ADA+ patients after the 104-week treatment (**Table 23**). Among the ADA+ patients, there was no clear trend of ADA effect by ADA titer (**Table 24**). The overall data indicate that eGFR may not be a sensitive endpoint for the assessment of immunogenicity impact on efficacy, considering the significant ADA effect on PK and PD (e.g., lyso-Gb3).

Table 22 Summary of eGFR by ADA Status (Study PB-102-F20)

ADA Status	Pegunigalsidase alfa		Fabrazyme	
	Negative	Positive	Negative	Positive
# of Patients (n)	34	18	17	8
Mean (SE) Baseline eGFR mL/min/1.73 m^2 [Min; Max]	72.51 (3.42) [35.4; 125.9]	75.25 (4.99) [30.2; 113.7]	77.26 (5.33) [34.1; 107.6]	67.59 (6.44) [45.7; 105.0]
Mean (SE) eGFR Slope at Baseline (mL/min/1.73 m^2/year)	-7.81 (1.13)	-8.45 (1.59)	-8.75 (0.92)	-7.18 (1.86)
N (number of patients) W104	31	16	16	8
Mean (SE) Week 104 eGFR mL/min/1.73 m^2 [Min; Max]	72.16 (3.83) [27.6; 113.7]	67.38 (5.79) [29.2; 112.6]	76.11 (6.22) [24.4; 114.8]	63.94 (6.07) [48.8; 99.5]
eGFR median slope (95% CI)	-2.22 (-4.020; -0.428)	-2.51 (-5.280; 0.252)	-2.16 (-4.055; -0.255)	-2.16 (-6.251; 1.933)
Mean (SE) eGFR change from Baseline to Week 104; mL/min/1.73 m^2 [Min; Max]	-1.05 (1.70) [-20.0; 21.8]	-8.54 (2.96) [-36.9; 7.9]	-1.13 (2.08) [-18.0; 16.8]	-3.65 (1.88) [-11.7; 3.2]
Median (Min; Max) eGFR change from Baseline to Week 104; mL/min/1.73 m^2	-1.79 [-20.0, 21.8]	-5.87 [-36.9, 7.9]	-2.34 [-18.0, 16.8]	-3.2 [-11.7, 3.2]

[a] ADA status at baseline

Source: Table 54, Immunogenicity summary

Table 23 Summary of eGFR Slope by Sex in ADA Positive and Negative Patients (Study PB-102-F20)

		Male		Female	
		ADA+	ADA-	ADA+	ADA-
		N=18	N=11	N=3	N=20
eGFR slope (mL/min/1.73 m^2/year) [a]					
	Mean (SD)	-2.8 (6.18)	-6.8 (13.7)	-0.25 (2.8)	0.1 (7.6)
	Median (min, max)	-2.5 (-16.2, 6.5)	-4.1 (-45, 10)	0.95 (-3.4, 1.7)	-1.3 (-6.3, 29.0)

[a] The individual annualized mean change (slope) in eGFR are estimated for each patient with at least 4 eGFR observations using a linear regression model and excluding any eGFR values measured during an AKI episode.

Source of data: Table 14.2.1.1.1_new3 in IR response (dated April 11, 2023)

Table 24 Summary of eGFR Slope by ADA Titer Category (Study PB-102-F20)

	ADA+ Male			ADA+ Female		
eGFR slope (mL/min/1.73 m^2/year)	Low titer	Medium titer	High titer	Low titer	Medium titer	High titer
	N=3	N=9	N=5	N=2	N=1	N=0
Mean (SD)	0.5 (4.8)	-3.7 (5.5)	-3.2 (8.4)	1.3 (0.6)	-3.4	-
Median (min, max)	-1.8 (-2.7, 6.0)	-4.0 (-16, 2.7)	-2.5 (-16.2, 6.5)	-	-	-

Titer categorization is based on the highest titer level on/after Baseline. Values lower than the 25% Quartile (900) are categorized as low. Values higher than the 75% Quartile (20900) are categorized as high. Values between these limits are categorized as medium.

Source of data: Table 14.2.1.1.1_new8 in IR response (dated April 11, 2023)

Treatment related mild or moderate TEAEs, serious TEAEs, and infusion-related reactions (IRR) within 2h of infusion were more frequently reported in ADA positive patients than in ADA negative patients, which were more frequently reported in the ADA positive agalsidase beta arm than in the ADA positive pegunigalsidase alfa arm (**Table 25**, **Table 26**, and **Table 27**).

Table 25 Summary of TEAE, Related TEAE, and 2h-IRR by ADA Status (Study PB-102-F20)

	Pegunigalsidase Alfa		Agalsidase beta	
	ADA-	**ADA+**	**ADA-**	**ADA+**
n (%)	N=34	N=18	N=17	N=8
Any TEAE	31 (91.2%)	16 (88.9%)	16 (94.1%)	8 (100.0%)
Serious TEAEs	4 (11.8%)	4 (22.2%)	3 (17.6%)	3 (37.5%)
Related Serious TEAEs leading to withdrawal	1 (2.9%)	1 (5.6%)	0	0
Treatment related mild/ moderate TEAEs	10 (29.4%)	11 (61.1%)	4 (23.5%)	7 (87.5%)
2h-IRR	5 (14.7%)	6 (33.3%)	2 (11.8%)	4 (50.0%)

ADA status at baseline

2h-IRR are those TEAEs which occurred during the infusion or within 2 hours after the completion of the infusion and causality was assessed as definitely, probably, or possibly related.

Source of data: Tables 57 and 59, Immunogenicity summary.

Table 26 TEAE and Related TEAE in ADA-Positive and ADA-Negative Patients (Study PB-102-F20)

	PRX-102 ADA Status		Agalsidase beta ADA Status	
	Negative N=34	Positive N=18	Negative N=17	Positive N=8
All adverse events				
Number of any TEAE (rate) [a]	382 (589.96)	179 (538.10)	218 (651.22)	188 (1158.5)
Number of subjects with any TEAE (n (%))	31 (91.2%)	16 (88.9%)	16 (94.1%)	8 (100.0%)
Number of severe[2] TEAEs (rate) [a]	15 (23.17)	11 (33.07)	12 (35.85)	7 (43.14)
Number of subjects with severe [b] TEAEs (n (%))	10 (29.4%)	5 (27.8%)	5 (29.4%)	2 (25.0%)
Number of serious TEAEs (rate) [a]	5 (7.72)	9 (27.06)	6 (17.92)	5 (30.81)
Number of subjects with serious TEAEs (n (%))	4 (11.8%)	4 (22.2%)	3 (17.6%)	3 (37.5%)
Related [c] adverse events only				
Number of related TEAEs (rate) [a]	13 (20.08)	29 (87.18)	28 (83.64)	48 (295.80)
Number of subjects with related TEAEs (n (%))	10 (29.4%)	11 (61.1%)	4 (23.5%)	7 (87.5%)
Number of related severe [b] TEAEs (rate) [b]	0	2 (6.01)	0	1 (6.16)
Number of subjects with related severe [b] TEAEs (n (%))	0	2 (11.1%)	0	1 (12.5%)
Number of related serious TEAEs (rate) [a]	0	1 (3.01)	0	0
Number of subjects with related serious TEAEs (n (%))	0	1 (5.6%)	0	0
Number of TEAEs Leading to Withdrawal (rate)	1 (1.54)	1 (3.01)	0	0
Number of Subjects with TEAEs Leading to Withdrawal (n (%))	1 (2.9%)	1 (5.6%)	0	0
Number of Related TEAEs Leading to Withdrawal (rate)	0	1 (3.01)	0	0
Number of Subjects with Related TEAEs Leading to Withdrawal (n (%))	0	1 (5.6%)	0	0

a Rate is calculated as the adjusted number of events per 100 years of exposure.
b Events classified as "Very Severe" per CTCAE severity in the eCRF are included in the category "Severe".
c A TEAE was defined as related if was reported as poss bly, probably, or definitely related to study drug.
Source: Table 57, Immunogenicity summary.

Table 27 Summary of IRR by ADA Status at 2 Hours Post-Infusion (Study PB-102-F20)

IRR Information	Pegunigalsidase alfa (N=52)		Fabrazyme (N=25)	
	Positive (N=18)	Negative (N=34)	Positive (N=8)	Negative (N=17)
Total # of IRRs (2h) (rate)	8 (0.9)	5 (0.3)	32 (7.5)	19 (2.2)
# of patients-2h, n (%)	6 (33.3%)	5 (14.7%)	4 (50.0%)	2 (11.8%)
# (rate) of Severe IRRs (2h)	1 (0.1)	0	0	0

IRR-2H are those TEAEs which occurred during the infusion or within 2 hours after the completion of the infusion and causality was assessed as definitely, probably, or possibly related. Rate is presented as number of IRR per 100 infusions.
Source: Table 59, Immunogenicity summary.

4.1.2 Study PB-102-F50

Study PB-102-F50 was an open-label study to assess the safety, efficacy and PK of PRX-102 2 mg/kg Q4W for 12 months in adult patients with Fabry disease who were previously treated with agalsidase beta (Fabrazyme) or agalsidase alfa (Replagal) for at least 3 years and have been on a stable dose for at least 6 months. A total of 30 patients were enrolled in this study, including 6 female patients (~20%).

Pharmacokinetics

PK of pegunigalsidase alfa following 2 mg/kg Q4W were generally consistent across visits throughout the study, but with Cmax lower at Visit 1 compared to other visits, which was due to longer infusion duration for Visit 1 than the subsequent visits for tolerability consideration during the study (**Table 28**). At the end of each dosing interval (i.e., 4 weeks post-dose) for each visits (Day 1, Weeks 24, 40 and 52), the mean plasma concentrations of pegunigalsidase alfa were above the LLOQ of 19.50 ng/mL and ranged from 167.0 to 301.5 ng/mL (**Table 29**).

Table 28 PK Parameters for Pegunigalsidase alfa Following 2 mg/kg Q4W by Visit (Study PB-102-F50)

Parameter (Unit)	Timepoint	N	Mean (SD)	CV%	Median (min; max)	Geometric Mean (95% CI)	Geometric CV%
C_{max} (ng/mL)	V1 (Baseline)	30	35876.7 (11942.2)	33.3	35600.0 (4900.0; 67400.0)	33303.3 (28112.5; 39451.8)	47.8
	V7 (Week 24)	11	43315.3 (20001.4)	46.2	39300.0 (168.0; 68800.0)	27388.5 (8650.5; 86715.3)	423.9
	V11 (Week 40)	14	36318.6 (17847.7)	49.1	37700.0 (5360.0; 66000.0)	29871.6 (19133.7; 46635.7)	90.2
	V14 (Week 52)	28	46829.6 (27865.0)	59.5	45350.0 (6830.0; 174400.0)	41406.2 (33837.6; 50667.7)	55.8
$AUC_{0\text{-}last}$ (hr*ng/mL)	V1 (Baseline)	30	1757492.0 (810170.7)	46.1	1817967.1 (20378.8; 3508022.6)	1376958.3 (947396.7; 2001288.6)	131.4
	V7 (Week 24)	10	2178927.4 (463071.4)	21.3	2208980.2 (1519383.1; 3030050.6)	2135548.7 (1835927.6; 2484067.7)	21.4
	V11 (Week 40)	14	1647842.1 (1049327.8)	63.7	1883745.4 (15750.2; 3222938.8)	855684.4 (308363.2; 2374459.5)	466.4
	V14 (Week 52)	28	1990784.0 (908259.3)	45.6	2015247.0 (32698.4; 3417922.3)	1484761.4 (967082.8; 2279553.1)	154.8
T_{max} (hours)	V1 (Baseline)	30	5.4 (2.2)	40.2	4.6 (1.5; 14.1)	5.1 (4.4; 5.8)	36.9
	V7 (Week 24)	11	2.2 (1.1)	50.4	2.0 (0.0; 4.0)	NC	NC
	V11 (Week 40)	14	2.8 (1.4)	50.6	2.2 (1.0; 6.0)	2.5 (1.9; 3.4)	51.6
	V14 (Week 52)	28	2.6 (2.1)	81.2	2.0 (1.0; 12.9)	2.3 (1.9; 2.7)	46.1
$t_{1/2}$ (hours)	V1 (Baseline)	30	100.1 (58.3)	58.2	112.4 (1.1; 212.9)	68.0 (43.3; 106.7)	181.3
	V7 (Week 24)	10	132.7 (28.0)	21.1	136.1 (92.9; 185.8)	130.0 (111.5; 151.5)	21.7
	V11 (Week 40)	13	106.1 (78.3)	73.8	109.0 (2.1; 290.5)	57.7 (22.3; 149.2)	328.9
	V14 (Week 52)	26	133.7 (47.8)	35.7	142.5 (3.9; 203.1)	111.5 (78.7; 157.9)	104.9
CL (mL/hr)	V1 (Baseline)	30	290.9 (868.6)	298.6	84.0 (41.3; 4807.8)	112.6 (78.6; 161.3)	78.6
	V7 (Week 24)	10	77.1 (19.1)	24.8	71.5 (53.4; 113.9)	75.1 (63.3; 89.0)	63.3
	V11 (Week 40)	13	854.7 (1757.3)	205.6	86.5 (51.4; 4869.9)	165.2 (60.9; 447.8)	60.9
	V14 (Week 52)	26	217.0 (595.1)	274.2	76.5 (33.4; 3028.2)	88.1 (60.5; 128.1)	60.5
V_z (mL)	V1 (Baseline)	30	12540.3 (6521.1)	52.0	11187.2 (4219.4; 32523.1)	11044.9 (9103.3; 13400.5)	55.4
	V7 (Week 24)	10	14622.3 (4508.6)	30.8	13477.8 (9924.2; 24177.9)	14081.7 (11517.3; 17217.0)	28.7
	V11 (Week 40)	13	14922.1 (6207.0)	41.6	13612.2 (6605.6; 26411.6)	13751.2 (10627.5; 17793.0)	44.7
	V14 (Week 52)	26	15103.0 (5007.9)	33.2	16110.9 (5153.3; 23562.0)	14169.4 (12127.0; 16555.7)	40.0

Source: Table 25, Summary of Clinical Pharmacology

Table 29 Mean Plasma Concentrations of Pegunigalsidase alfa Over Time by Visit (Study PB-102-F50)

	Visit 1 / Baseline			Visit 7 / Week 24			Visit 11 / Week 40			Visit 14 / Week 52		
Time (Hour)	Mean	CV%	N	Mean	CV%	N	Mean	CV%	N	Mean	CV%	N
Pre-dose	6.4	547.7	30	1158.0	274.0	11	247.1	116.5	15	239.7	69.8	28
1-hour PSOI	10266.9	85.7	30	24783.0	69.7	10	19307.9	48.6	14	25888.6	116.4	28
0.02	34620.0	29.6	30	46666.7	26.1	9	38275.7	41.4	14	41526.1	29.4	28
1	31183.3	35.3	30	36680.0	23.8	10	28665.3	55.4	15	33256.7	29.8	27
2	27496.7	31.6	30	31920.0	20.9	10	28200.0	47.5	14	30885.2	29.4	27
4	25416.0	27.9	30	27430.0	22.6	10	23427.6	56.3	10	26145.4	29.2	28
8	23548.3	53.1	24	23100.0	26.4	10	20471.4	52.2	13	23378.4	36.5	27
24	13668.7	40.2	27	14049.0	30.3	10	13791.7	52.3	12	14561.8	36.2	26
48	8921.0	48.8	30	9571.0	33.4	10	8707.0	66.5	10	8495.8	45.4	24
96	4922.5	55.2	29	5905.0	30.6	10	4649.8	57.3	14	5653.0	50.0	27
336	834.4	80.5	28	1454.3	70.6	10	792.9	77.2	12	1142.0	57.3	27
504	342.3	86.1	27	564.3	39.4	10	371.9	85.6	13	534.4	55.8	24
672	167.0	88.0	29	230.7	47.6	10	193.2	76.9	13	301.5	80.6	27

Source: Table 17, Summary of Clinical Pharmacology Studies

Pharmacodynamics

After the 52-Week treatment, plasma Lyso-Gb3 concentrations were increased slightly with a greater increase observed in male patients compared to female patients (**Table 30**).

Table 30 Summary of Plasma Lyso-Gb3 Concentrations by Sex and Overall (Study PB-102-F50)

		Male Patients N=23	Female Patients N=6	Overall N=29
Baseline	n	23	6	29
Absolute value (ng/mL)	Mean (SE)	23.27 (3.82)	4.35 (1.00)	19.36 (3.35)
	Median (min; max)	17.20 (0.5; 75.1)	4.40 (0.7; 7.8)	14.50 (0.5; 75.1)
Week 12 (Visit 4)	n	23	6	29
Change from Baseline (ng/mL)	Mean (SE)	2.42 (0.84)	-0.02 (0.23)	1.92 (0.69)
	Median (min; max)	1.60 (-4.3; 13.2)	-0.15 (-0.6; 0.7)	0.80 (-4.3; 13.2)
Week 24 (Visit 7)	n	23	6	29
Change from Baseline (ng/mL)	Mean (SE)	5.03 (1.54)	0.75 (0.76)	4.14 (1.27)
	Median (min; max)	3.60 (-3.6; 31.0)	0.15 (-0.5; 4.5)	2.30 (-3.6; 31.0)
Week 40 (Visit 11)	n	23	6	29
Change from Baseline (ng/mL)	Mean (SE)	4.28 (1.28)	0.17 (0.44)	3.43 (1.06)
	Median (min; max)	4.00 (-9.7; 17.3)	-0.05 (-1.0; 2.2)	2.20 (-9.7; 17.3)
Week 52 (Visit 14)	n	22	6	28
Change from Baseline (ng/mL)	Mean (SE)	3.79 (1.14)	0.17 (0.34)	3.01 (0.94)
	Median (min; max)	5.05 (-9.9; 12.0)	-0.10 (-0.4; 1.8)	2.65 (-9.9; 12.0)

Source: Table 18, Summary of Clinical Pharmacology Studies

Immunogenicity

At baseline, pre-existing antibodies were detected in 33.3% (10/30) of patients; all the 10 ADA positive patients were males and were previously treated with agalsidase beta (**Table 31**). During the 12 months of treatment, 27.6% (8/29) of patients were ADA positive to pegunigalsidase alfa; all these 8 ADA positive patients had pre-existing antibodies at baseline and 1 of 8 had a treatment boosted response; 1 patient with pre-existing antibodies became negative. No new patients became ADA positive. Most of the ADA positive patients at baseline or post-treatment were positive for NAbs and to the enzyme moiety (BCL) of pegunigalsidase alfa; none were positive for antibodies to the PEG or plant glycan moieties.

Table 31 Summary of Antibodies to Pegunigalsidase alfa (Study PB-102-F50)

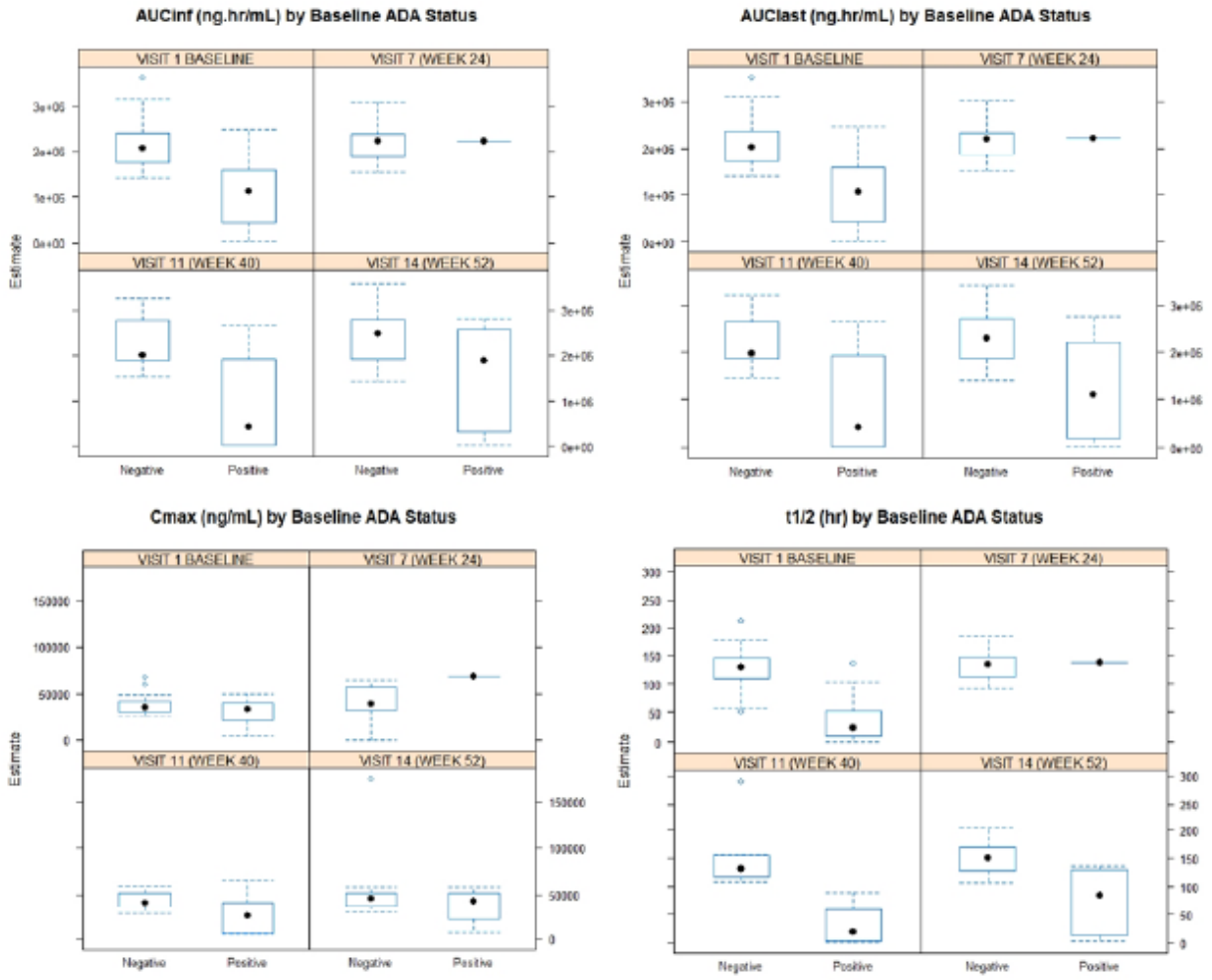
Antibody and Immune Response Characterization [a]	Baseline Prevalence	Post-Treatment Prevalence	Post-Treatment Incidence	Last Visit Prevalence
	(# Positive/ #Evaluable Patients)			
IgG anti-pegunigalsidase alfa	33.3% (10/30)	27.6% (8/29)	3.4% (1/29)	20.7% (6/29)
Titers min-max (median)	<60 – 17482 (1852)	<60 – 30578 (4418)		--
Anti-enzyme moiety (BCL)	30.0% (9/30)	24.1% (7/29)	3.4% (1/29)	20.7% (6/29)
Anti-PEG moieties	0% (0/30)	0% (0/29)	0% (0/29)	0% (0/29)
Anti-plant glycan moieties	0% (0/30)	0% (0/29)	0% (0/29)	0% (0/29)
Neutralizing (anti-pegunigalsidase alfa)	33.3% (10/30)	24.1% (7/29)	3.4% (1/29)	13.8% (4/29)
IgE anti-pegunigalsidase alfa [a]	NA (4/4)	NA (3/4)	NA	NA
Transient (seroreverted) responses (negative at last time point) [b]	3/9 (33.3%)			
Duration of "immune tolerance periods"	3-12 M			

a IgE only performed on patients with suspected hypersensitivity reactions, therefore prevalence not determined. 4/4 patients had detectable IgE at screening and 3/4 had detectable IgE in the sample collected after the suspected event.
b Based on 9 baseline positive patients that completed study.
Source: Table 77, Immunogenicity summary

Impact of Immunogenicity

Anti-pegunigalsidase alfa antibodies affected the PK of pegunigalsidase alfa. In the ADA positive patient group, mean AUC and $t_{1/2}$ from baseline through Week 52 were lower than the respective values of the ADA-negative group (**Figure 9**). In addition, patients who had the higher ADA titers were associated with lower AUC and Cmax values.

Figure 9 PK Parameters (AUC, Cmax, and $t_{1/2}$) by ADA Status at Each Study Visit (Study PB-102-F50)



ADA status at baseline
Source: Figure 24, Immunogenicity summary

ADA-positive patients had higher plasma lyso-Gb3 concentrations at baseline and post-treatment than ADA-negative patients (**Table 32**). The highest plasma lyso-Gb3 levels were observed in the ADA-positive patients [redacted] (b) (6) (87.3 nM and 88.8 nM, respectively at Week 24), and both patients had pre-existing ADA and high ADA titers (ranging from 6363 to 10410 and 7629 to 16647, respectively) throughout the study.

Patients who were ADA-positive at baseline had lower negative mean annualized eGFR slope post-switch (i.e., more pronounced decrease in eGFR over the course of the study) compared to ADA negative patients (**Table 33**).

The most frequent treatment-related AEs associated with antibody positive status were IRR (**Table 34**). IRR were observed in 4 ADA positive patients and 1 ADA negative patient, all rated as moderate or mild.

Table 32 Plasma Lyso-Gb3 by ADA Status (Study PB-102-F50)

Plasma Lyso-Gb3 (nM)		ADA Status	
		Negative (N = 20)	Positive (N = 9)
Baseline	N	20	9
	Mean (SE)	12.26 (2.42)	35.13 (7.12)
	SD	10.83	21.36
	Median (Min; Max)	9.25 (0.5; 39)	29 (13.8; 75.1)
Visit 4 (Week 12)	N	20	9
	Mean (SE)	13.15 (2.33)	39.32 (6.85)
	SD	10.4	20.54
	Median (Min; Max)	10.75 (0.5; 35.6)	30.6 (17.7; 79.8)
	Change from Baseline (nM); Mean (SE)	0.90 (0.64)	4.19 (1.50)
	Percent Change from Baseline; Mean (SE)	10.19 (4.64)	18.32 (6.33)
Visit 7 (Week 24)	N	20	9
	Mean (SE)	14.28 (2.44)	43.99 (8.98)
	SD	10.91	26.94
	Median (Min; Max)	11.7 (0.5; 35.7)	32 (19.3; 88.8)
	Change from Baseline (nM); Mean (SE)	2.02 (0.95)	8.86 (3.05)
	Percent Change from Baseline; Mean (SE)	20.72 (7.85)	27.25 (5.69)
Visit 11 (Week 40)	N	20	9
	Mean (SE)	14.14 (2.35)	42.00 (6.85)
	SD	10.5	20.54
	Median (Min; Max)	12.1 (0.6; 37.2)	41.9 (19.7; 75.1)
	Change from Baseline (nM); Mean (SE)	1.89 (0.92)	6.87 (2.47)
	Percent Change from Baseline; Mean (SE)	20.91 (6.22)	28.89 (8.37)
Visit 14 (Week 52)	N	20	8
	Mean (SE)	14.37 (2.44)	41.88 (7.60)
	SD	10.9	21.51
	Median (Min; Max)	12.35 (0.6; 37.9)	39.35 (20.4; 80.8)
	Change from Baseline (nM); Mean (SE)	2.11 (0.9)	5.26 (2.32)
	Percent Change from Baseline; Mean (SE)	21.3 (6.47)	24.07 (8.95)

ADA status at Baseline
Source: Table 79, Immunogenicity summary

Table 33 Annualized eGFR Slopes and eGFR by ADA Status (Study PB-102-F50)

ADA Status	eGFR Absolute Value (mL/min/1.73 m^2)			Annualized eGFR Slope (mL/min/1.73 m^2/year)	
	Baseline	Week 52	Change from Baseline	Pre-Switch	Post-Switch
Negative (N=20)	96.17 (3.88)	96.12 (3.69)	-0.04 (1.70)	-2.31 (0.94)	-1.45 (1.11)
Positive (N=9)	106.72 (10.25)	111.96 (3.87)	-4.32 (2.19)	-0.63 (0.71)	-6.19 (1.99)

ADA status at Baseline
Mean (SE)
Source: Table 80, Immunogenicity summary

Table 34 Treatment Related TEAEs in ADA Positive Patients (Study PB-102-F50)

Patient	Anti-Pegunigalsidase Ab Detected at:	Related TEAEs Reported [a]	Action Taken, Treatment or Pre-Medication Received [a]
(b) (6)	Baseline, 1-3M	None	
	All scheduled time points	None	
	All scheduled time points and hypersensitivity visit	IRR, 12 events, probably related, Mild/Moderate	Infusion interrupted, paused and restarted. Diphenhydramine. Resolved recovered dose not changed
	All scheduled time points	None	
	All scheduled time points and hypersensitivity visit	IRR definitely, Moderate	IV Demerol x2, IV Benadryl, IV Ondansetron and Methlyprednisolone recovered resolved drug interrupted
	All scheduled time points and hypersensitivity visit	Nausea, vomiting, pain, probably related, asthenia, chest discomfort, possibly related, Moderate-Mild	Rx or OTC Tx recovered resolved
	All scheduled time points and hypersensitivity Visit	Hypersensitivity, Moderate, Probably related; IRR, Mild, Definitely related; Myalgia, Moderate, Probably related; Tremor, Mild, possibly related	Drug interrupted Rx or OTC Tx Recovered/ resolved
	Baseline only	None	
	All scheduled time points through 6M	UPCR increased, Mild, possibly related; White blood cell in urine positive, Mild, possibly related	

ADA status at Baseline
Source: Table 81, Immunogenicity summary

4.2 Pharmacometrics Review

4.2.1 Applicant's Population Pharmacokinetics Analysis

Title: Update of the Population Pharmacokinetic (PPK) and Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis of Pegunigalsidase Alfa with Data from Studies F50, F20, and F01/F02.

Objectives:

- Update the PPK report (ICX-B173 MSAR1, using data from studies PB-102-F01/F02, PB-102-F50 and interim data from Study PB-102-F20), with final data from PB-102-F20
- Assess the covariate effect on pegunigalsidase alfa PK parameters
- Compare pegunigalsidase alfa exposures between Q2W 1 mg/kg and Q4W 2 mg/kg
- Develop a population PKPD (PPKPD) model for plasma Lyso-Gb3, compare magnitude of changes in Lyso-Gb3 for treatment naïve patients (Studies F01/F02) versus those who are switching from other ERT (Studies PB-102-F20 and PB-102-F50), and predict Lyso-Gb3 change from baseline (CFB) for the mentioned 2 clinical doses.

Data: This analysis evaluated PK data from 4 studies as detailed in **Table 35**, **Table 36**, and **Table 37**.

Table 35 Summary of Studies Included in the Population Pharmacokinetics Analysis

Study	IV Dose (mg/kg)	PK Sample
PB-102-F01 is a Phase 1/2, open label, dose ranging study to evaluate the safety, tolerability, pharmacokinetics and exploratory efficacy of PRX-102 administered by IV infusion every 2 weeks for 12 weeks to adult (>18 years of age) Fabry patients who have never received ERT in the past, or patients who have not received ERT in the past 6 months and have a negative anti PRX-102 antibody test.	0.2 mg/kg Q2W (n=6), 1.0 mg/kg Q2W (n=9), 2.0 mg/kg Q2W (n=4). 16 patients completed the 3-mo study and enrolled into the 9-mo extension study (PB-102-F02).	Day 1: pre-dose, 1 h after the beginning of the infusion, end of infusion (EOI), and 1, 4, 8, 24, 48 ±3, 72±3, and 96±3 h post EOI and 2 weeks post-EOI (prior to next infusion). Day 85: pre-dose, 1 h after the beginning of the infusion, EOI, 1, 4, 8, 24, 48 ±3, 72±3, and 96±3 h post-EOI, and 2 weeks post-EOI (pre-dose on Study F02 Day 1).
PB-102-F02 is an extension of phase 1/2, open label, dose ranging study to evaluate the safety, tolerability, pharmacokinetics and exploratory efficacy of PRX-102 administered by IV infusion every 2 weeks for 38 weeks (9 Months) to adult Fabry patients. All 16 patients completed the 9-month extension study (PB-102-F02).	0.2 mg/kg Q2W (n=6), 1.0 mg/kg Q2W (n=6), 2.0 mg/kg Q2W (n=4). Each patient received the same dose as received in Study F01	Visit 7 (Month 3, total treatment of 6 months): predose, 1 h after the beginning of the infusion, EOI, 1, 4, 8, 24, 48±3, 72±3, and 96±3 hours and 2 weeks post EOI (predose of visit 8). Visit 20 (Month 9, total of 12 months of treatment): predose, 1 h after the beginning of the infusion, EOI, 1, 4, 8, 24, 48±3, 72±3, and 96±3 h and 2 weeks post EOI.
PB-102-F20 is a Phase 3, randomized, double blind active control study of the safety and efficacy of PRX-102 compared to agalsidase beta in Fabry disease patients with impaired renal	1.0 mg/kg Q2W (n=17),	Visit 1 (Day 1 of the study), Visit 14 (Week 26±3 Days, 6 months) and Visit 27 (Week 52±3 Days, Month 12) and at Visit 53 (Week 104±3 Days, Month 24). On visit, samples were drawn at pre-

function previously treated with agalsidase beta for approximately 1 year and on a stable dose for at least 6 months. Patients were randomized in a 17:13 ratio to either receive 1 mg/kg of PRX-102 or to continue with 1 mg/kg of agalsidase beta.		infusion; 0.5 and 1 h after the beginning of the infusion, EOI, and 0.5±0.05, 1±0.25, 2±0.25, 4±0.25, 8±0.25, 24±0.5, 48±3, and 96±3 h post EOI and 14±3 days post EOI
PB-102-F50 is a Phase 3, open label, switch over study to assess the safety, efficacy and PK of 2 mg/kg of PRX-102 administered by IV infusion every 4 weeks for 52 weeks in patients with Fabry disease currently treated with ERT: Fabrazyme® (agalsidase beta) or Replagal™ (agalsidase alfa). Thirty (30) subjects were part of the Study PB-102-F50 and contributed at least one blood sample for determination of PRX-102 plasma concentration levels.	2 mg/kg Q4W (n=30)	Visit 1 (Day 1) and Visit 14 (Week 52) of all patients. Visit 7 (Week 24) for patients who signed inform consent to Version 4/Version 4.1 before reaching Visit 7. Visit 11 (Week 40) for patients who passed Visit 7 at the time of signing the inform consent to protocol Version 4/Version 4.1. On each visit, samples were drawn at pre-infusion; 1 h after the beginning of the infusion; EOI, 1±0.25, 2±0.25, 4±0.25, 8±0.25, 24±0.5, 48±3, and 96±3 h post EOI and at 14±3, 21±3 and 28±3 days post EOI.
Source: *Section 10.2.1 of applicant's PPK report.*		

Table 36: Pegunigalsidase Alfa PK sample Information by Study

Categories	Study F01/F02	Study F20	Study F50
Number of patients	16	17	30
Total number of PK samples	680	769	1021
Number of samples BLQ at pre-first-dose	15	14	28
Number (%) of samples BLQ post-first-dose	30 (5%)	68 (9%)	61 (6%)
Number (%) of missing samples prior to the 1st dose	0 (0%)	2 (0.26%)	1 (0.1%)
Source: *Table 10-1 of applicant's PPK report.*			

Table 37: Demographics and Baseline Characteristics of the PPK dataset

		Study F01/F02	Study F20	Study F50
N		**16**	**17**	**30**
Gender	Number (%) of Males	9 (56%)	7 (41%)	24 (80%)
	Number (%) of Females	7 (44%)	10 (59%)	6 (20%)
Race	Number (%) of White	12 (75%)	17 (100%)	30 (100%)
	Number (%) of Black	3 (19%)	0 (0%)	0 (0%)
	Number (%) of Other	1 (6%)	0 (0%)	0 (0%)
Ethnicity	Number (%) of Hispanic	3 (19%)	0 (0%)	1 (3%)
	Number (%) of non-Hispanic	13 (81%)	17 (100%)	29 (97%)
Age (years)	Median (Min, Max)	30 (17, 54)	47 (28, 60)	40.5 (19, 58)
Weight (kg)	Median (Min, Max)	69 (52, 91)	72 (60, 129)	79 (50, 147)
BMI (kg/m^2)	Median (Min, Max)	23.6 (17.1, 32.2)	27.4(20.2, 39.1)	25.2 (16.4, 51.4)
Cr_{CL} (mL/min)	Median (Min, Max)	116 (71, 166)	85 (48, 170)	118 (70, 220)
Source: *Table 10-3 of applicant's PPK report.*				

Methods: The previously developed three-compartment mammillary model with zero-order infusion input remained to be the structural model. The following covariates were evaluated for their influence on PRX-102 clearances and volumes of distribution: anti-PRX-102 antibody [Pos/Neg] as a categorical covariate, anti-PRX-102 antibody Titer (IgG TIT) as a continuous covariate, body weight, age, gender, race, ethnicity, baseline creatinine clearance (evaluated on central clearance only), previous treatment with agalsidase alfa or agalsidase beta, study, and PRX-102 dose. The final population PK parameters were used to simulate AUCτ, Cave, Cmax, and Ctrough. The relationship between these exposure indices and Lyso-Gb3 were assessed graphically and by summary statistics split by visit, PRX-102 anti-drug antibody status at baseline and visit.

RESULTS

Modeling: A 3-compartment mammillary population PK model with zero-order infusion and first-order elimination, with IIV terms estimated on central and peripheral compartments (CL, V1, Q3, V3) and a covariance term on CL and V1 provided the best fit for the observed PRX-102 plasma concentrations. Residual error was best described by an additive and proportional terms and was stratified by Study PB-102-F01/F02 vs. the other two studies. IOV on bioavailability term F was needed (ICX-B173 MSAR1 Report). IOV terms were also tested on CL and V1 but were not found to be statistically significant. Two covariates resulted in a significant reduction ($p<0.0001$) in OFV: a) IgG Titer on CL and V1; b) Study F01/F02 flag on CL, V1, Q3, and V3. The parameter estimates of the final PRX-102 PPK model are listed in **Table 37**, and associated goodness-of-fit plots are shown by **Figure 10**.

Two covariates resulted in statistically significant OFV reduction. First, IgG titer on CL and V1, with E_{max} models explaining the relationship. Second, Study F01/F02 flag on CL, V1, Q3, and V3. The relationships are shown below:

$$CL(L/h) = \begin{cases} \theta_1 \cdot (1 + \theta_{21})^{Study\ F01/F02} \cdot e^{\eta_1} & if\ IGGTIT = 0 \\ \theta_1 \cdot (1 + \theta_{21})^{Study\ F01/F02} \cdot \dfrac{\theta_8 \cdot IGGTIT^{\theta_{17}}}{IGGTIT^{\theta_{17}} + \theta_{16}{}^{\theta_{17}}} \cdot e^{\eta_1} & if\ IGGTIT > 0 \end{cases}$$

$$V_1(L) = \begin{cases} \theta_2 \cdot (1 + \theta_{11})^{Study\ F01/F02} \cdot e^{\eta_2} & if\ IGGTIT = 0 \\ \theta_2 \cdot (1 + \theta_{11})^{Study\ F01/F02} \cdot \dfrac{\theta_{18} \cdot IGGTIT^{\theta_{20}}}{IGGTIT^{\theta_{20}} + \theta_{19}{}^{\theta_{20}}} \cdot e^{\eta_2} & if\ IGGTIT > 0 \end{cases}$$

$$Q_3(L/h) = \theta_5 \cdot (1 + \theta_{14})^{Study\ F01/F02} \cdot e^{\eta_3}; \qquad V_3(L) = \theta_6 \cdot (1 + \theta_{14})^{Study\ F01/F02} \cdot e^{\eta_4}$$

Table 38 Final Pegunigalsidase Alfa Population PK Model Parameter Estimates by IMP Method

Parameter	Estimate (Shrinkage%)	SE	RSE%
0_1: CL (L/hr)	0.0115	0.00242	21.0
0_{21}: CL ~ Study F01/F02	4.61	0.681	14.8
0_8: CL ~ IGGTIT: Emax	77.4	7.14	9.22
0_{16}: CL ~ IGGTIT: EI_{50}	4380, fixed	--	--

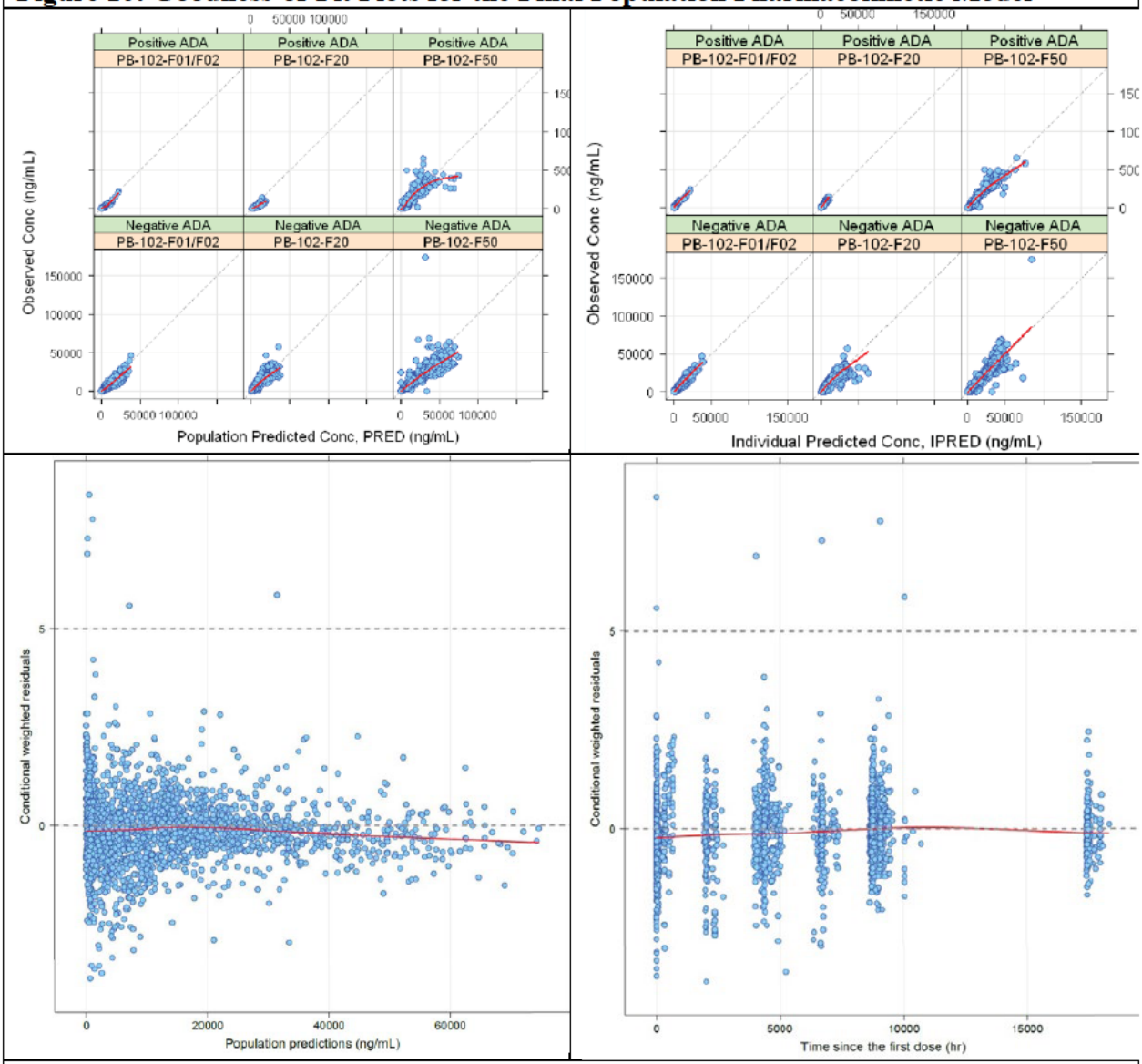
0_{17}: CL ~ TGGTTT: y	1.20, fixed	--	--
0_2: V_1 (L)	2.71	0.182	6.71
0_{11}: V_1 ~ Study F01/F02	0.583	0.142	24.4
0_{18}: V_1 ~ IGGTIT: Emax	3.97	0.309	7.77
0_{19}: V_1 ~ IGGTIT: EI_{50}	1200, fixed	--	--
0_{20}: V_1 ~ TGGTTT: y	0.420, fixed	--	--
0_3: Q_2 (L/hr)	0.218	0.0152	6.94
0_4: V_2 (L)	4.49	0.157	3.50
0_5: Q_3 (L/hr)	0.0460	0.00240	5.16
0_9: Q_3 ~ Study F01/F02	-0.0340	0.000292	0.86
0_6: V_3 (L)	11200	836	7.48
$I0_{14}$: V_3 ~ Study F01/F02	-0.998	0.0000874	0.01
Inter-Individual Variability			
η_{CL}^2	0.729 (10.2)	0.217	29.8
$\eta_{(CL,V1)}$	0.267	0.0742	27.8
η_{V1}^2	0.146 (5.13)	0.0212	14.5
η_{Q3}^2	0.0745 (27.6)	0.0340	45.6
η_{V3}^2	3.56 (27.6)	1.29	36.2
Inter-Occasion Variability			
η_{F1}^2	0.08014 (b) (4)	0.00575	7.18
Residual Variability			
Prop for Study F01/F02 σ_1^2	0.0575	0.00397	6.90
Add for Study F01/F02 σ_2^2	914	378	41.4
Prop for Study F20/F50 σ_3^2	0.0838	0.00359	4.30
Add for Study F20/F50 σ_4^2	4520	1100	24.3

Source: *Table 12-1 of applicant's PPK report with Corrections by FDA reviewer.*

For the IV infusion, the absolute bioavailability (F_1) was set as 1 with occasion as covariate:

$F_1 = 1*EXP(ETA(5)*OC1 + ETA(6)*OC2 + ETA(7)*OC3 + ETA(8)*OC4)$

Figure 10: Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



Source: Figures 12-6, 12-7, and Figure 16-5 of applicant's PPK report.

Simulation

The final pegunigalsidase alfa population PK model was used to assess the impact of IgG Titer on pegunigalsidase alfa PK. ADA positivity is expected to result in reduction of pegunigalsidase alfa exposures as shown in **Table 39** and **Figure 11**, and summarized as follows:

- AUCτ for a patient with IgG Titer of 750, 7,000, 20,000 and 130,000 are expected to be approximately 39%, 9%, 7% and 6%, respectively, as compared to AUCτ for an ADA-negative patient.
- Pegunigalsidase alfa exposures are estimated to have a steep (almost on and off) relationship with IgG Titer, that is at IgG Titer 750 and 7,000 compared to 0 there is 60% and 91% reduction in pegunigalsidase alfa AUCτ, respectively.
- Cmax for a patient with IgG Titer of 750, 7,000, 20,000 and 130,000 is expected to be

approximately 55%, 35%, 31% and 27%, respectively, as compared to Cmax for an ADA-negative patient.

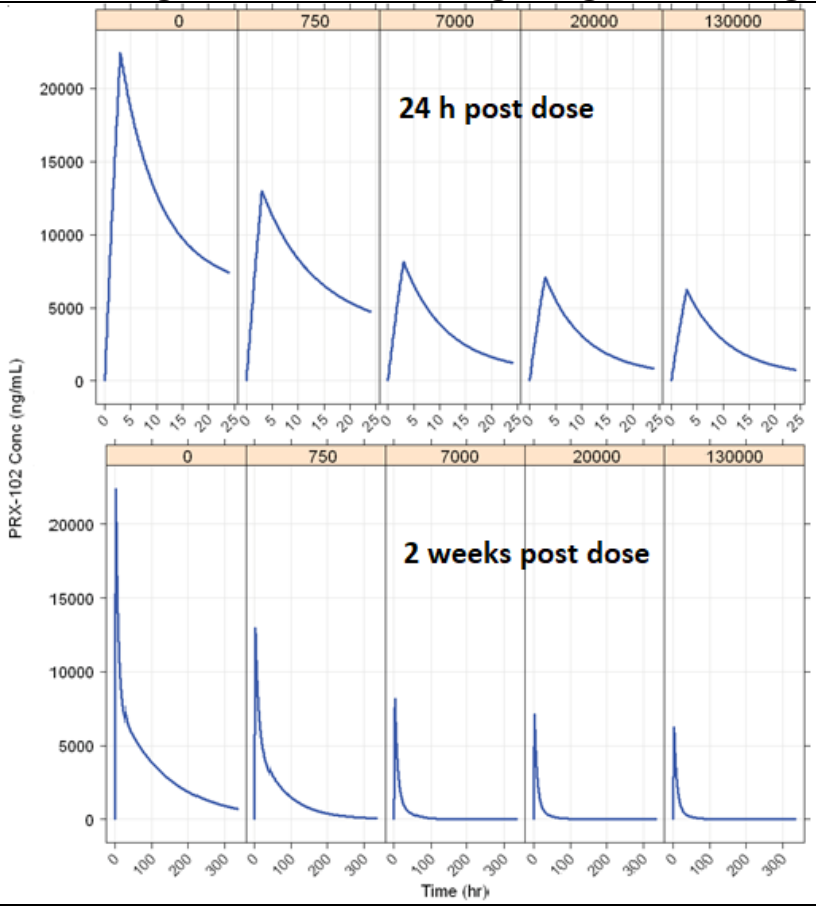
- Ctrough for a patient with IgG Titer of 750 is expected to be 11% of the Ctrough levels of an ADA-negative patient and Ctrough for a patient with IgG Titer >7,000 is expected to be <2% (i.e., near LLOQ) of the Ctrough levels of an ADA-negative patient.

Table 39 Comparison of Pegunigalsidase Steady-State Exposure for a 70 kg Patient Using the Final PK Model across Different IgG Titer Levels

IgG Titer	C_{trough} (µg/L)	C_{max} (µg/mL)	AUCτ (µg*hr/mL)	C_{trough} Ratios	C_{max} Ratio	AUCτ Ratios
1 mg/kg Q2W 1.5-h Infusion						
0	973	25	1286	1.00	1.000	1.00
750	102	13.8	503	0.105	0.552	0.391
7,000	1.80	8.85	115	0.0018	0.354	0.0892
20,000	1.00	7.76	86.5	0.0010	0.311	0.0672
130,000	0.800	6.79	76.1	0.0008	0.272	0.0592
2 mg/kg Q4W 2.5-h Infusion						
0	325	46.2	2570	1.00	1.00	1.00
750	33.7	26.5	1010	0.104	0.573	0.391
7,000	1.70	16.8	229	0.0052	0.363	0.0892
20,000	1.00	14.6	173	0.0030	0.317	0.0672
130,000	0.80	12.8	152	0.0023	0.278	0.0592

Source: Table 12-2 of applicant's PPK report.

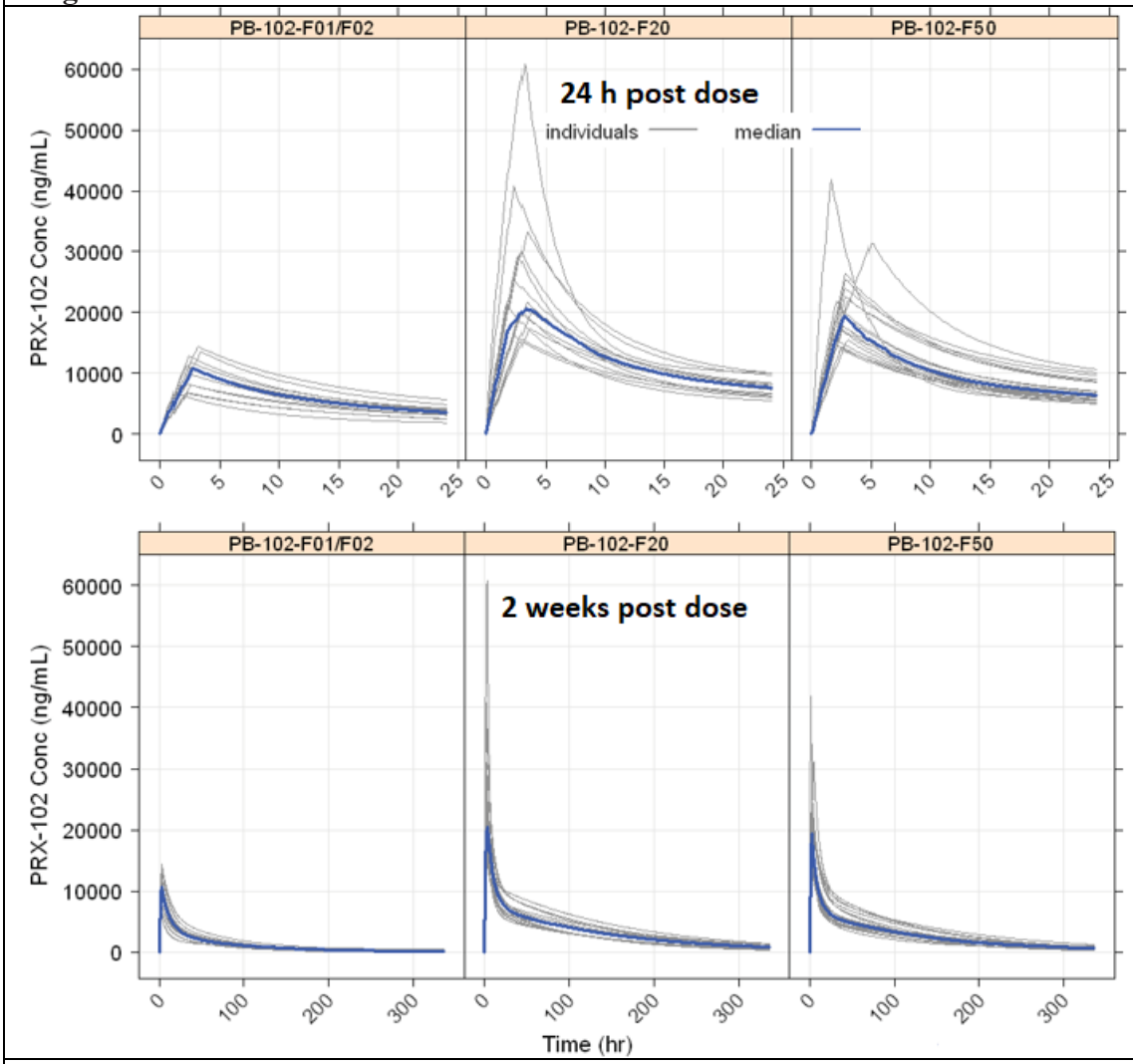
Figure 11: Comparison of PRX-102 Plasma Concentrations Using the Final PK Model across Different IgG Titer Levels Following a Single Dose of 1 mg/kg



Source: Figure 12-9 of applicant's PPK report.

The predictions show that pegunigalsidase alfa experienced patients in Studies PB-102-F20 and PB-102-F50 would be expected to have Cmax approximately 96% and 82% higher, respectively, and AUCτ approximately 68% and 39% higher, respectively, than the treatment-naïve patients in Study PB-102-F01/F02 (**Figure 12**).

Figure 12: Comparison of Pegunigalsidase Alfa Plasma Concentrations Using the Final PK Model across Studies for ADA- Negative Patients after the Administration of 1 mg/kg Single Dose



Source: Figure 12-10 of applicant's PPK report.

Table 40 shows the simulated exposure comparison between 2 mg/kg Q4W dose (D2) vs 1 mg/kg Q2W dose (D1).

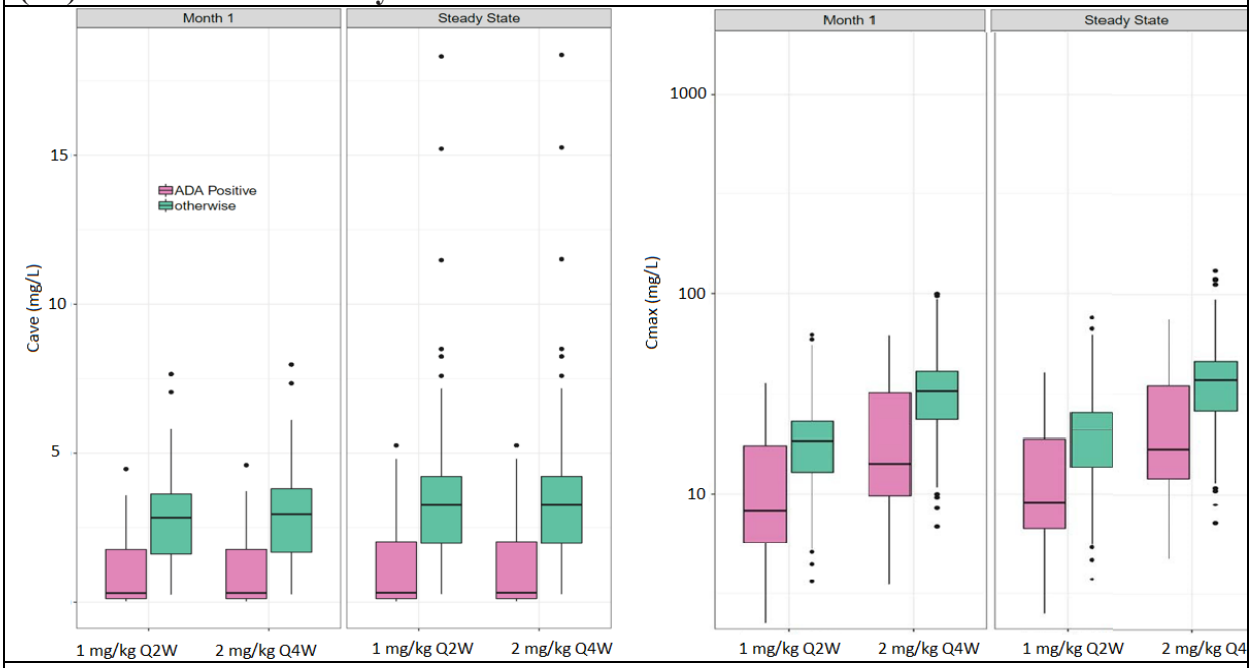
Table 40 Simulation of Pegunigalsidase Alfa Ctrough, Cmax, Cave4w, and AUC4w for 2 mg/kg Q4W vs 1 mg/kg Q2W for the Population with Median Weight of 83 kg with ADA Rate of 34%

Regimen	D1	D2	D1	D2
Infusion Time (h)	3	5	1.5	2.5
Month	1	1	24	24
Median (2.5th percentile, 97.5th percentile)				
C_{trough} (µg/L)	0 (0; 0)	0 (0; 0)	584 (0.0279; 4310)	218 (0.0279; 3930)
C_{max} (mg/L)	16.0 (2.50; 42.3)	28.9 (3.94; 73.0)	17.9 (3.08; 47.1)	32.8 (5.34; 87.7)

$C_{ave[0-4w]}$ (mg/L)	2.13 (0.0437; 4.84)	2.23 (0.0437; 5.00)	2.57 (0.0437; 7.61)	2.57 (0.0437; 7.62)
$AUC_{[0-4w]}$ (mg*hr/mL)	1.433 (0.0293; 3.25)	1.50 (0.0293; 3.36)	1.73 (0.0294; 5.12)	1.73 (0.0294; 5.12)
Median (2.5th percentile, 97.5th percentile) of D2 vs D1				
C_{trough} Ratios	Not available		0.47 (0.21; 1)	
C_{max} Ratios	1.8 (1.54; 1.89)		1.86 (1.64; 1.94)	
$C_{ave[0-4w]}$ Ratios	1.03 (1; 1.13)		1 (1; 1)	
$AUC_{[0-4w]}$ Ratios	1.03 (1; 1.13)		1 (1; 1)	
Source: Table 12-4 of applicant's PPK report.				

D1 and D2 are expected to have similar AUC and Cave. C_{max} is estimated to be 80% higher following the first dose and 86% higher at steady state for D2 as compared to D1 (**Figure 13**). C_{trough} is estimated to be detected for both doses and is expected to be approximately 53% lower at steady state for D2 as compared to D1 (**Table 40**).

Figure 13: Simulated PRX-102 Cave and Cmax for 1 mg/kg Q2W (D1) and 2 mg/kg Q4W (D2) at Month 1 and Steady-State

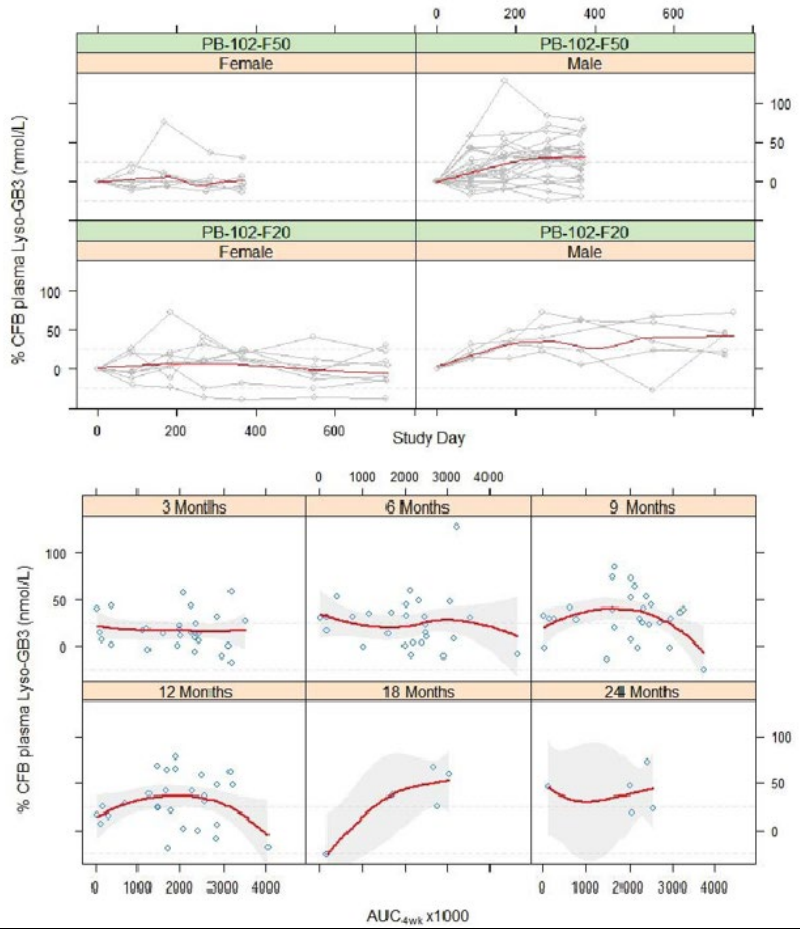


Source: Figure 12-11 and 12-13 of applicant's PPK report.

Figure 14 shows percentage change from baseline in plasma Lyso-Gb3 concentration (CFB%) versus time and CFB% exposure for female Patients (Bottom Panel) from Studies F20 and F50. The mean percent change from baseline in Lyso-Gb3 after 12 months of treatment is -0.233 nM (-1.91%) and 4.92 nM (26.2%) in females and males, respectively. Overall, the changes in plasma Lyso-Gb3 from baseline are not considered to be clinically meaningful and indicate stability. There seem to be a trend for an increase in plasma Lyso-Gb3 compared to baseline at 24 months. Overall, treatment naïve patients have a greater reduction in Lyso-Gb3. In general, Lyso-Gb3

levels remain stable after switching to pegunigalsidase alfa and not correlated with pegunigalsidase alfa exposures in Studies PB-102-F20 and PB-102-F50.

Figure 14: Percentage Change from Baseline in Plasma Lyso-Gb3 Concentration (CFB%) versus Time and CFB% Exposure for Female Patients (Bottom Panel) from Studies F20 and F50



Source: Figure 12-15 and 12-16 of applicant's PPK report.

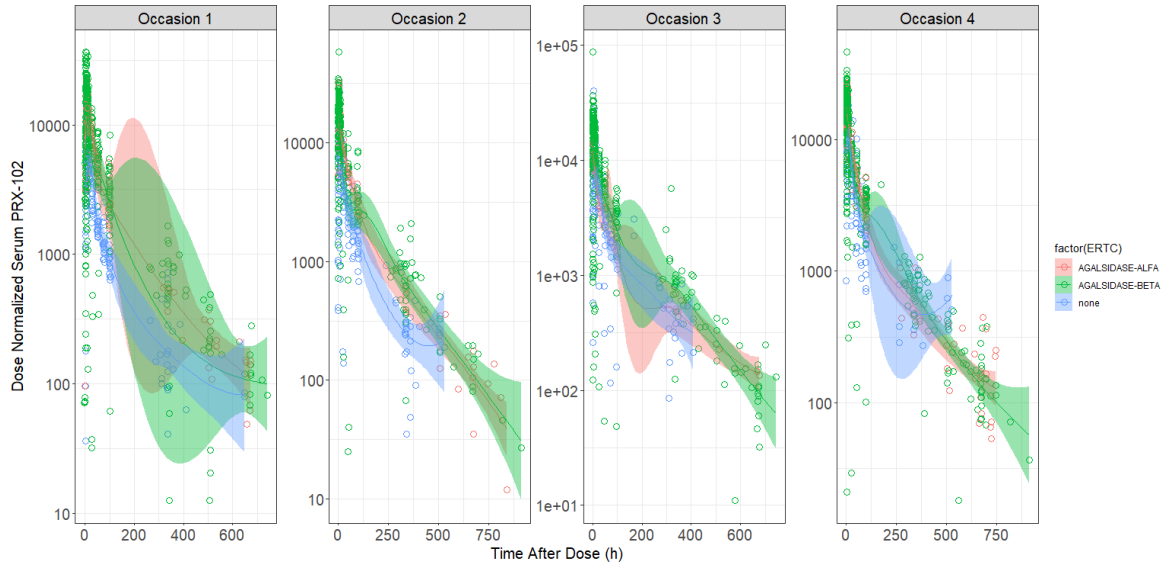
Reviewer's Comments about Applicant's PPK Analyses*: The submitted PPK analysis showed multiple issues: 1). Basic mistakes shown in Table 12-1 of "report icx-b173-stage2.pdf" such as RSE% was mistaken for SE and CV% was mistaken for RSE% etc; 2). The 4 PK occasions were neither defined in "define.pdf" nor described in the PPK report; 3).* ***Table 35****,* ***Table 36****, and* ***Table 37*** *are expected to be provided in the PPK report; 4). The absolute bioavailability of the intravenous dose of PRX-102 was not fixed as 100% and was allowed to vary on different occasions.*

4.2.2 FDA Reviewer's Analysis

Introduction: The observed PK data of ERT-naïve (legend labeled as "none") vs ERT-experienced (agalsidase alfa or agalsidase beta used) was shown in **Figure 15**, where Occasions were defined

by the applicant as the following: Occasion 1 is the first dose in all studies; Occasion 2 is the planned Month 3 visit in study PB-102-F01/F02, and planned Month 6 visit in studies PB-102-F50 and PB-102-F20; Occasion 3 is the planned Month 6 visit in study PB-102-F01/F02, planned Month 10 visit in study PB-102-F50 and planned Month 12 visit in study PB-102-F20, respectively; and Occasion 4 is the planned visit of Month 12 in studies PB-102-F01/F02 and PB-102-F50, and planned Month 24 visit in Study PB-102-F20.

Figure 15: Predicted Exposure Comparison of Q2W 1 mg/kg between ERT-Naïve and ERT-Experienced Patients



Note: The line is for median prediction and the polygon covers 5th and 95th percentiles of the prediction
Source: Reviewer's analysis based on PK parameters of ADA negative patients.

From **Figure 15**, it is observed that: 1). On Occasions 1 and 2, ERT-naïve patients showed lower exposure than ERT-experienced patients; and 2). The exposure is comparable among all patients on Occasions 3 and 4, for which naming the 16 patients from Studies F01/F02 as ERT-naïve could be inappropriate after months of agalsidase-alfa treatment. Fortunately, ERT-naïve vs ERT-experienced was not identified as a covariate of the PPK model. In addition, the applicant used Occasion as a covariate of absolute bioavailability as defined in **Table 41**, which is not scientifically sound from two perspectives:

1. Absolute bioavailability of pegunigalsidase alfa intravenous doses should always be 100%, therefore should not be associated with any occasion variables.
2. The time windows of the same occasion in **Table 41** are significantly different across different studies. This cannot be explained appropriately for the PPK analysis.

Table 41 Study Weeks of Different Occasions in the NONMEM Dataset

	Occasion 1	Occasion 1	Occasion 1	Occasion 1
F01/F02	0-14	12-53	25-55	51-60
F20	0-36	0-102	52-105	104-109
F50	0-52	23-56	39-64	51-57

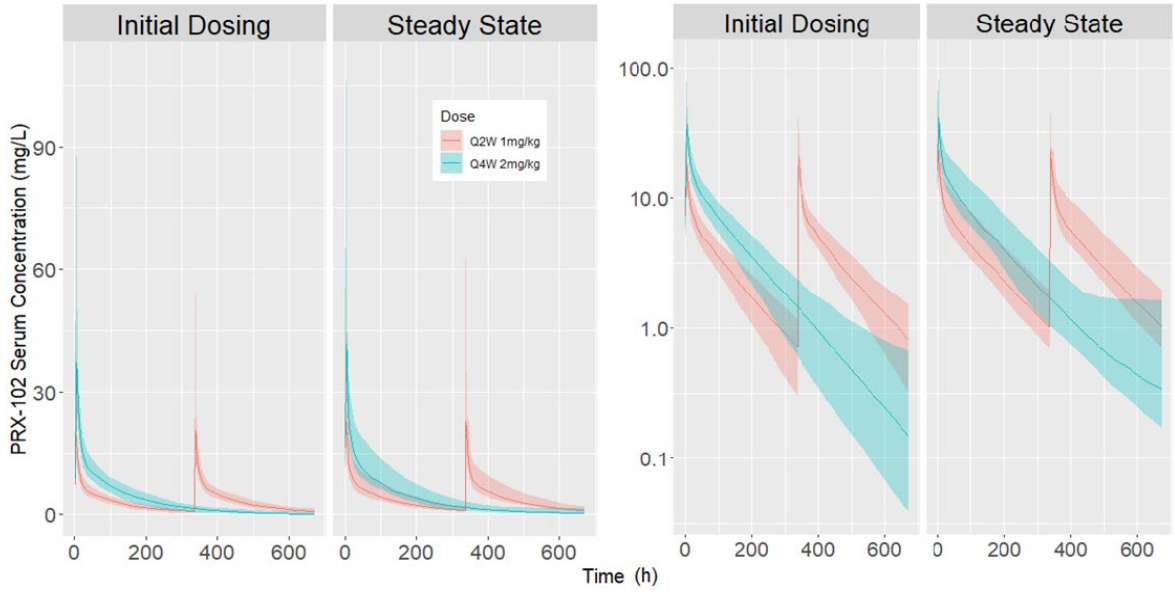
Source: *Reviewer's analysis based on PPK dataset poppk2.xpt.*

Objectives: The FDA reviewer's analysis was to visualize the exposure difference between Q2W 1 mg/kg and Q4W 2 mg/kg doses, and to explore exposure-response relationship of different pharmacodynamic biomarkers.

Methods: To best capture the exposure difference between Q2W 1 mg/kg and Q4W 2 mg/kg doses, the PK data from Studies F01/F02 and from ADA positive patients of all studies were removed from the NONMEM dataset "poppk2.xpt" before applicant's final model (where occasion variability on absolute bioavailability was removed) was applied in NOMEM v7.5.4. Median and 90% prediction intervals based on resulted individual PK parameters were generated. For the exposure-response analysis, plasma Lyso-GB3 data from "adgb3.xpt" and plasma eGFR from "adegfr.xpt" for Studies F20 and F50, respectively, were used for analysis. R 4.1.0 was used for analysis.

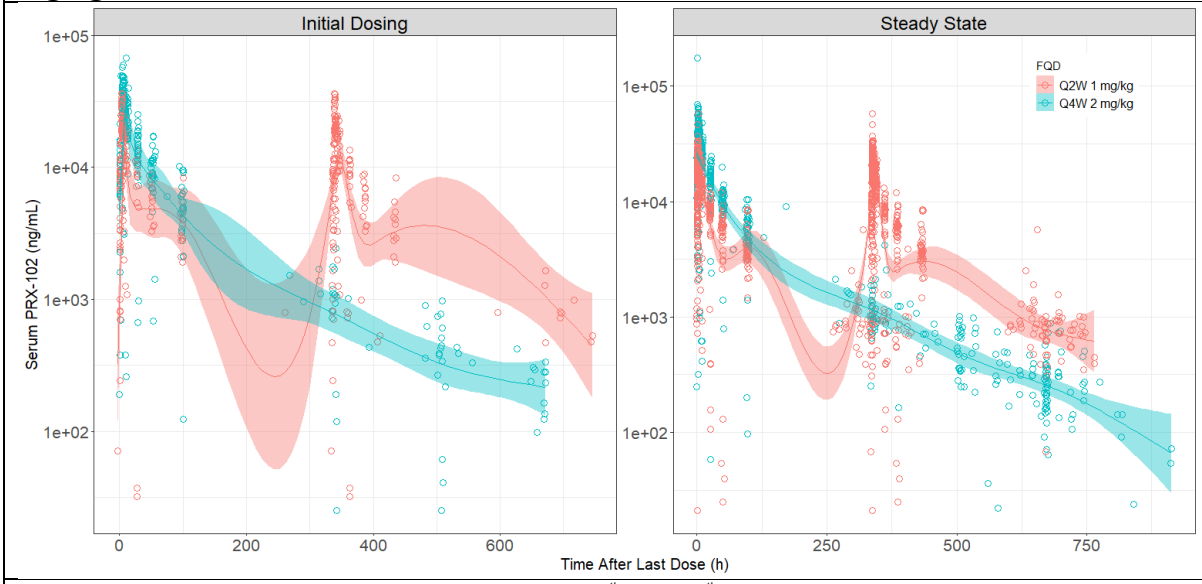
PPK Results: The Predicted exposure comparison between Q4W 2 mg/kg and Q2W 1 mg/kg for single dose and multiple doses should be provided as **Figure 16** with left panel for linear scales and right panel for semi-log scale. This plot is consistent with observed PK data from Studies F20 and F50 as shown in **Figure 17** where PK data for both ADA positive and negative patients were included.

Figure 16: Predicted Exposure of PRX-102 for the Q4W 2 mg/kg Dose versus Q2W 1 mg/kg



Note: The line is for median prediction and the polygon covers 5th and 95th percentiles of the prediction. ADA negative patients from Studies F20 and F50 were used for simulation. See next figure for the reason why patients from Studies F01/F02 were excluded.
Source: *Reviewer's analysis based on PK parameters of ADA negative patients.*

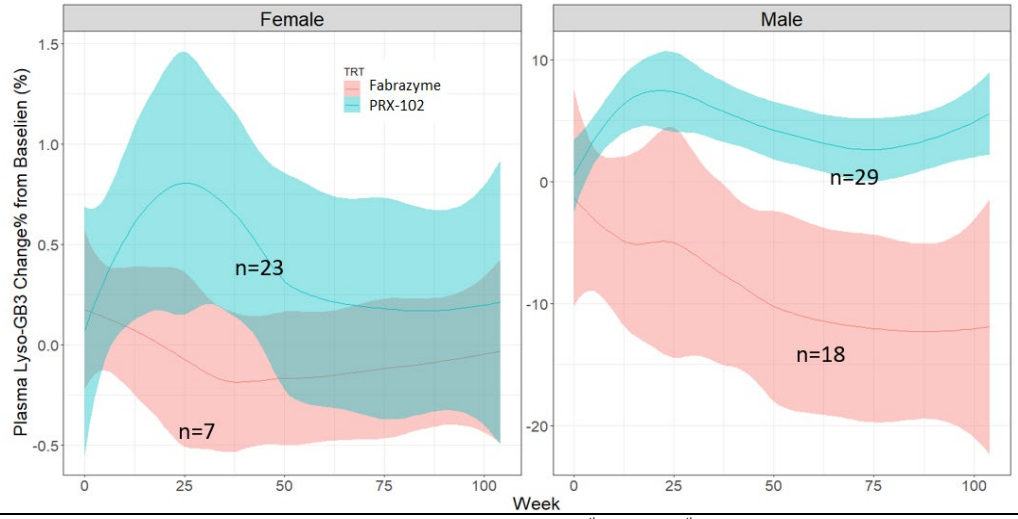
Figure 17: Observed Exposure of Pegunigalsidase Alfa Q2W 1 mg/kg versus Q4W 2 mg/kg Q4W



Note: The line is for mean prediction and the polygon covers 2.5th and 97.5th of the loess smooth.
Source: *Reviewer's analysis based on PPK dataset "poppk2.xpt".*

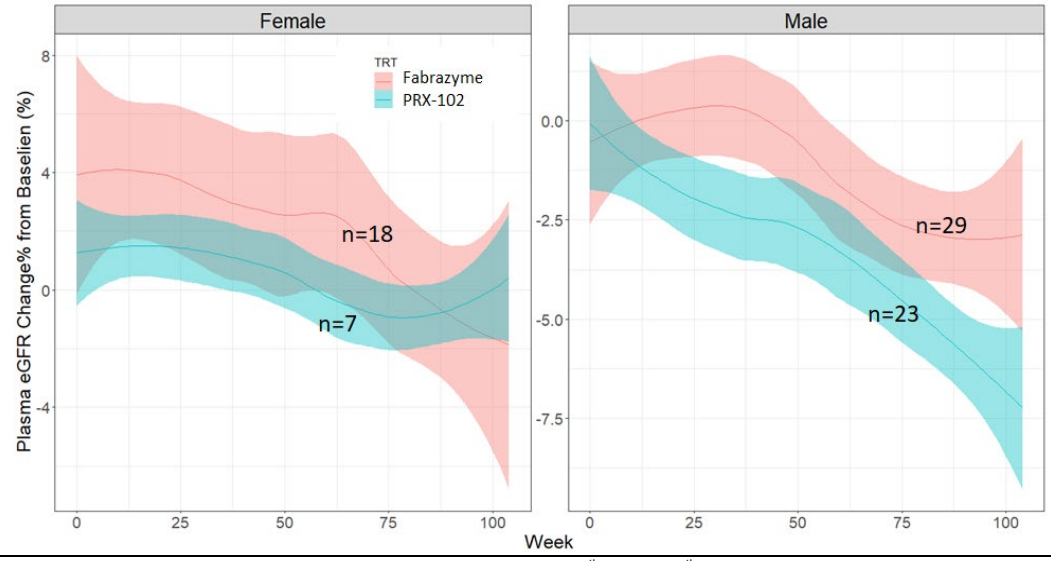
Exposure-Response Results: In Stud F20, agalsidase beta showed better PD effect than PRX-102 in both plasma Lyso-GB3 and plasma eGFR, particularly in male patients (**Figure 18** and **Figure 19**). Sex is not balanced between 2 treatment arms.

Figure 18: Plasma Lyso-Gb3 Change% from Baseline over Time by Treatment (TRT) and Sex for Study F20



Note: The line is for mean prediction and the polygon covers 2.5th and 97.5th of the loess smooth.
Source: *Reviewer's analysis based on "adgb3.xpt" for both studies.*

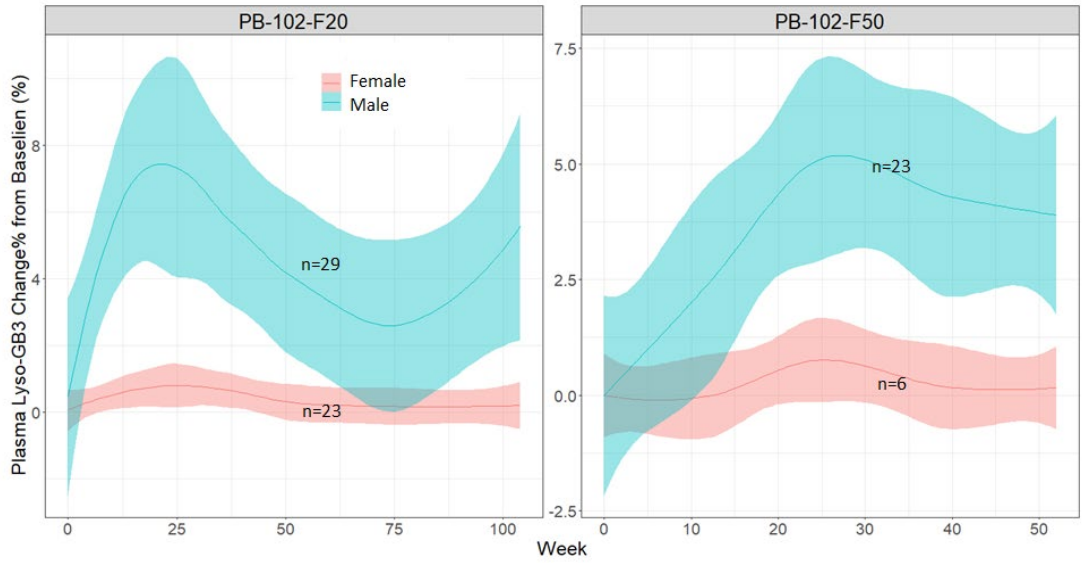
Figure 19: Plasma eGFR Change% from Baseline over Time by Treatment (TRT) and Sex for Study F20



Note: The line is for mean prediction and the polygon covers 2.5th and 97.5th of the loess smooth.
Source: *Reviewer's analysis based on "adegfr.xpt" for both studies.*

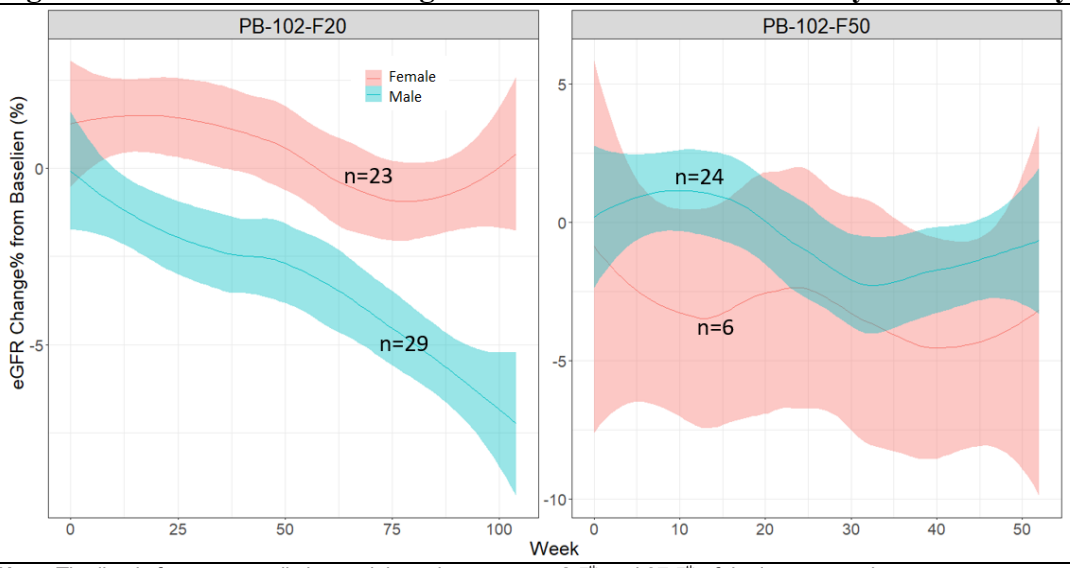
Pegunigalsidase alfa showed similar patterns of PD effect between F20 and F50 where pegunigalsidase alfa maintained the PD response better and less variable in female patients (**Figure 20** and **Figure 21**).

Figure 20: Plasma Lyso-GB3 Change% from Baseline over Time by Gender and Study



Note: The line is for mean prediction and the polygon covers 2.5th and 97.5th of the loess smooth.
Source: *Reviewer's analysis based on "adgb3.xpt" for both studies.*

Figure 21: Plasma eGFR Change% from Baseline over Time by Sex and Study



Note: The line is for mean prediction and the polygon covers 2.5th and 97.5th of the loess smooth.
Source: *Reviewer's analysis based on "adegfr.xpt" for both studies.*

Summary

- Comparing to 2 mg/kg Q4W, 1 mg/kg Q2W provides more consistent drug exposure over the dosing intervals.
- Pegunigalsidase alfa appeared to be not as effective as agalsidase beta in terms of maintaining PD response in ERT-experienced patients.
- Pegunigalsidase alfa PD effect appeared to be better and less variable in female ERT-experienced patients than males.

- The PD/efficacy of pegunigalsidase alfa 2 mg/kg Q4W in ERT-naïve patients are unknown.

(b) (4)

[redacted]

4.3 Bioanalytical Methods

4.3.1 PK assay: bioanalytical method for determination of pegunigalsidase alfa concentrations in human plasma

The concentrations of pegunigalsidase alfa (PRX-102) in human plasma PK samples were determined by ELISA assay. Refer to the Multi-Disciplinary Review and Evaluation for the original BLA application (Document ID: 4786588, by SMPOKOU, PATROULA I, dated 04/27/2021) for the validation of the ELISA assay as well as the in-study assay performance in study PB-102-F01/F02. The following provides a summary of the in-study assay performance in studies PB-102-F20 and PB-102-F50 (**Table 42**).

Table 42 Performance of the ELISA Assay Used to Determine the Concentrations of Pegunigalsidase Alfa in Human Plasma

Method performance in study PB-102-F20 (PCL-19-001/R)		
Assay passing rate	ISR was done as part of PCL-12-015/R study.	Acceptable
Standard curve performance	Standard calibrators from LLOQ to ULOQ (ng/mL): 0.20, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5 Cumulative bias: -20.0 to 23.1%	Acceptable
QC performance	Cumulative bias: --24.8 to 21.6%	Acceptable
Method reproducibility	ISR was done as part of PCL-12-015/R study. 87.5%: of a total of 72 plates, 63 plates met all the procedure's acceptance criteria, while 9 plates failed to meet at least one of the assay criteria.	Acceptable
Study sample analysis/ stability	The long-term stability study evaluated samples (assay's QCs) for 5 years at a storage temperature of -70°C (Addendum no.1 to Development Report #80-50-014). In PCL-19-001/R, the longest storage duration of the clinical samples was 3 years and 10 months.	
Method performance in study PB-102-F50 (PCL-18-003/R)		

Assay passing rate	ISR was done as part of PCL-12-015/R study.	Acceptable
Standard curve performance	Standard calibrators from LLOQ to ULOQ (ng/mL): 0.20, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5 Cumulative bias: -23.1 to 23.1%	Acceptable
QC performance	Cumulative bias: -29.6 to 29.1%	Acceptable
Method reproducibility	ISR was done as part of PCL-12-015/R study. 84.5%: of a total of 97 plates, 82 plates met all the procedure's acceptance criteria, while 15 plates failed to meet at least one of the assay criteria (additional 5 plates failed due to known technical error and are not counting as part of the assay passing rate).	Acceptable
Study sample analysis/ stability	The long-term stability study evaluated samples (assay QCs) for 26 months at a storage temperature of -70°C. In PCL-18-003/R, the longest storage duration of the clinical samples was less than 2 years	

[a] %TE was calculated as the maximal %bias + maximal %CV; it was not calculated as part of the validation report; CV-Coefficient of Variation; LLOQ-Lower Limit of Quantification; ULOQ-Upper Limit of Quantification; High Quality Control (HQC) = 750 ng/mL; Medium Quality Control (MQC) = 250 ng/mL; Low Quality Control (LQC) = 62.5 ng/mL

4.3.2 PD assays: bioanalytical methods for determination of Lyso-Gb3 concentrations in human plasma

The Applicant used LC-MS/MS and UPLC-MS/MS methods for determination of plasma Lyso-Gb3 concentrations in pegunigalsidase alfa clinical studies.

- The plasma Lyso-Gb3 concentrations in Studies PB-102-F01/F02, and F03 were analyzed in the (b) (4) using the analytical method based on the method described in Boutin 2012, et al. The validation of this assay was performed by (b) (4) (Validation Report (b) (4) VR003). Refer to the Multi-Disciplinary Review and Evaluation for the original BLA application (Document ID: 4786588, by SMPOKOU, PATROULA I, dated 04/27/2021) for the validation of the assay. Of note, the Applicant did not submit in-study validation report for the assay performance in studies PB-102-F01/F02 or study PB-102-F03, which indicates a limitation of the PD data.
- The bioanalytical method for the PD assay for Study PB-102-F30, PB-102-F20 and PB-102-F50 was validated at (b) (4) (Validation report SOP-WCECCMS-002). Refer to the Multi-Disciplinary Review and Evaluation for the original BLA application (Document ID: 4786588, by SMPOKOU, PATROULA I, dated 04/27/2021) for the validation of the assay as well as the in-study assay performance in study PB-102-F30. The following provides a summary of the in-study assay performance in studies PB-102-F20 and PB-102-F50 (**Table 43**).

Table 43 Validation Parameters and Performance of the UPLC-MS/MS Assay for Determination of Plasma Lyso-Gb3 Concentration in Studies PB-102-F30, PB-102-F20, and PB-102-F50

Bioanalytical method review summary	SOP-WCECCMS-002: The analytical method for Lyso-Gb3 in human plasma (validation report: SOP-WCECCMS-002) met acceptance criteria in general, with respect to sensitivity, precision, and accuracy, spanning a theoretical concentration range of 0.2 nM to 400 nM. Linearity, dilution integrity, interference, and selectivity were not evaluated. Stability evaluations in matrix and solutions met acceptance criteria in general.		
Method description	A UPLC-MS/MS assay that uses for the quantification of globotriaosylsphingosine (lyso-Gb3) in plasma. Briefly, plasma samples are mixed with the internal standard (IS), then a solid phase extraction (SPE) procedure using Oasis MCX (Mixed-mode Cation eXchange) cartridges is performed. Lyso-Gb3 is analyzed using an ultra-performance liquid chromatography (UPLC) system hyphenated with electrospray-tandem mass spectrometry detection (ESI-MS/MS). Lyso-Gb3 is quantified according to a calibration curve, using the response factor (area of the molecule/area of the internal standard). Plasma lyso-Gb3 concentrations are reported in nmol/L. Detailed information and parameters regarding this assay were previously published UPLC-MS/MS assay that we use for the quantification of globotriaosylsphingosine (lyso-Gb3) in plasma specimens.		
Materials used for calibration curve & concentration	The calibration curve, ranging from 0 to 400 nM (0.2, 2, 10, 40, 140, 400), is prepared in 4X depleted charcoal plasma.		
Validated assay range	Concentration range: 0-400 nM LOD = 0.23 nmol/L LOQ = 0.77 nmol/L		
Material used for QCs & concentration	Pooled plasma samples from Fabry patients having low (30 nM) and high (200 nM) concentrations of lyso-Gb3. For accuracy, using charcoal-stripped plasma spiked with a lyso-Gb3 standard to obtain concentrations of 5 nM (n = 2) and 200 nM (n = 2).		
Minimum required dilutions (MRDs)	not applicable		
Source & lot of reagents (LBA)	Not provided		
Regression model & weighting	The 1/x weighing is an automated curve-fitting algorithm, provided as part of the quantification software		
Validation parameters	**Method validation summary**		**Acceptability**
	No of standard calibrators from LLOQ to ULOQ	6	Acceptable

Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) from LLOQ to ULOQ	NA	
	Cumulative precision (%CV) from LLOQ to ULOQ	NA	
QCs performance during accuracy & precision	Number of QCs	2	Acceptable
	Inter-run accuracy (%bias)	0.6% to 2.2%	
	Inter-run precision(%CV)	Not provided	
Bench-top/process stability	• Fabry patient plasma samples were aliquoted and aliquots (n=3) were stored at room temperature (22°C) and in a refrigerator (4°C) for 72 hours. Aliquots were analyzed every 24 hours to assess the stability. Bias was ≤14.6% for plasma Lyso-Gb3 samples at both temperatures (22°C and 4°C) for at least 72 hours. • Prepared samples (N=15; ranging from 9.9 to 233.8 nM) left in the autosampler at 10°C for 24 hours, then in the refrigerator at 4°C for 24 hours, and 48 hours. Bias ≤ 10.0%for plasma Lyso-Gb3 in processed plasma specimens left for 24 h in the UPLC autosampler, then in the refrigerator at 4°C for 48 hours.		Acceptable
Freeze-Thaw stability	Not evaluated		
Long-Term storage	Plasma samples stored for a known period of time, 1.6 year (n=5, ranging from 7.9 to 199.8 nM), 2.0 years (n=5, ranging from 12.4 to 224.8 nM), and 3.2 years (n=5, ranging from 16.5 to 133 nM), in a freezer (-20°C). Bias was ranging from -9.9 to 24.4%, 4.0 to 23.3%, and 4.4 to 25.1%, respectively, for the store duration of 1.6, 2 and 3.2 years.		Acceptable
Method performance in study PB-102-F30 (Analytical study report: PB-102-F30-001)			
Assay passing rate	Incurred sample reanalysis [ISR]) 100%		Acceptable
Standard curve performance	The concentrations of the standard calibrators from LLOQ to ULOQ are: 0.2, 2, 10, 40, 140, 400 nmol/L Cumulative bias range: -11 to 6.3% Cumulative precision: ≤ 4.54% CV		Acceptable
QC performance	2 QCs (LQ and HQ) Cumulative bias range: -12.5 to 17.9% Cumulative precision: ≤ 11.1% CV		Acceptable

Method reproducibility	Incurred sample reanalysis was performed in 10 of 124 study samples and 100% of ISR samples met the prespecified criteria.	Acceptable
Study sample analysis/ stability	None of the sample storage period exceeded the 3 years long term stability period	
Method performance in study PB-102-F20 (Analytical study report: PB-102-F20-001)		
Assay passing rate	Incurred sample reanalysis [ISR]) 100%	Acceptable
Standard curve performance	The concentrations of the standard calibrators from LLOQ to ULOQ are: 0.2, 2, 10, 40, 140, 400 nmol/L Cumulative bias range: -11.1 to 9.4 % Cumulative precision: ≤ 5.0% CV	Acceptable
QC performance	Cumulative bias range: -10.2 to 15.5% Cumulative precision: ≤6.8% CV	Acceptable
Method reproducibility	Incurred sample reanalysis was performed in 8% of study samples and 100 % of samples met the pre-specified criteria	Acceptable
Study sample analysis/ stability	None of the sample storage period exceeded the 3 years long term stability period	
Method performance in study PB-102-F50 (Analytical study report: PB-102-F50-001)		
Assay passing rate	Incurred sample reanalysis [ISR]) 100%	Acceptable
Standard curve performance	The concentrations of the standard calibrators from LLOQ to ULOQ are: 0.2, 2, 10, 40, 140, 400 nmol/L Cumulative bias range: -8.1 to 6.3%Cumulative precision: ≤4.08 % CV	Acceptable
QC performance	Cumulative bias range: -5.2 to 12.1 % Cumulative precision: ≤ 5.5% CV	Acceptable
Method reproducibility	Incurred sample reanalysis was performed in 8% of study samples and 100 % of samples met the pre-specified criteria	Acceptable
Study sample analysis/ stability	None of the sample storage period exceeded the 3 years long term stability period	

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/s/

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HONGSHAN LI
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YOUWEI N BI on behalf of JIANG LIU
05/08/2023 02:12:18 PM

MICHAEL A PACANOWSKI
05/08/2023 02:52:52 PM

BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761161
Priority or Standard	Priority with major amendment
Submit Date(s)	05/27/2020
Received Date(s)	05/27/2020
PDUFA Goal Date	04/27/2021
Division/Office	DRDMG/ ORPURM
Review Completion Date	April 27, 2021
Established/Proper Name	Pegunigalsidase alfa
(Proposed) Trade Name	ELFABRIO
Pharmacologic Class	Hydrolytic lysosomal neutral glycosphingolipid-specific enzyme
Code name	PRX-102
Applicant	Chiesi USA
Dosage form	Injection, Solution, Concentrate
Applicant proposed Dosing Regimen	1 mg/kg (actual body weight) intravenously every 2 weeks
Applicant Proposed Indication(s)/Population(s)	Fabry disease
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	16652001 Fabry disease (disorder)
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	N/A
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	N/A
Recommended Dosing Regimen	N/A

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Nicolas Kong, Michael G. White
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Clinical Pharmacology Team Leader	Jie (Jack) Wang
Pharmacometrics Reviewer	Hongshan Li
Pharmacometrics Team Leader	Lian Ma
Clinical Reviewer	Anita Zaidi
Clinical Team Leader	Patroula Smpokou
Statistical Reviewer	Yared Gurmu
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DTPM: Division of Translational and Precision Medicine
OB: Office of Biostatistics
DB IV: Division of Biometrics IV

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DPMH	Tinya Sensie RPM; George Greeley RPM TL; Wenjie Sun (Reviewer); Miriam Dinatale (TL); Lynne Yao (Director)
OPDP	TBD

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Nonclinical Director	Mukesh Summan	OND/ORPURM/DPT/RPURM	Sections:	**Select one:** ___ Authored _X_ Approved
Clinical Pharmacology Reviewer	Xiaohui Li	OTS/OCP/DTPM	Sections: 6, Appendix. 3	**Select one:** _X_ Authored ___ Approved

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Jie (Jack) Wang	OTS/OCP/DTPM	Sections: 6, Appendix.3	**Select one:** ___ Authored _X_ Approved
Pharmacometrics Reviewer	Hongshan Li	OTS/OCP/DPM	Sections: 6, Appendix.3	**Select one:** _X_ Authored ___ Approved
Pharmacometrics Team Leader	Lian Ma	OTS/OCP/DPM	Sections: 6, Appendix.3	**Select one:** ___ Authored _X_ Approved
Clinical Pharmacology Division Director	Michael Pacanowski	OTS/OCP/DTPM	Sections: 6, Appendix.3	**Select one:** ___ Authored _X_ Approved
Clinical Reviewer	Anita Zaidi	OND/ORPURM/DRDMG	Sections: 1, 2, 3, 4, 7, 8.2, 9, 10, 12, 13	**Select one:** _X_ Authored ___ Approved

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Deputy Division Director (Clinical)	Patroula Smpokou	OND/ORPURM/DRDMG	Sections: all	**Select one:** ___ Authored _X_ Approved
Statistical Reviewer	Yared Gurmu	OTS/OB/DBIV	Sections: 1, 7, 8.1, Appendix.5-.8	**Select one:** _X_ Authored ___ Approved
Statistical Team Leader	Yan Wang	OTS/OB/DBIV	Sections: 1, 7, 8.1, Appendix.5-.8	**Select one:** _X_ Authored _X_ Approved
OBP ATL	Kelley Burridge	OPQ/OBP/DBRRIV	Sections: 4.2	**Select one:** _X_ Authored _X_ Approved
Biometrics Division Director (OB, DB IV)	Dionne Price	OTS/OB/DBIV	Sections: 1, 7, 8.1, Appendix.5-.8	**Select one:** ___ Authored _X_ Approved

1

Glossary

AC	advisory committee
ADA	anti-drug antibodies
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AET	analytical evaluation threshold
AR	adverse reaction
AUC	area under the curve
BLA	biologics license application
BLISS	Barisoni Lipid Inclusion Scoring System
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CCS	container closure system
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DPH	diphenhydramine
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FD	Fabry disease
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FSS	Fabrazyme Scoring System
Gb3	globotriaosylceramide
GD	gestational day
GCP	good clinical practice
GRMP	good review management practice
HED	Human equivalent dose
ICH	International Conference on Harmonisation

IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
Lyso-Gb3	globotriaosylsphingosine
MedDRA	Medical Dictionary for Regulatory Activities
mFSS	modified Fabrazyme Scoring System
mITT	modified intent to treat
MRHD	Maximum recommended human dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NDA	new drug application
NME	new molecular entity
NOAEL	no observable adverse effect level
NOEL	no observable effect level
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PDE	permitted daily exposure
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PTC	Peritubular Capillary
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SCT	safety concern threshold
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TTC	threshold of toxicological concern

1 Executive Summary

1.1. Product Introduction

Pegunigalsidase alfa is a PEGylated, covalently cross-linked, recombinant human α-galactosidase A (α-GAL-A) enzyme expressed in genetically modified Bright Yellow 2 (BY2) *Nicotiana tabacum* plant cells. Pegunigalsidase alfa supplements or replaces the endogenous α-GAL-A, which is missing or reduced in Fabry disease (FD) patients. Providing an exogenous source of the enzyme reduces the accumulation of globotriaosylceramide (Gb-3) and globotriaosylsphingosine (lyso-Gb3) which accumulates in FD.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The OPQ review of this application identified major deficiencies specific to product manufacturing given Unsatisfactory Drug Product 704(a)(4) Records Review, which preclude approval. In addition, an in-person, pre-license inspection of the manufacturing facilities are required and those cannot be conducted at this time given pandemic-related travel restrictions. As such, the review team recommends a CR action. In addition, the applicant is seeking accelerated approval but late in the review cycle Fabrazyme received full approval for the treatment for Fabry disease, becoming available therapy. For accelerated approval, the applicant will need to show that pegunigalsidase alfa provides a therapeutic advantage over Fabrazyme. Alternatively, the applicant could show that the reductions in Gb3 renal inclusions predict clinical benefit to support full approval. These late-developing issues have not been resolved in this review cycle and will need to be resolved in the next review cycle.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Fabry disease (FD) is a rare and serious inborn error of glycosphingolipid metabolism characterized by deficiency of a single lysosomal enzyme, alpha-galactosidase A. This single enzyme defect leads to progressive accumulation of the upstream metabolite (substrate) globotriaosylceramide (Gb3) due to the enzymatic block in the pathway of its degradation. The major clinical manifestations, which are chronically progressive, severely debilitating, and sometimes life-threatening, include chronic renal impairment leading to renal failure; myocardial infarction; and arrhythmias leading to sudden death, strokes; and chronic neuropathic pain and gastrointestinal dysmotility.

Pegunigalsidase alfa is a pegylated, covalently cross-linked recombinant human protein α-galactosidase A enzyme that replaces the deficient enzyme in FD. The pegunigalsidase alfa clinical trial assessed the effect on Gb3 inclusions in the peritubular capillaries in the kidney assessed by light microscopy using the BLISS methodology. This endpoint was also used for accelerated approval for Galafold and for Fabrazyme (using a different scoring system). The histological endpoint assesses changes in disease-specific substrate burden in the kidney which is one of the major organs affected by FD as published literature has shown that accumulation of Gb3 can lead to structural damage and functional loss.

The demonstration of efficacy comes from trial PB-102-F01/F02 which was an open-label, dose ranging trial that evaluated pegunigalsidase alfa every 2 weeks in adult Fabry disease patients. Patients enrolled in three different dose groups (0.2, 1.0, 2.0 mg/kg). During enrollment of the 2.0 mg/kg group, the applicant opted to stop enrollment of 2.0mg/kg treatment group and made the decision to use 1.0 mg/kg for future trials based on preliminary PK/PD and safety data. A total of 14 patients had kidney biopsies to assess at baseline and at 6 months. Using the BLISS methodology, the median Gb3 score at baseline was 3.2 (range: 0.4, 9) and the median absolute reduction in the renal Gb3 score was -2.5 (range: -8.5, 0.5). The mean absolute reduction was -3.1 (95%CI:-4.8, -1.4;$p<0.001$). There was a large difference between males and females in terms of Gb3 inclusion burden and reduction which is expected as the larger Gb3 burden would more likely be seen in males as they typically have more severe disease given the x-linked nature of the disease. Plasma lyso-Gb3, a metabolite of Gb3 and a pharmacodynamic marker that may correlate with disease severity and treatment effect was noted to be reduced by 49% at 1 year and 81% at 2 years, providing confirmatory evidence of efficacy. Although the efficacy endpoints were exploratory in this trial, the considerable reductions in renal Gb3 inclusions on blinded biospies in 11 of 14 treated patients are compelling for a drug effect given that these inclusions do not spontaneously improve and any variability between biopsy sites would not be expected to bias towards such a treatment effect.

The safety of pegunigalsidase alfa was assessed in 53 patients who received treatment in the open label trials PB-102-F01/F02/F03, open label cross over PB-102-F30 and open label PB-102-F60 trial. No deaths were associated with treatment. Three patients developed anaphylaxis and were withdrawn from treatment. Infusion related reactions occurred in 11 patients. The most frequently reported adverse events were musculoskeletal pain, respiratory tract infections, nasopharyngitis, abdominal pain and headache. Without a concurrent control group, it is unclear whether all these adverse events were related to treatment. Overall, the safety profile is consistent with that expected for an enzyme replacement therapy.

At the present time, we are unable to conclude that the benefits of pegunigalsidase alfa outweigh its risks. Records inspection of the drug product manufacturing site in (b) (4) led to a withhold recommendation on the facility, and inspection of the drug substance site has not yet occurred. Therefore, we are not assured that the product has sufficient quality for approval, and we will be issuing a Complete Response letter based on the withhold recommendation. In addition, the applicant is seeking accelerated approval but late in the review cycle Fabrazyme received full approval for the treatment for Fabry disease, becoming available therapy. For accelerated approval, the applicant will need to show that pegunigalsidase alfa provides a therapeutic advantage over Fabrazyme. Alternatively, the applicant could show that the reductions in Gb3 renal inclusions predict clinical benefit to support full approval. These late-developing issues have not been resolved in this review cycle and will need to be resolved in the next review cycle before we can conclude that the benefits of the drug outweigh its risks and can be approved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	· Fabry disease (FD) is a rare, X-linked, slowly progressive, monogenic disease caused by deficiency of the lysosomal enzyme galactosidase A (alpha-Gal A), which metabolizes glycosphingolipid globotriaosylceramide (Gb3) in lysosomes. · Progressive intralysosomal accumulation of the substrates Gb3 and its related product lyso-Gb3 in affected tissues cause tissue damage and organ dysfunction with progressive and life-threatening complications, including chronic renal failure, cardiac arrhythmias, myocardial infarction, sudden death, and stroke. • Both males and females are affected. The disease course is heterogeneous, especially in females, and generally depends on the amount of residual alpha-Gal A enzyme activity in males and females and on the degree of X-inactivation in affected tissues in females	• FD is a serious and rare disease with chronic, life-threatening complications. • Gb3 and lyso-Gb3 are the tissue-toxic intermediates, which accumulate in affected tissues and mediate the disease pathophysiological mechanism. • Reduction of accumulated GL-3 in affected tissues is expected to ameliorate and/or prevent the clinical effects from the cellular and tissue damage and organ dysfunction caused by this single enzyme deficiency.
Current Treatment Options	• Fabrazyme previously received accelerated approval based on the histological clearance of Gb3 in the peritubular capillaries (PTC) of the kidney and received full approval in March 2021 based on a preponderance of evidence showing that the reduction in Gb3 inclusions predicts clinical benefit. Safety concerns with Fabrazyme include serious allergic reactions and infusion-related reactions.	• Fabrazyme is an enzyme replacement therapy (ERT) that may lead to immune mediated reactions in patients that could lead to intolerance to Fabrazyme therapy. Infusion related reactions have been reported with over half of patients that

	• Galafold, a chaperone therapy was approved under accelerated approval for adults with FD who have specific gene variants that are "amenable" to treatment with the drug based on results of an in-vitro assay (human embryonic kidney, HEK, assay)	have received the therapy in clinical trials. • Galafold is currently approved for only a subset of patients that are considered "amenable" to therapy and its clinical benefit is still unverified as it received accelerated approval and the required postmarketing trial has not been completed.
Benefit	• Efficacy was based on trial PB-102-F01/F02 which assessed the histological decrease in accumulated Gb3 substrate in the kidney PTC. • Trial PB-102-F01/F02 was an open label, dose ranging study that evaluated 3 different doses of pegunigalsidase alfa in adult FD patients. • Among the 14 patients with Gb3 inclusions assessed at both baseline and 6 months, the median baseline number of Gb3 inclusions was 3.2 (range: 0.4, 9) and the median absolute reduction in the number of Gb3 inclusions was -2.5 (range: -8.5, 0.5). The mean absolute reduction in the number of Gb3 inclusions was -3.1 (95% CI: -4.8, -1.4). • Eleven out of 14 patients had a significant reduction in Gb3 inclusions. • Although there was no concurrent control arm, the reduction of renal Gb3 substrate was unlikely due to chance or other factors because of the progressive nature of Fabry disease, and published data indicate no spontaneous reduction in Gb3 inclusions for untreated patients. • At baseline, there was a large difference between males and females in terms of Gb3 inclusion burden, which is expected given that the	• A significant reduction from baseline in Gb3 inclusions in the kidney was seen at 6 months. • Efficacy results appeared to be driven by the treatment effect in males who also had the highest level of substrate deposition. However, this is expected based on the pathophysiology and natural history of FD as males typically have a more severe form of disease due to its x-linked nature. • Plasma lyso-Gb3 is a pharmacodynamic marker that correlates with the severity of disease and may correlate with treatment effect. The long term reduction of plasma lyso-Gb3 is supportive of the continued treatment effect of pegunigalsidase alfa. • The applicant is seeking accelerated approval based on a reduction in Gb3 renal

	disease is X-linked. The median baseline number of Gb3 inclusions was 1.1 for females and 6.8 for males. The mean absolute change from baseline was -0.7 for females and -5.3 for males. • Plasma lyso-Gb3, a metabolite of Gb3 was reduced by 49% reduction at 1 year and 81% at 2 years and correlated well with the 6 month change in kidney Gb3 at 6 months, 9 months and 12 months, providing confirmatory evidence of efficacy.	inclusions. However, late in the review cycle, Fabrazyme received full approval and is now available therapy for Fabry Disease. For accelerated approval the applicant will need to show that pegunigalsidease alfa provides a therapeutic advantage over Fabrazyme. Alternatively, the applicant could provide data to show that their Gb3 inclusion reductions predicts clinical benefit to support full approval.
Risk and Risk Management	• There is a withhold on the drug product manufacturing facility in (b) (4) major deficiencies identified which have not been addressed by the applicant and prevent approvability of the product). In addition, an in-person manufacturing facility inspection of the drug substance facility in Israel is needed and cannot be completed during this review cycle due to pandemic-related restrictions on travel. • The safety of pegunigalsidase alfa was assessed in 53 patients throughout short-term and long-term treatment in the open label trials PB-102-F01/F02/F03, open-label cross-over PB-102-F30 and patients that transitioned from PB-102-F20 to the open label PB-102-F60 trial. • Mean exposure was 21.3 (±2.9) months with 17.0 (±1.9) months mean exposure to the proposed 1.0 mg/kg dose for marketing. • No deaths were associated with pegunigalsidase alfa treatment. Three patients (3/53 or 6%) developed anaphylaxis and were	• Because of inspection issues, we cannot assure that the drug substance and product quality is adequate for approval and, thus, recommend a CR action on the BLA. • The submitted safety database was adequate in terms of duration of exposure and number of patients in a rare disease population such as FD. • Overall, the safety profile appears consistent with what is expected for an enzyme replacement therapy. • The post marketing ongoing confirmatory trial will further assess adverse events that may be related to treatment as it will have

	withdrawn from treatment. Infusion related reactions occurring with 2 hours of the infusion were reported in 11 (11/53 or 21%) patients. This may be an underestimate as additional events were attributed to the infusion procedure and it is unclear whether some of those events may be drug-related. • The most frequently reported adverse events (AEs) reported were musculoskeletal pain, respiratory tract infections, nasopharyngitis, abdominal pain and headache. However, as there was no control group, it is unclear if these AEs were related to treatment.	an active comparator.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
x	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Fabry disease (FD) is an X-linked, slowly progressive, lysosomal disease affecting both males and females. With an estimated incidence of 1:40,000- 1:117,000,[1] it is the second most common lysosomal storage disorder after Gaucher disease. FD is caused by biallelic variants in the *GLA* gene, which encodes the lysosomal enzyme alpha-galactosidase A (alpha-Gal A) that breaks down the glycosphingolipid globotriaosylceramide (Gb3) in lysosomes. Pathogenic *GLA* variants result in complete or partial deficiency of alpha-Gal A, which in turn causes progressive intralysosomal accumulation of the substrate glycosphingolipids globotriaosylceramide (Gb3) and its metabolite globotriaosylsphingosine (lyso-Gb3) in vascular, endothelial, epithelial, smooth muscle, and ganglion cells[1,2] of the kidneys, cardiovascular system, cerebrovascular system, gastrointestinal (GI) tract, peripheral nerves, and skin.

FD spans a spectrum of disease severity ranging from severe, early-onset disease (classic FD) to later-onset, milder disease (late-onset FD) in males. Affected females can have either symptomatic or asymptomatic disease and a wide range of manifestations and severity (depending on X-inactivation in the corresponding cells/tissues). The first clinical manifestations in the classic form of the disease in males typically appear in childhood starting around age 5 years with development of diarrhea or abdominal pain, neuropathic pain crises, and/or hypo/anhidrosis. Females with FD typically present at age 9. Typically, chronic renal insufficiency (initially manifesting as proteinuria, on average appearing in the 20s in classic FD males) slowly progresses to renal failure and end-stage renal disease. Gradual decline in renal function and the development of azotemia typically occur in the third to fifth decades and are managed with hemodialysis and renal transplantation.[2] Males with classic FD with untreated end-stage renal disease (ESRD) typically die in their early 40s.[3] Major causes of mortality in FD include life-threatening cardiovascular (sudden cardiac death, arrhythimas, myocardial infarction) and cerebrovascular complications (stroke). The cardiovascular manifestations can include hypertension, left ventricular hypertrophy, and ischemic heart disease, which

[1] Germain, DP, 2010, Fabry disease, Orphanet J Rare Dis, 5:30, doi: 10.1186/1750-1172-5-30.
[2] Spada, M, S Pagliardini, M Yasuda, T Tukel, G Thiagarajan, H Sakuraba, A Ponzone, and RJ Desnick, 2006, High incidence of later-onset fabry disease revealed by newborn screening, Am J Hum Genet, 79(1):31-40
[3] Waldek S and S Feriozzi, 2014, Fabry nephropathy: a review - how can we optimize the management of Fabry nephropathy? BMC Nephrol, 15:72.

can progress to heart failure, myocardial infarction or arrhythmias.[4] Cardiac disease is progressive and is typically present in most males with classic FD by middle age. Certain cardiac phenotypes can develop hypertrophic cardiomyopathy that may lead to cardiovascular events. Cardiac manifestations tend to occur earlier in affected males than in females.[5] The disease course in late-onset FD is highly variable with some patients experiencing severe manifestations and a more rapid rate of disease progression, while others only have mild or slowly progressive symptoms over their lifetime. Typically, affected males experience more severe disease manifestations and a faster rate of disease progression compared to females due to the X-linked nature of the disease but this is highly variable.[3]

2.2. Analysis of Current Treatment Options

Fabrazyme (agalsidase beta) is a recombinant human alpha-Gal A. It is given as an IV infusion once every 2 weeks at a dose of 1 mg/kg. It was originally approved under subpart E, section 351 of the PHS act in 2003 for the treatment of FD based on histological clearance of the substrate GL-3 inclusions in the kidney interstitial capillary cell globotriaosylceramide (KIC GL-3). This randomized, placebo-controlled, phase 3 trial of Fabrazyme included patients with a diagnosis of FD, plasma alpha-Gal A activity ≤ 1.5 nmol/hr/mL, and plasma GL-3 level ≥ 5 ng/μL. Treatment with Fabrazyme resulted in a statistically significant clearance of GL-3 inclusions in 20 of 29 (69%) treated patients (based on the Genzyme renal histologic methodology) compared to no clearance among patients treated with placebo. Fabrazyme received full approval in March 2021 based on a preponderance of evidence establishing that the reductions in GL-3 inclusions predict clinical benefit. This evidence included several published studies establishing that the central pathophysiological role of tissue GL-3 accumulation in FD has a progressive, detrimental effect on tissue structure and organ function in FD. In addition, exploratory analyses from a long-term observational study suggested that treatment may be associated with slower renal disease progression (eGFR slope) when compared to untreated FD patients. Exploratory analyses from a randomized, placebo-controlled clinical trial also suggested a comparatively favorable clinical effect of Fabrazyme on the incidence of Fabry associated clinical events (renal, cardiac, cerebrovascular events, or death).

Galafold (migalastat) is an α-galactosidase A (α-Gal A) pharmacological chaperone that was approved under the accelerated approval regulations, 21 CFR 314.510 (subpart H) in 2018 in the United Stated and is indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase α gene (GLA) variant based on in-vitro assay data.

[4] Patel, MR, F Cecchi, M Cizmarik, I Kantola, A Linhart, K Nicholls, J Strotmann, J Tallaj, TC Tran, ML West, D Beitner-Johnson, and A Abiose, 2011, Cardiovascular events in patients with fabry disease natural history data from the fabry registry, J Am Coll Cardiol, 57(9):1093-1099.
[5] Linhart, A, C Kampmann, JL Zamorano, G Sunder-Plassmann, M Beck, A Mehta, and PM Elliott, 2007, Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey, Eur Heart J, 28(10):1228-1235

It is given as an oral dose of 123 mg every other day. The phase 3 trial of Galafold included patients with a diagnosis of FD with a GLA variant responsive to Galafold based on the clinical trial human embryonic kidney (HEK) assay. Treatment with Galafold resulted in a greater reduction in GL-3 deposition in the KIC endothelial cells, as assessed by renal biopsy using the BLISS methodology, after 6 months of treatment, compared to placebo. The indication was approved under accelerated approval based on reduction in kidney interstitial capillary cell globotriaosylceramide (KIC GL-3) substrate.

Other approved products (outside of the U.S.):
Replagal (agalsidase alpha) is a recombinant human alpha-Gal A enzyme (containing modified mannose residues) approved in multiple countries including in Europe, Australia, Canada, and Japan for long-term treatment of FD.

Fabagal (agalsidase-beta) is a recombinant analogue of human alpha-galactosidase A and is produced by recombinant DNA technology using Chinese hamster ovary (CHO) cell culture. Fabagal was approved in South Korea for long term treatment of patients with FD.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Pegunigalsidase alfa is a pegylated, covalently cross-linked recombinant human protein α-galactosidase A (α-GAL-A) that is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

Pegunigalsidase alfa was studied under IND 110161 which opened in the United States in 2012 for the indication of FD.

Table 1 below summarizes key pre-submission regulatory interactions between FDA and the applicant.

Table 1: Key Pre-Submission Regulatory Activity

Date	Interaction	Topic
July 15, 2012	IND safety review	Placed on clinical hold because of insufficient nonclinical information
August 9, 2012	IND allowed to proceed	Clinical hold was removed after division accepted follow up information by the Applicant
November 3, 2015	End of Phase 2 meeting	The proposed phase 3 study would be adequate to support a BLA in a superiority study using Fabrazyme as a comparator
January 29, 2018	Fast Track Designation	Applicant was granted Fast Track Designation
February 27 2019	Type C meeting	The Agency agreed that the Applicant can use the Accelerated approval Pathway based on histological reduction of Gb3 in kidney peritubular capillaries in treated patients from trials PB-102-F01/F01. The proposed confirmatory trial would be the ongoing F20 trial which assesses eGFR changes over 24 months in

		patients treated with PRX-102 vs. Fabrazyme
October 15, 2019	Pre-BLA meeting	The Agency asked the Applicant to also provide individual graphical patient profiles on the Gb3 scores over time and more details in the immunogenicity section of the BLA
January 29, 2020	Pediatric Study Plan	Agreed iPSP was accepted

Source: Applicant's table with reviewer's edits

3.3. Foreign Regulatory Actions and Marketing History

Pegunigalsidase alfa is not currently marketed in any other country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Three clinical investigators (CI) were inspected in support of this BLA, covering protocols PB-102-F01 and PB-102-F02 (see Section 7 for a description of these trials). An inspection of the Applicant was not conducted because, at the current time, the COVID-19 global pandemic significantly limits the ability to conduct on-site GCP inspections and instead, the applicant provided the requested certified copies of source documents that were needed to verify the primary endpoint data. During the CI inspections, several discrepancies in the BLISS scores were identified between source documents and the submitted data as well as wide variability between reader scores were noted for 2 of 16 enrolled subjects. The Applicant provided an updated listing of all BLISS scores and a new, revised dataset for the primary efficacy endpoint was submitted for review (which triggered a major amendment). The Applicant provided an acceptable justification regarding the variability between reader scores. Overall, the OSI concluded that the studies were conducted adequately and the data generated at these sites were acceptable in support of the proposed indication. See separate review in DARRTS by Cara Alfaro, Pharm.D. dated 03/02/2021.

4.2. Product Quality

Pegunigalsidase alfa-iwxj, a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme, is a PEGylated, crosslinked, chemically modified, recombinant human alpha-galactosidase A (alpha-Gal A) enzyme that is produced by genetically modified Bright Yellow 2 (Nicotiana tabacum) plant cells. Pegunigalsidase alfa-iwxj is a homodimeric glycoprotein covalently crosslinked with an average of nine 2.3 kD PEG per dimer. The total molecular weight of the cross-linked dimer is approximately 116 kDa. Pegunigalsidase alfa-iwxj has specific activity of approximately (b) (4) U/mg (one enzyme unit is defined as the amount of enzyme which catalyzes the hydrolysis of one micromole of synthetic substrate, p-nitrophenyl-α-D-galactopyranoside per minute at 37°C). Pegunigalsidase alfa-iwxj injection is a sterile, preservative-free, 20 mg/10 mL (2 mg/mL) solution in a single-dose vial for intravenous infusion. Each mL contains 2 mg of pegunigalsidase alfa-iwxj, and citric acid (0.2 mg), sodium chloride (7.06 mg), sodium citrate (b) (4) (b) (4) mg), and Water for Injection, USP. The pH is approximately 5.9 to 6.4.

Drug Substance, Drug Product, Analytical Methods, and Immunogenicity Assays:
This is the first manufacturing process using BY2 cells at Protalix. Plant cells are not commonly used in commercial manufacture of biotechnology products. The controls of the cell culture steps are unusual compared to commonly used cell lines such as Chinese Hamster Ovary and E. coli. The final decision on the adequacy of the process controls will be made after the pre-license inspection.

Proposed post-marketing requirements and commitments (if an approval action is

recommended) are as follows:

1. PMR XXXX-4: Develop and validate an assay for detection of neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa-iwxj.
2. PMR XXXX-5: Develop and validate an anti-PEG IgE antibody assay.
3. PMR XXXX-6: Improve the current anti-pegunigalsidase alfa-iwxj IgG antibody assay or develop a new assay to improve the drug tolerance. Validate the assay.
4. PMR XXXX-7: Revise and re-validate the anti-pegunigalsidase alfa-iwxj IgM antibody assay with anti-pegunigalsidase alfa-iwxj IgM antibodies to be used as positive controls.

(b) (4)

6. PMC XXXX-14: Conduct a drug product (DP) shipping validation study using (b) (4) the first three commercial shipments of finished DP vials from Chiesi Farmaceutici (Parma, Italy) to Chiesi USA (Cary, NC, USA). Include at minimum the following testing on DP samples at release and post-shipping: appearance by visual inspection, particulate matter, non-denatured and denatured SE-HPLC, peptide map purity assay, enzyme kinetics assay, protein content and container closure integrity.
7. PMC XXXX-15: Improve and revalidate the peptide mapping purity method for the drug substance and drug product to quantify the relative concentrations of product-related substances. Characterize oxidized product-related substances and identify those that may be critical quality attributes or stability-indicating; update the drug substance and drug product specifications accordingly with quantitative acceptance criteria for the relevant substances.

(b) (4)

Microbiology:

This BLA was reviewed from a microbial control and product quality microbiology standpoint and is recommended for approval with the following post-marketing commitments:

(b) (4)

Product Quality Team Overall Recommendation: Complete Response (due to Unsatisfactory Drug Product 704(a)(4) Records Review)

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of STN 761161 for ELFABRIO (pegunigalsidase alfa-iwxj) manufactured by Chiesi USA. See the separate Quality Executive Summary in DARRTS dated April 26, 2021. The data submitted in this application are not sufficient to support a conclusion that the manufacture of ELFABRIO is well-controlled and will lead to a product that is pure and potent for the duration of the shelflife. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Chiesi USA to outline the deficiency noted below and the information and data that will be required to support approval.

Facilities
During a review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, the FDA communicated issues with the (b) (4) manufacturing facility named in your application. Satisfactory resolution of the remaining issues is required before this application may be approved. The FDA will communicate the outstanding issues to the facility no later than 10 business days from issuing this complete response letter. Please contact (b) (4) manufacturing facility for additional information.

In addition to the deficiency presented above, OPQ has the following additional comment.

An inspection of the Protalix Ltd. (FEI# 3008289067), Carmiel, Israel manufacturing facility is required before this application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we were unable to conduct an inspection during the current review cycle for your application. You may respond to deficiencies in this Complete Response Letter while the travel restrictions remain in effect. However, even if these deficiencies are addressed, the application cannot be approved until the required FDA inspection is conducted and any findings are assessed with regard to your application. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID 19.

4.3. Clinical Microbiology

N/A

4.4. Devices and Companion Diagnostic Issues

N/A

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

From the nonclinical perspective, no approvability issues have been identified at the proposed dose of 1 mg/kg, administered via intravenous infusion every 2 weeks.

In a mouse model of Fabry disease (alpha-galactosidase A gene knockout; alpha-galactosidase-A deficient), pegunigalsidase alfa (coded as PRX-102) at ≤0.16x the maximum recommended human dose (MRHD) based on human equivalent dose (HED) reduced accumulated levels of globotriaosylceramide (Gb_3) in various tissues including the kidney, skin, heart, spleen, and liver, and reduced damage to peripheral sensory nerves.

Six-month toxicity studies in two species (mice and monkeys) were conducted to support chronic use. Allergic reactions to pegunigalsidase alfa were observed in both species, though more severe in mice. No adverse effects were observed in mice or monkeys at doses up to 1.9x and 4.2x, respectively, the MRHD, based on AUC comparison.

No effects on fertility or reproductive capacity were observed in rats at doses ≤3.6x the MRHD (based on AUC). Pegunigalsidase alfa had no effect on embryonic and fetal development in pregnant rats at doses ≤3.6x the MRHD (based on AUC). However, maternal toxicity was observed in pregnant rabbits at doses ≥3.2x the MRHD (based on HED). Death and increased abortion was observed at doses ≥3.2x the MRHD, and death, increased abortion, body weight loss, decreased body weight gain, increased late resorptions, increased number of dams with resorptions, and increased post-implantation loss were observed at 6.5x the MRHD (based on HED). A pre- and post-natal development study in rats with pegunigalsidase alfa will be conducted as a post-marketing requirement. Genetic toxicity and carcinogenicity studies with pegunigalsidase alfa were not necessary for this biologic product.

The Applicant provided data to support the levels of excipients used in the drug product, and conducted a risk assessment for elemental impurities as recommended in ICH Q3D. An extractables/leachables assessment for the container closure system was also conducted, in line with ICH Q3C(R7) and ICH M7(R1). All excipients in the drug product are at acceptable levels. All identified leachables and elemental impurities were similar to or below the calculated permitted daily exposures (PDE). Thus, there are no safety concerns for leachables from the drug product container closure system or elemental impurities.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Pegunigalsidase alfa is a recombinant human a-galactosidase A enzyme that is internalized and localized to the lysosome of various cells to hydrolyze the substrate globotriaosylceramide (Gb3). In vitro, pegunigalsidase alfa hydrolyzed a synthetic substrate (p-nitrophenyl-alpha-D-galactopyranoside) similarly to agalsidase alfa and agalsidase beta, but was more stable in plasma (pH 7; 37°C) and under lysosomal conditions (pH 4.6, 37°C) than agalsidase alfa and agalsidase beta (1). Following single or repeated administration in a mouse model of Fabry disease, pegunigalsidase alfa decreased accumulated levels of Gb_3 in various tissues including kidney, heart, skin, spleen, and liver, and reduced damage to peripheral sensory nerves.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	Not conducted
Distribution	Not conducted
Metabolism	Not conducted
Excretion	Not conducted

Type of Study	Major Findings
TK data from general toxicology studies • 6-month toxicity study in rats; Study# PRT/040/RIT o NOAEL: 40 mg/kg (high dose) • 6-month toxicity study in monkeys; Study# 1171-011 o NOAEL 40 mg/kg (high dose)	Mouse T1/2: 4.4-6.3 hours Accumulation: No evidence Dose proportionality: Generally linear. AUC of pegunigalsidase alfa decreased over time in males and females, but not Cmax. Monkey T1/2: 12.6-15.0 hours Accumulation: No evidence Dose proportionality: Cmax of pegunigalsidase alfa increased proportionally to dose. AUC of pegunigalsidase alfa increased less than proportionally to dose from 2 to 10 mg/kg, but supraproportionally to dose from 10 to 40 mg/kg after repeated administration. AUC and Cmax of pegunigalsidase alfa decreased over time in males and females.

Type of Study	Major Findings
TK data from reproductive toxicology studies • Blood Collection in Sprague Dawley Rats Exposed to PRX-102 by Intravenous Injection; Study# G10525 o Maternal NOAEL: 40 mg/kg (Study# G9415) o Developmental NOAEL: 40 mg/kg (Study# G9415) • PRX-102: Toxicokinetic Study in New Zealand White Rabbits by Intravenous Injection; Study# PCL-17-009 o Maternal NOAEL: 2 mg/kg (Study# G9416) o Developmental NOAEL: 2 mg/kg (Study# G9416)	<u>Rat</u> 40 mg/kg GD[1] 6 AUC0-48: 5,067,713 ng*h/mL 40 mg/kg GD 15 AUC0-48: 5,086,432 ng*h/mL <u>Rabbit</u> 2 mg/kg GD 6 AUC0-t: 956,599 ng*h/mL 2 mg/kg GD 18 AUC0-t: 125 ng*h/mL • A marked decrease in AUC of pegunigalsidase alfa was observed in rabbits, but not rats, at the end of dosing likely due to the development of anti-drug antibodies in rabbits, but not rats.

[1]GD = gestation day

5.5. Toxicology

5.5.1. General Toxicology

Six-month toxicity studies in two species (mice and monkeys) were conducted to support the chronic use of pegunigalsidase alfa. Allergic reactions to pegunigalsidase alfa were observed in both species, though more severe in mice. No adverse effects were observed in mice or monkeys at doses up to 1.9x and 4.2x, respectively, the MRHD, based on AUC comparison.

PRX-102: Repeated Intravenous (IV) Toxicity in the Mouse with Recovery/ Study PRT/040/RIT

- Mortalities in this study appear to be due to allergic reactions to a humanized enzyme; pre-treatment with diphenhydramine (DPH) decreased the incidence of mortality.

- Anti-drug antibodies were observed in almost half of the animals tested, though only one sample tested positive for pegunigalsidase alfa neutralizing antibodies.
- Histopathological findings at the injection sites were observed in control and pegunigalsidase alfa treated animals, but resolved following the recovery period.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	2, 10, 40 mg/kg/dose; once every 2 weeks (11-17 days)
Route of administration:	Intravenous injection
Formulation/Vehicle:	(b) (4) Citrate buffer, (b) (4) 0.01% Tween 80 and (b) (4) NaCl
Species/Strain:	Mouse/ (b) (4)
Number/Sex/Group:	Interim (Week 12; 7 doses): 15/sex/group Terminal (Week 26; 14 doses): 20/sex/group Recovery (Week 32): 5/sex/group
Age:	7-8 weeks old at initiation
Satellite groups/ unique design:	• Satellite groups were utilized to collect serum and/or plasma samples for antibody and TK analyses • Beginning on the 4th (satellite groups) or 5th (toxicity groups) dose, all animals were pre-treated (30 min prior) with 3-5 mg/kg of diphenhydramine (DPH)
Deviation from study protocol affecting interpretation of results:	None

Observations and Results: changes from control

Parameters	Major findings
NOAEL	40 mg/kg; based on lack of adverse treatment-related findings (excluding allergic reaction to enzyme, as immunogenicity in animals is not considered relevant to predicting potential immunogenicity in humans)
Mortality	Multiple mortalities occurred at all doses, including 2 controls (not allergy-related); likely due to allergic reaction to humanized enzyme. Mortalities decreased after pre-treatment with DPH prior to dosing.
Clinical Signs	Decreased motor activity, dyspnea, cyanosis, abdominal position, and jerks were observed in one 2 mg/kg male and four 2 mg/kg females found dead. These findings were not observed in 10 or 40 mg/kg animals found dead and are likely allergic reactions.
Body Weights	No effect
Ophthalmoscopy	No effect
Hematology	No effect
Clinical Chemistry	No effect
Urinalysis	No effect
Gross Pathology	No effect
Organ Weights	Lung weight increased 17% in 2 and 10 mg/kg males and 21-27% in all pegunigalsidase alfa-treated females. Following the recovery period, absolute lung weight increased further in males; 43%, 21%, and 23% at 2, 10, and 40 mg/kg.
Histopathology Adequate battery: Yes	Injection site reactions (e.g., blood vessel necrosis, perivascular inflammation, and ulceration of the epidermis) were observed in control and high dose males and females at the interim and terminal necropsies. These findings were not present in the recovery animals.
Allergy Evaluation	Platelet activating factor was detected in blood samples from mice, correlating to the allergic reactions observed in most mice without DPH.

PRX-102: A 6-Month Intravenous Infusion Toxicity Study in Cynomolgus Monkeys/ Study 1171-011

- Allergic-type symptoms were observed in a few animals, but did not correlate with the development of anti-drug antibodies; DPH was only administered as needed.
- Histopathological findings at the injection sites were observed in control and pegunigalsidase alfa -treated animals, but resolved following the recovery period.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	2, 10, 40 mg/kg/dose; once every 2 weeks (11-17 days)
Route of administration:	Intravenous injection
Formulation/Vehicle:	(b) (4) Citrate buffer, (b) (4) 0.01% Tween 80 and (b) (4) NaCl
Species/Strain:	Monkey/ Cynomolgus
Number/Sex/Group:	Interim (Week 12; 7 doses): 3-4/sex/group Terminal (Week 26; 14 doses): 4/sex/group Recovery (Week 32): 2/sex/group
Age:	2.33-4.16 years old at initiation
Satellite groups/ unique design:	• 30 minutes prior to the dose administration on Day 43, all animals in the interim group and one in the terminal group were administered 5 mg/kg of DPH. • 30 min prior to the dose administration on Day 57, all animals were administered 5 mg/kg of DPH.

	• After dosing on Day 57, only those animals exhibiting potential allergic-type signs during dosing were to be pre-treated with 5 mg/kg DPH.
Deviation from study protocol affecting interpretation of results:	None

Observations and Results: changes from control

Parameters	Major findings
NOAEL	40 mg/kg; based on lack of adverse treatment-related findings (excluding allergic reaction to enzyme, as immunogenicity in animals is not considered relevant to predicting potential immunogenicity in humans)
Mortality	Unrelated to treatment with pegunigalsidase alfa
Clinical Signs	Allergic reactions (e.g., discolored skin, decreased activity during dosing)
Body Weights	No effect
Ophthalmoscopy	No effect
ECG	No effect
Hematology	No effect
Clinical Chemistry	No effect
Gross Pathology	Red discoloration at the last injection site was observed in control and PRX-102-treated interim and terminal animals.
Organ Weights	Males: Increased weight of epididymides (up to 74%), testes (up to 106%), pituitary gland (up to 44%), thymus (up to 38%), and heart (up to 12%). No correlation to histopathological findings. Females: Decreased weight of ovaries (up to -19%) and adrenal glands (up to -21%), increased weight of salivary glands (up to 29%) and pituitary glands (up to 19%). No correlation to histopathological findings.

Histopathology Adequate battery: Yes	Injection site reactions (e.g., vascular degeneration/necrosis, erosion/ulceration, fibrosis, hemorrhage, and inflammation) were observed in control and pegunigalsidase alfa -treated males and females. These findings were not present in the recovery animals. Minimal to mild lymphocytic infiltration was observed in numerous tissues in control and pegunigalsidase alfa -treated animals.

5.5.2. Genetic Toxicology

Not conducted, in line with ICH S6(R1).

5.5.3. Carcinogenicity

Not conducted, in line with ICH S6(R1).

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

PRX-102: Male and Female Fertility Study (Segment I) by Intravenous Route in Sprague Dawley Rats/ Study G9141

Key Study Findings

- No treatment-related adverse effects were observed.

Conducting laboratory and location	(b) (4) [redacted]
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	2, 10, 40 mg/kg/dose;

	Males: twice weekly four weeks prior to mating, during mating, and for two weeks post-mating Females: twice weekly two weeks prior to mating, during mating, and on GD 0, 4, and 7 for sperm-positive rats
Route of administration:	Intravenous injection
Formulation/Vehicle:	(b) (4) Citrate buffer, (b) (4) 0.01% Tween 80 and (D) (4) NaCl
Species/Strain:	Rat/ Sprague Dawley
Number/Sex/Group:	25/sex/group
Satellite groups:	None
Study design:	• Toxicokinetics not conducted • Different pegunigalsidase alfa lots were administered to different dose groups. Lot# 102DS-011114RD was used in the 2 and 10 mg/kg groups, while lot# 102DS-070314RD was used in the 40 mg/kg group • Pregnant females were terminated on GD 15
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major findings**
NOAEL	40 mg/kg; based on lack of adverse effects
Mortality	None
Clinical Signs	None
Body Weights	No effect
Necropsy findings *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc]*	None

Embryo-Fetal Development

PRX-102: Embryofetal Development Toxicity Study in Sprague Dawley Rats by Intravenous Injection/ Study G9415

Key Study Findings

- No treatment-related adverse effects were observed.

Conducting laboratory and location:	[redacted] (b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	2, 10, 40 mg/kg; GD 6, 9, 12, and 15
Route of administration:	Intravenous injection
Formulation/Vehicle:	Citrate Buffer (pegunigalsidase alfa, 0 mg/mL)
Species/Strain:	Rat/ Sprague Dawley
Number/Sex/Group:	24 females/group
Satellite groups:	None
Study design:	None
Deviation from study protocol affecting interpretation of results:	None

Observations and Results

Parameters	Major findings
NOAEL	40 mg/kg; based on lack of adverse effects
Mortality	None
Clinical Signs	None
Body Weights	No effect

Necropsy findings Cesarean Section Data	None
Necropsy findings Offspring	None

PRX-102: Embryofetal Development Study in New Zealand White Rabbits by Intravenous Injection/ Study G9416

Key Study Findings

- Maternal toxicity at 10 mg/kg (death, increased abortions) and 20 mg/kg (death, increased abortions, body weight loss, increased late resorptions, increased number of dams with resorptions, and increased post-implantation loss).
- Small fetuses at 20 mg/kg and decreased weight of live fetuses at 10 and 20 mg/kg.
- At the maternal and developmental NOAEL, the $AUC_{0\text{-}48h}$ of PRX-102 was 956,599 ng*h/mL on GD 6 and 125 ng*h/mL on GD 18. The decrease in AUC in rabbits at the low dose (2 mg/kg) is likely due to the development of anti-drug antibodies.

Conducting laboratory and location:	(b) (4) [redacted]
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	2, 10, 20 mg/kg; GD 6, 9, 12, 15, and 18
Route of administration:	Intravenous injection
Formulation/Vehicle:	Citrate Buffer (pegunigalsidase alfa, 0 mg/mL)
Species/Strain:	Rabbit/ New Zealand White
Number/Sex/Group:	24 females/group
Satellite groups:	None
Study design:	None

Deviation from study protocol affecting interpretation of results:	None

Observations and Results

Parameters	Major findings
NOAEL	2 mg/kg; based on maternal and developmental toxicity ≥10 mg/kg
Mortality	Low Dose (LD): 0/24 Mid Dose (MD): 2/24 High Dose (HD): 2/24
Abortions	LD: 2/24 MD: 2/24 HD: 4/24
Clinical Signs	None reported
Body Weights	LD: No effect MD: No effect HD: Body weight loss between GD 18-29 (0.146 kg) and over course of gestation (-0.024 kg)
Necropsy findings Cesarean Section Data	LD: No effect MD: No effect HD: Increased late resorptions (1.06 vs 0.42 controls), dams with resorptions (13/17 vs. 9/19 controls), post-implantation loss (1.59 vs. 0.74 controls)
Necropsy findings Offspring	LD: No effect MD: Decreased live weight (-14.5%) HD: Decreased live weight (-27%), small fetuses (2 of 104 fetuses)
Toxicokinetics *Supportive study PCL-17-009*	NOAEL 2 mg/kg GD 6 AUC0-t: 956,599 ng*h/mL NOAEL 2 mg/kg GD 18 AUC0-t: 125 ng*h/mL A marked decrease in AUC of pegunigalsidase alfa was observed in rabbits, but not rats, at the end of dosing likely due to the development of anti-drug antibodies in rabbits, but not rats.

5.5.5. Other Toxicology Studies

Excipients, Leachables, and Elemental Impurities Assessment

Pegunigalsidase alfa is administered once every two weeks via intravenous infusion at a recommended dose of 1 mg/kg (maximum of 140 mg). Pegunigalsidase alfa is an aqueous solution containing 2 mg/mL of the drug substance. Therefore, the maximum dose volume is 70 mL. All identified leachables and elemental impurities were similar to or below the calculated permitted daily exposure (PDEs). Thus, there are no safety concerns for leachables or elemental impurities. There are no novel excipients, or excipients of human or animal origin used in the manufacturing of pegunigalsidase alfa drug product. Levels used in this drug product are similar to or lower than those used in other FDA approved products

The container closure system (CCS) for pegunigalsidase alfa consists of a glass vial closed with a rubber stopper and sealed with aluminum flip-off caps. Leachables testing using the drug formulation in the CCS was conducted on drug product samples from (b) (4) batch representing the worst-case manufacturing process ((b) (4) . The samples were taken from batch number 9942924. A set of six CCS each with 10 mL of the drug product were incubated in an inverted position at 40°C for 1 month (28 days). After the incubation the 6 vials were pooled. Neat solvent was used as the blank and analyzed in parallel with the samples.

The analytical evaluation threshold (AET) was calculated based on ICH M7(R1). Leachables of concern were identified at the threshold of toxicological concern (TTC) for chronic exposure to a genotoxic or carcinogenic compound of 1.5 µg/day, used as the Safety Concern Threshold (SCT). This was used to derive an AET of (b) (4) µg/mL or (b) (4) µg/vial.

Numerous potential leachables were identified and evaluated for safety to yield a quantitative extraction profile (Table 2). The potential daily exposure to each leachable was calculated by multiplying the level of each compound by the maximum volume of drug product per day (70 mL). For all compounds identified at levels higher than 5 µg/day, a complete toxicity assessment was conducted per ICH Q3C or Q3D (as appropriate), and the daily exposure was compared to the calculated PDE. PDEs were calculated based on the most appropriate point of departure (NOAEL, LOAEL, etc.), which was determined by the route of administration, study duration, and level of confidence in the study or value. For all compounds identified at levels between 1.5 and 5 µg/day, a mutagenicity assessment was conducted per ICH M7(R1).

The TTC for leachables identified from the CCS for pegunigalsidase alfa was calculated based on a less than lifetime exposure considering the dosing regimen and patient population. Pegunigalsidase alfa will be administered to patients with FD once every two weeks via intravenous infusion. While the drug is administered chronically, it is not administered daily (i.e., less than lifetime [LTL]). There are three factors that affect the total number of exposure or dosing days for this drug:

1. The earliest age of administration of the drug is 18 years (based on the clinical trial data)
2. Pegunigalsidase alfa is administered once every 2 weeks
3. The life expectancy of Fabry patients is approximately 15 years shorter than in healthy individuals (i.e., approximately 55 years) (Meta and Widmer 2006)

Based on this, the longest that a Fabry adult patient might receive pegunigalsidase alfa treatment is 37 years. Considering that dosing occurs once every two weeks (26 times per year), this corresponds to 962 total doses for a patient in their lifespan. Using the calculation described in ICH M7(R1) to calculate the LTL acceptable daily intake, the adjusted TTC for leachables identified from the CCS for pegunigalsidase alfa is 40 µg/day: Where appropriate, the PDE for each compound or the 40 µg/day TTC was used to calculate the margin of exposure (Table 2).

(1.5 µg/day x 365 days/year x 70 years) ÷ Total number of treatment days = LTL ADI
(1.5 µg/day x 365 days/year x 70 years) ÷ 962 days = 40 µg/day

Table 2: Leachables and Elemental Impurities Risk Assessment

Compound	CAS#	Daily Exposure (µg/day)	Mutagenicity	PDE	Margin of Exposure
(b) (4)					

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6 Clinical Pharmacology

6.1. Executive Summary

The Applicant has submitted results from four clinical studies to support the proposed indication and dosing regimen in adult patients with Fabry disease. The proposed dosing regimen is 1 mg/kg administered every 2 weeks (EVERY 2 WEEKS) by intravenous (IV) infusion. See section 7 for a detailed description of the clinical studies. The Applicant is pursuing accelerated approval based on the effect of pegunigalsidase alfa treatment on reduction of globotriaosylceramide (Gb3) inclusion bodies in the kidney peritubular capillary cells. The pharmacodynamic (PD) effect of pegunigalsidase alfa on reduction of plasma globotriaosylsphingosine (Lyso-Gb3), a metabolite of Gb3, was assessed in enzyme replacement therapy (ERT)-naive patients (studies PB-102-F01/F02 and PB-102-F03) and ERT-experienced patients (study PB-102-F30). ERT-naïve patients were defined as patients who had never received ERT or had not received ERT in the past 6 months and had a negative anti-pegunigalsidase alfa antibody at screening. Pharmacokinetics (PK) of pegunigalsidase alfa was evaluated in the Phase 1/2 dose ranging studies PB-102-F01/F02 in ERT-naive patients. The immunogenicity of pegunigalsidase alfa was evaluated in ERT-naive patients (studies PB-102-F01/F02 and PB-102-F03) and in ERT-experienced patients (study PB-102-F30).

The key review findings are summarized in **Table 3.**

Table 3 Summary of Clinical Pharmacology Findings

Review Issues	Recommendations and Comments
Evidence of effectiveness	• Treatment with pegunigalsidase alfa reduced Gb3 inclusions in kidney peritubular capillary cells in studies PB-102-F01/F02, which is proposed by the Applicant as evidence of effectiveness (for accelerated approval) of pegunigalsidase alfa for the treatment of adult patients with Fabry disease. Refer to Section 8 of this multi-disciplinaryreview for more information. • Treatment with pegunigalsidase alfa reduced plasma Lyso-Gb3 levels in ERT-naïve patients with Fabry disease in studies PB-102-F01/F02. Additionally, reduction in plasma Lyso-Gb3 was also observed in ERT-experienced patients with Fabry disease following treatment with pegunigalsidase alfa in study PB-102-F30. The pharmacodynamic (PD) effect on plasma Lyso-Gb3 reduction demonstrated pharmacologic effect of pegunigalsidase alfa in humans and provided confirmatory evidence of effectiveness.

General dosing instructions	• The proposed dosage of 1 mg/kg administered as an intravenous infusion every 2 weeks was used in clinical trials and is supported by the overall efficacy and safety results.
Dosing in patients subgroups (intrinsic and extrinsic factors)	• Individualization for dose is not necessary because no intrinsic or extrinsic factors were identified that significantly affect PK of pegunigalsidase alfa.
Immunogenicity	• Among 32 patients (16 ERT-naïve patients and 16 ERT-experienced patients), 3 (19%; all males) ERT-naïve patients and 6 (38%; 4 males and 2 females) ERT-experienced patients developed anti-pegunigalsidase alfa IgG antibodies after treatment. • Among the 3 ERT-naïve patients who developed anti-pegunigalsidase alfa IgG antibodies, 2 patients who received the 0.2 mg/kg dose had decreased plasma pegunigalsidase alfa concentrations. • A definitive conclusion of the effect of anti-pegunigalsidase alfa antibodies on PD, efficacy or safety could not be made due to the small number of subjects.
Bridge between the to-be-marketed and clinical trial formulations	• The to-be-marketed formulation of pegunigalsidase alfa was used in clinical trials; therefore, there is no need to bridge between the to-be-marketed formulation to the clinical trial formulation. Of note, 4 manufacturing processes were used to produce pegunigalsidase alfa during the clinical trials of pegunigalsidase alfa. Refer to the OPQ review for the analytical data that support the manufacturing process changes.

6.1.1. Recommendations

From a clinical pharmacology standpoint, this BLA is acceptable to support the approval of pegunigalsidase alfa for the treatment of adults with Fabry disease.

6.1.2. Post-Marketing Requirements and Commitments

The Office of Clinical Pharmacology (OCP) review team agrees with the Office of Biotechnology Products review team's recommendations for the Applicant to conduct post-marketing studies to develop new or improve the current immunogenicity assays. The OCP review team additionally recommends that the Applicant conduct a post-marketing study to evaluate neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa in clinical samples

from studies PB-102-F01/02, PB-102-F03, and PB-102-F30. The recommended post-marketing studies and rationale are summarized in **Table 4**.

Table 4 Post-Marketing Requirement and Commitments

PMR or PMC	Recommended studies and key issues to be addressed	Rationale and key considerations
PMR-4	Develop and validate an assay for detection of neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa.	Pegunigalsidase alfa is a lysosomal ERT that requires cellular internalization for achieving pharmacological activity. Antibodies inhibiting the cellular uptake of pegunigalsidase alfa are expected to reduce the drug effect and should be considered as neutralizing antibodies (NAb). The Applicant did not evaluate NAb inhibiting cellular uptake of pegunigalsidase alfa in the BLA because the assay was not available. Therefore, in order to adequately assess this risk, the Applicant should develop and validate an assay for detection of neutralizing antibodies that inhibit the cellular uptake activity of pegunigalsidase alfa. (b) (4) Additionally, as a separate PMR (PMR-9), the Applicant should assess banked clinical samples from studies PB-102-F01/02, PB-102-F03, and PB-102-F30.
PMR-5	Develop and validate an anti-PEG IgE assay.	An assay that is able to detect anti-PEG IgE antibodies was not developed in the BLA. Therefore, in order to adequately assess the immunogenicity risk, the Applicant should develop and validate an assay that specifically detects anti-PEG IgE antibodies. (b) (4)
PMR-6	Improve the current anti-pegunigalsidase alfa IgG antibody assay or develop a new assay to improve the drug tolerance. Validate the assay.	The current assay used in the BLA can tolerate PRX-102 concentrations up to 500 ng/mL for sensitive detection of low ADA concentrations (250 ng/mL) and can tolerate PRX-102 concentrations up to 4000 ng/mL for sensitive detection of high ADA concentrations (2000 ng/mL). The assessment of the PK data indicates that PRX-102 in plasma at the 2 mg/kg dose level could interfere with the detection of low ADA

		concentrations (250 ng/mL) because the mean concentrations of PRX-102 were all above the drug tolerance level of 500 ng/mL for the ADA assay. PRX-102 in plasma could also interfere with some immunogenicity samples at the 1 mg/kg dose level especially at later timepoints (e.g., Month 12). Immunogenicity samples at the 0.2 mg/kg dose do not have the drug interference issue because the mean drug concentrations were all below the drug tolerance level. Of note, for the detection of high ADA concentrations (2000 ng/mL), the current assay was able to tolerate the drug concentrations across the three dose levels.
PMR-7	Revise and re-validate the anti-pegunigalsidase alfa IgM antibody assay with anti-pegunigalsidase alfa IgM antibodies to be used as positive controls.	The anti-drug IgM assay validation in the BLA was not adequate because the positive control used in the method validation was not appropriate. The revised method will be implemented in future clinical studies.
[redacted]		(b) (4)
PMR-9	Evaluate neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa in clinical samples from studies PB-102-F01/02, PB-102-F03, and PB-102-F30 using the assay developed and validated under PMR-4. Assess the impact of cellular uptake neutralizing antibodies on the pharmacokinetics, pharmacodynamics, efficacy and safety of	See PMR-4.

	pegunigalsidase alfa in a representative sample of patients with Fabry disease treated with the product in clinical trials.	

Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action
Pegunigalsidase alfa provides an exogenous source of alpha-galactosidase A (α-GAL-A), which is internalized and transported into lysosomes where it exerts its enzymatic activity and reduces accumulated globotriaosylceramide (Gb3).

Pharmacodynamics (PD)
Patients with Fabry disease have elevated plasma globotriaosylsphingosine (Lyso-Gb3, a metabolite of Gb3) levels due to low or absent enzyme activity of the lysosomal enzyme α-GAL-A. The PD effect of pegunigalsidase alfa on plasma Lyso-Gb3 was assessed in ERT-naive patients (studies PB-102-F01/F02 and PB-102-F03) and ERT-experienced patients (study PB-102-F30). The results showed treatment with pegunigalsidase alfa reduced plasma Lyso-Gb3 levels in both ERT-naive patients and ERT-experienced patients with Fabry disease.

Pharmacokinetics (PK)
Following IV infusion of pegunigalsidase alfa 0.2, 1 or 2 mg/kg every 2 weeks (EVERY 2 WEEKS) in ERT-naïve patients with Fabry disease, the exposure of pegunigalsidase alfa increased with dose in a more than dose-proportional manner following multiple dose administrations. The PK of pegunigalsidase alfa in plasma at Day 1, Month 3, Month 6, and Month 12 following IV infusion 1 mg/kg EVERY 2 WEEKS are summarized in **Table 5**.

Table 5 Pharmacokinetics [Mean (±SD)] of Pegunigalsidase Alfa in Adult Patients With Fabry Disease Following Intravenous Infusion of Pegunigalsidase Alfa 1 mg/kg Every 2 weeks in Study PB-102-F01/F02

PK Parameters	Pegunigalsidase Alfa			
	Day 1	Month 3	Month 6	Month 12
Mean Infusion Duration (hr)	5.5	4.4	3.9	3.3
C_{max} (mcg/mL)	11.1±2.4	11.9±2.4	13.3±3.0	17.3±6.1
AUC (mcg•hr/mL)	391±136	510±174	748±200	1428±875
Vz (mL/kg)	321±71	271±89	226±116	186±91
$t_{1/2}$ (hr)	78.9±10.3	85.7±28.4	96.5±31.4	121±22
CL (mL/hr/kg)	2.9±1	2.3±1	1.6±1	1.1±1

Source: Table 1 in Module 2.7.2
C_{max}=maximum plasma concentration; AUC=area under the plasma concentration-time curve; Vz=volume of distribution; $t_{1/2}$=elimination half-life; CL=clearance

Immunogenicity
The presence of anti-pegunigalsidase alfa IgG antibodies (anti-drug antibodies or ADA) was assessed in both ERT-naïve and ERT-experienced patients with Fabry disease.

- In study PB-102-F01/F02/F03 in the ERT-naïve patients (N=16) receiving pegunigalsidase alfa treatment at 0.2, 1, or 2 mg/kg EVERY 2 WEEKS, 3 (19%) patients developed IgG ADA. Among the 3 ADA positive patients, 2 patients tested positive for antibodies to plant-specific glycans and 2 patients tested positive for neutralizing antibodies (NAb) inhibiting enzymatic activity.
- In study PB-102-F30, in the ERT-experieced patients (N=16) receiving pegunigalsidase alfa treatment at 1 mg/kg EVERY 2 WEEKS, 6 (38%) patients developed IgG ADA. Among the 6 ADA positive patients, 1 patient tested positive for antibodies to plant-specific glycans and 1 patient tested positive for NAb inhibiting enzymatic activity.

In study PB-102-F01/02, among three subjects who developed antibodies to pegunigalsidase alfa, lower plasma pegunigalsidase alfa concentrations were observed in two patients who received the 0.2 mg/kg dose and no clear antibody effect on PK was observed in the third subject who received 1 mg/kg dose. Anti-pegunigalsidase alfa antibody responses had no apparent effect on efficacy or PD responses (kidney Gb3 inclusions and plasma Lyso-Gb3) in studies PB-102-F01/02/03 and study PB-102-F30. No significant effect of ADA on the safety of pegunigalsidase alfa, as assessed by treatment emergent adverse events (TEAE) and infusion related reactions (IRR), was identified in studies PB-102-F01/02 and study PB-102-F30. However, a definitive conclusion of the effect of ADA on PD, efficacy or safety could not be made due to the small number of subjects although the limited data did not identify significant effects.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The efficacy and safety results in clinical studies in ERT-naïve and ERT-experienced patients with Fabry disease overall support that the proposed pegunigalsidase alfa dosing regimen of 1.0 mg/kg administered IV every 2 weeks is acceptable.

Therapeutic Individualization

The recommended dosage regimen of pegunigalsidase alfa in patients with Fabry disease is based on body weight, which is the approach used in the clinical trials. Of note, body weight was not identified as a significant covariate affecting pegunigalsidase alfa PK in the population PK analyses. The currently available data do not support a need for further therapeutic individualization based on other intrinsic factors.

Outstanding Issues

There are no outstanding issues that would preclude the approval of pegunigalsidase alfa from a clinical pharmacology perspective.

The OBP and OCP review teams identified a few review issues related to the limitation of the immunogenicity assays used in the BLA. We recommend the use of product labeling to communicate the current immunogenicity findings and recommend PMR studies to address the outstanding issues. See **Table 4** for detailed discussion of the review issues and PMR recommendations.

Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology aspects of pegunigalsidase alfa that are relevant to the interpretation of benefit and risk are summarized in Table 6.

Table 6. Summary of Clinical Pharmacology

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Pegunigalsidase alfa is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme.
Mechanism of action	Pegunigalsidase alfa provides an exogenous source of alpha-galactosidase A (α-GAL-A). Pegunigalsidase alfa is internalized and transported into lysosomes where it exerts its enzymatic activity on globotriaosylceramide (Gb3).
Active moieties	The activie moiety is pegunigalsidase alfa. Pegunigalsidase alfa is a PEGylated, covalently cross-linked, recombinant human α-Gal A that is produced by genetically modified Bright Yellow 2 (Nicotiana tabacum) plant cells.
	General Information
Bioanalysis	An enzyme-linked immunosorbent assay (ELISA) was used to quantify pegunigalsidase alfa concentrations in human plasma in PK samples collected in clinical trials. The performance of the bioanalytical method was acceptable.
Healthy subjects vs patients	Pegunigalsidase alfa has not been studied in healthy subjects.
Drug exposure at steady state following the therapeutic dosing regimen	The PK of pegunigalsidase alfa in patients with Fabry disease following IV infusion at the recommended dose regimen 1 mg/kg every 2 weeks (EVERY 2 WEEKS) are summarized in Table 5. The exposure (AUC and Cmax) of pegunigalsidase alfa increased from Day 1 to Month 12 following multiple dose administration; therefore, the drug exposure at steady-state has not been well characterized.
Range of effective dosage(s) or exposure	The recommended dose of pegunigalsidase alfa is 1 mg/kg every 2 weeks. Higher concentrations were associated with greater plasma Lyso-Gb3 reductions in Study PB-102-F01/02 at doses ranging from 0.2 mg/kg to 2 mg/kg.

Characteristic	Drug Information
Accumulation	Following pegunigalsidase alfa IV infusion EVERY 2 WEEKS for 12 months, the mean accumulation ratio based on AUCtau was 1.3 for the 0.2 mg/kg dose and approximately 3.3 for the 1 mg/kg and 2 mg/kg doses.
Time to achieve steady-state	It was predicted by the population PK modeling that steady-state would be achieved at 6 weeks following IV infusion 1 mg/kg EVERY 2 WEEKS. However, the exposure (AUC and Cmax) of pegunigalsidase alfa continued to increase from Day 1 to Month 12 following multiple dose administration; therefore, the time to achieve steady-state has not been well characterized.
Bridge between to-be-marketed and clinical trial formulations	The to-be-marketed formulation of pegunigalsidase alfa was used in the clinical trials; therefore, there is no need to bridge the to-be-marketed formulation to the clinical trial formulation.
	Absorption
Bioavailability	100% since pegunigalsidase alfa is administered via IV infusion.
T_{max}	The T_{max} is expected to be achieved at the end of IV infusion. In clinical trials in patients with Fabry disease, the median T_{max} was 4 to 5 hours (with the mean infusion time of 3.3 to 5.5 hours) in patients with Fabry disease.
	Distribution
Volume of distribution	Following 1 mg/kg IV infusion in patients with Fabry disease, the volume of distribution during the elimination phase was 321 mL/kg after a single dose and ranged from 186 to 271 mL/kg following IV infusion every 2 weeks.
	Elimination
Clearance	Pegunigalsidase alfa exhibited nonlinear PK with the clearance decreasing as the dose increased following multiple dose administration. At 1 mg/kg, the mean systemic clearance (CL) of pegunigalsidase alfa was 2.9 mL/hr/kg following a single IV infusion and 1.1 to 2.3 mL/hr/kg following EVERY 2 WEEKS IV infusion.
Half-life	At the proposed dose of 1 mg/kg, the mean terminal elimination half-life ($t_{1/2}$) of pegunigalsidase alfa was 79 hours following a single dose and 86 to 121 hours after EVERY 2 WEEKS dosing up to 12 months in patients with Fabry disease.
Metabolic pathway(s)	The metabolic pathway of pegunigalsidase alfa has not been characterized. As a lysosomal neutral glycosphingolipid-specific enzyme, pegunigalsidase alfa is expected to be degraded via peptide hydrolysis in a manner similar to endogenous protein.
Primary excretion pathways (% dosage)	The excretion pathways of pegunigalsidase alfa has not been characterized.
	Intrinsic Factors and Specific Populations
Body weight	The population PK analysis results did not identify body weight as a significant covariate effecting the PK of pegunigalsidase alfa. Within the same body weight-based dose level (e.g., 1 mg/kg), the population PK model predicted that the exposure of pegunigalsidase alfa increased with increasing body weight.
Age and gender	Based on population PK analysis, age or gender did not significantly affect the PK of pegunigalsidase alfa.
Renal impairment	No formal trial was conducted to evaluate the effect of renal impairment on the PK of pegunigalsidase alfa.

Characteristic	Drug Information
Hepatic impairment	No formal trial was conducted to evaluate the effect of hepatic impairment on the PK of pegunigalsidase alfa.
	Pharmacodynamics
Biomarker	The concentrations of Lyso-Gb3 in plasma were reduced from baseline in ERT-naïve patients after treatment with pegunigalsidase alfa at doses of 0.2, 1 and 2 mg/kg EVERY 2 WEEKS and in the ERT-experienced patients after treatment with pegunigalsidase alfa at 1 mg/kg EVERY 2 WEEKS.
	Immunogenicity
Bioanalysis	The following bioanalytical methods for immunogenicity assessment were used in the BLA: • ELISA for detecting anti-pegunigalsidase alfa IgG antibodies • ELISA for detecting anti-pegunigalsidase alfa IgM antibodies • ELISA for detecting anti-pegunigalsidase alfa IgE antibodies • Enzymatic activity assay for detecting neutralizing antibodies specific to pegunigalsidase alfa • Assay for detecting antibodies specific for plant glycan motifs in pegunigalsidase alfa • ELISA for detecting antibodies to PEG crosslinker on pegunigalsidase alfa Specific issues related to the limitation of the immunogenicity assays were identified. See **Table 4** for detailed discussion of the review issues and PMR recommendations.
Incidence	Incidence for treatment emergent IgG anti-drug antibodies (ADA) was 19% (3 patients: 2 at 0.2 mg/kg and 1 at 1 mg/kg) in 16 ERT-naïve subjects receiving pegunigalsidase alfa 0.2, 1, or 2 mg/kg EVERY 2 WEEKS and 38% (6/16) in ERT-experienced subjects receiving pegunigalsidase alfa 1 mg/kg EVERY 2 WEEKS. Two of the 3 ERT-naïve subjects and one of the six ERT-experienced subjects who developed antibodies to pegunigalsidase alfa had antibodies that were classified as neutralizing (NAb) inhibiting enzyme active. Antibodies to plant-specific glycan moieties were detected in 1 ERT-naïve patient (1/16, 6.3%) and 1 ERT-experienced patient (1/16, 6.3%). Antibodies reactive with the PEG moieties were detected in 1 ERT-naïve patient and none in ERT-experienced patients.
Clinical impact	Of the 3 ERT naïve subjects who developed antibodies to pegunigalsidase alfa, lower plasma pegunigalsidase alfa concentrations were observed in 2 of the patients. There was no identified significant effect of pegunigalsidase alfa antibodies on the reduction of plasma Lyso-Gb3 levels. Antibodies to pegunigalsidase alfa were generally not associated with changes in the efficacy or safety of pegunigalsidase alfa. However, a definitive conclusion of the effect of anti-pegunigalsidase alfa antibodies on PD, efficacy or safety could not be made due to the small number of subjects.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the pharmacodynamic effect of the product on reduction of plasma Lyso-Gb3 levels in ERT-naïve and ERT-experienced patients in the trials demonstrated the pharmacologic effect of

pegunigalsidase alfa and provides confirmatory evidence of the effectiveness of pegunigalsidase alfa in the treated patients with Fabry disease in the trials.

Pharmacodynamic effect on reduction of plasma Lyso-Gb3

In study PB-102-F01/F02/F03 (see Section 7 for a description of these studies) in ERT-naïve FD patients, all patients experienced a reduction in plasma Lyso-Gb3 concentration from baseline following treatment with pegunigalsidase alfa for 24 months. Treatment naïve patients were defined as patients with FD who had either never received ERT or who had not received ERT in the preceding 6 months and had a negative anti-pegunigalsidase alfa antibody test before enrollment into study PB-102-F01/F02. Individual patient plasma Lyso-Gb3 concentrations, absolute changes from baseline, and percentage changes from baseline following treatment with pegunigalsidase alfa are summarized in **Table 7**. Males had higher concentrations of plasma Lyso-Gb3 at baseline compared to females. The individual percentage change from baseline ranged from -5% to -79% at Month 12 across all patients. Based on the data from the patients who had plasma Lyso-Gb3 at both Months 12 and 24, it appears there is trend in plasma Lyso-Gb3 reduction over time. Overall, greater mean percentage reductions from baseline were observed in males compared to those in females.

In study PB-102-F30 in ERT-experienced FD patients who had been receiving ERT treatment for at least two years prior to enrollment and stayed on ERT during the screening period then were immediately switched to pegunigalsidase alfa, the mean plasma Lyso-Gb3 concentration at baseline was 53.6 nM (42.2 ng/mL, normal <1.8 ng/mL) in males and 13.8 nM (10.9 ng/mL) in females. The mean reductions of plasma Lyso-Gb3 from baseline by sex are shown in **Figure 1**. As shown, by Month 12, none of the patients achieved normal plasma lyso-Gb3 (i.e. <1.8 ng/mL); however, by month 24, three females achieved normal lyso-Gb3(two with level <1.8 and one with level 1.9 ng/mL).

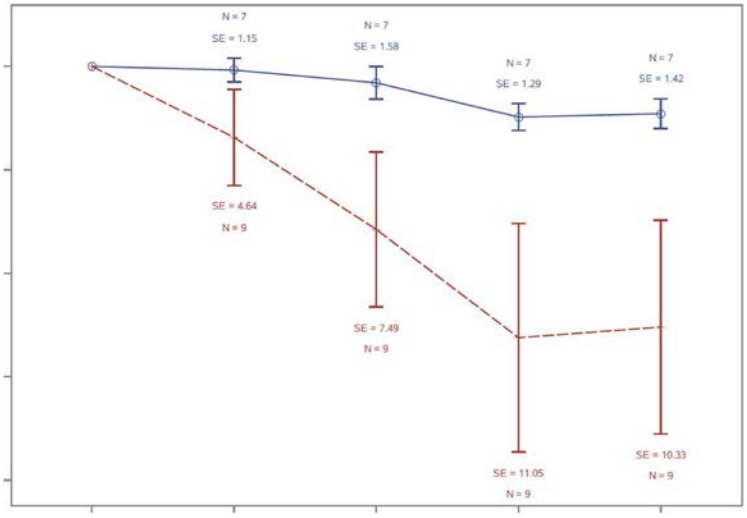
Table 7. Individual Plasma Lyso-Gb3 Levels in Study PB102-F01/F02 and PB102-F03

			Plasma Lyso-Gb3 (ng/mL) (normal < 1.8 ng/mL)				% change from baseline	
Subject ID	PRX-102 dose (mg/kg)	Sex	Study PB-102-F01/F02			Study PB-102-F03	Month 12	Month 24
			Baseline	Month 6	Month 12	Month 24		
(b) (6)	0.2	F	19.2	NA	17.7	NA	-7.8%	NA
	1	M	5.1	2.9	2.8	NA	-45.1%	NA
	1	F	14.4	NA	7.1	NA	-50.7%	NA
	1	M	193.4	NA	46.7	9.2	-75.9%	-95.2%
	1	M	123.0	24.5	35.6	13.7	-71.0%	-88.9%
	2	M	61.8	NA	30.8	11.2	-50.2%	-81.9%
	0.2	M	66.5	6.7	25.2	10.7	-62.1%	-83.9%
	1	M	80.8	34.7	17.2	NA	-78.7%	NA
	1	F	6.8	5.5	4.2	NA	-38.2%	NA
	0.2	M	112.5	NA	40.0	20.7	-64.5%	-81.6%
	2	F	3.4	NA	2.6	1.0	-23.5%	-70.6%
	2	F	5.0	NA	2.2	1.0	-55.6%	-80.0%
	0.2	M	272.9	142.3	69.5	10.3	-74.5%	-96.2%

(b) (6)								
	2	F	10.8	6.6	7.3	1.9	-32.4%	-82.4%
	0.2	M	84.7	44.5	45.7	21.1	-46.0%	-75.1%
	0.2	F	7.5	16.2	7.1	3.3	-5.3%	-56.0%

*This patient did not enroll into Study PB-102-F03.
Source of data: Table 2, Summary of Clinical Pharmacology Studies.

Figure 1. Mean Change from Baseline in Plasma Lyso-Gb3 Concentration by Sex in Study PB-102-F30



Lyso-Gb3 conversion factor: 1 ng/mL=1.27 nmol/L
N=9 for males and N=7 for females at each of the timepoint (Weeks 12, 26, 38 and 52).
Source of data: Figure 11, CSR for Study PB-102-F30

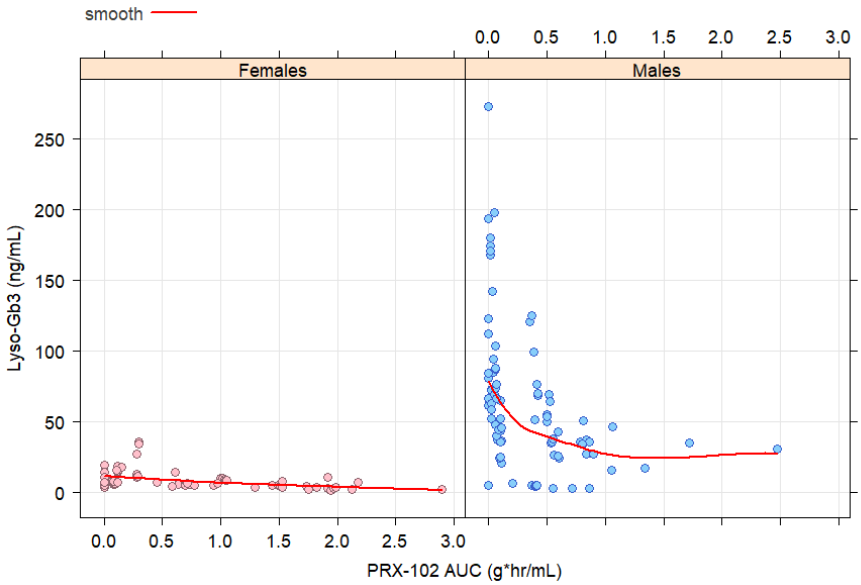
The review team noted a few deficiencies in assessing the submitted assay validations for the bioanalytical methods used to quantify plasma Lyso-Gb3 concentrations. Some assay validation parameters were based on published literature. See OCP appendix for detailed assay performance information. Because the PD effect on plasma Lyso-Gb3 reduction was consistently observed in individual patients in pegunigalsidase alfa clinical trials, and the reduction of plasma Lyso-Gb3 showed statistical correlation with the primary efficacy result based on renal Gb3 inclusion changes from baseline (see section 8), we consider that the observed PD effect of the product on reducing plasma Lyso-Gb3 demonstrates the pharmacological activity of pegunigalsidase alfa in patients with Fabry disease, and this PD effect can be used as confirmatory evidence of effectiveness of pegunigalsidase alfa. However, given the lyso-Gb3 assay limitations, we do not recommend reporting absolute values of plasma Lyso-Gb3 concentrations in product labeling.

Exposure-response for plasma Lyso-Gb3

The exposure-response (E-R) relationships for plasma Lyso-Gb3, based on the data in 16 ERT-naïve patients in study PB-102-F01/F02 over 12 months of treatment, are shown in **Figure 2**. The E-R relationship showed greater reduction in plasma Lyso-Gb3 with increasing

pegunigalsidase alfa exposure (e.g., AUCtau) in males. The trend of E-R relationship was less recognizable in females due to the low baseline plasma Lyso-Gb3 concentrations.

Figure 2. Relationship Between Predicted AUCτ of Pegunigalsidase Alfa and Plasma Lyso-Gb3 in Studies PB-102-F01/F02



The observations are the red and blue circles.
AUC is population PK model predicted AUC over the 2-week dosing interval
Source of data: Figure 12-7, Applicant's PPK and PKPD report

The E-R analysis was limited by the small number of subjects and could have been confounded by factors including varying baseline values of lyso-Gb3 across dose levels and imbalanced distribution in sex. In addition, the E-R analysis for plasma Lyso-Gb3 was based on absolute values and pooled data over time which have included multiple datapoints per subject. See OCP Appendix for additional analyses that further explored the E-R relationships for plasma Lyso-Gb3 based on percent change from baseline as the PD endpoint, which did not show a significant E-R relationship. As such, the overall E-R relationships for plasma Lyso-Gb3 are considered inconclusive.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the general patient population. The proposed EVERY 2 WEEKS dosing regimen was studied in trial PB-102-F01/F02 and overall supported by efficacy and safety findings.

Dose selection Rationale for clinical trials

The Applicant selected three dose levels (0.2, 1.0 and 2.0 mg/kg IV EVERY 2 WEEKS) of pegunigalsidase alfa in the first-in-human (FIH) study PB-102-F01/F02. The selection of the 1.0 mg/kg dose was in consideration of the approved dose of 1.0 mg/kg for Fabrazyme because

pegunigalsidase alfa exhibits the same mechanism of action as Fabrazyme. In the 26-week nonclinical study in monkeys, the most representative species for predicting effects in humans, the no-observed-adverse-effect (NOAEL) dose was 40 mg/kg which supported the safety of the selected doses in the FIH study. Overall, the selected three dose levels in study PB-102-F01/F02 are considered reasonable to explore the dose-response relationships of pegunigalsidase alfa in patients with Fabry disease.

Dose-/exposure-response for efficacy and safety

Kidney biopsy was performed at baseline in study PB-102-F01/F02 and following a total of 6 months of treatment with pegunigalsidase alfa. The average number of Gb3 inclusions in renal peritubular capillaries was assessed as the primary efficacy endpoint. No clear dose-response relationship was identified when comparing the change from baseline in renal Gb3 inclusions or plasma Lyso-Gb3 across the three doses (0.2 mg/kg, 1 mg/kg and 2 mg/kg), which may be due to the small number of subjects per dose group, confounding factors (e.g., sex), and the lack of randomization in the study design. Similar safety profiles were observed across the three dose levels, except for the higher incidence of ADA associated with the 0.2 mg/kg dose. See Section 8 of this multi-discipline review for details of the efficacy results.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No, an alternative dosing regimen or management strategy is not necessary for subpopulations based on intrinsic factors. The only intrinsic factor identified to have an impact on PK of pegunigalsidase alfa was the presence of NAbs, which resulted in a transient decrease in pegunigalsidase alfa exposure. The currently available data are too limited to support a dose adjustment based on a subject's immunogenicity status.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interaction is unlikely for pegunigalsidase alfa because pegunigalsidase alfa is administered by IV infusion.

Drug interaction studies have not been studied with pegunigalsidase alfa. The enzyme portion of pegunigalsidase alfa is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous proteins. To our knowledge, cytochrome P450 (CYP) enzymes do not play a considerable role in PEG elimination, although the exact route of elimination of the PEG portion of pegunigalsidase alfa has not been studied. Direct drug interactions between pegunigalsidase alfa and small molecule drugs that are metabolized by cytochrome P450 (CYP) enzymes are unlikely.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 8. Table of Clinical Studies

Trial Identity	Design, Phase	Regimen/Schedule /Route	Endpoints	Duration/ follow up	# of patients	Population	# of centers a countries
Efficacy Trials							
PB-102-F01	Open-label (OL), dose-ranging, phase 1/2	0.2mg/1mg/2mg/kg IV Q2 weeks	Safety; eGFR, plasma Gb3, plasma lyso Gb3	12 weeks	16 patients (6 patients 0.2mg, 6 patients 1mg/kg; 4 patients 2mg/kg	Symptomatic adult FD patients: Males α gal activity < 3.2nmol/hr/ml Females – genetic test consistent with FD	13 study cen Paraguay, UK Serbia, Spain
PB-102-F02	OL, extension	0.2mg/1mg/2mg/kg IV Q2 weeks	Safety; eGFR, plasma Gb3, plasma lyso Gb3; KIC Gb3 inclusions	38 weeks	16 patients (6 patients 0.2mg, 6 patients 1mg/kg; 4 patients 2mg/kg	Rollover of patients from PB-102-F01	
Safety Trials							
PB-102-F03	OL, extension	1mg/kg IV Q2 weeks	Plasma lyso Gb3, GI symptoms, eGFR, left ventricular mass and myocardial fibrosis	Ongoing; up to 5 years	15 patients	Roll-over from PB-102-F02	13 study cen Paraguay, UK Serbia, Spain
PB-102-F30	OL, switch over from agalsidase alfa Phase 3	1mg/kg IV Q2 weeks	Change in eGFR, left ventricular mass index, plasma lyso-Gb3, plasma Gb3	2 years	22 patients	Symptomatic adult FD patients Males- α gal activity less than lower limit of normal Females – genetic test consistent with FD	10 study cen Spain, Austra Norway, Cana Netherlands, Slovenia
PB-102-F60	OL extension	1mg/kg IV Q2 weeks		Ongoing Up to 4 years	29 patients	Roll-over from PB-102-F30 and F20	
PB-102-F20 ongoing	R, DB Active control,	1mg/kg IV Q2 weeks	Comparison of mean annualized	Ongoing 2 years	78 patients	Symptomatic adult FD patients	Argentina, Australia, Bel Brazil, Canad

	Superiority Phase 3	Randomized 2:1 to treatment vs. Fabrazyme	change in eGFR				Czechia, Finla France, Germ Hungary, Italy Netherlands, Norway, Para Slovenia, Spa Switzerland, Turkey, UK, U

7.2. Review Strategy

7.1 provides an overview of the clinical studies that form the basis of support for the benefit-risk assessment of PRX-102. For this BLA review, data on histological decrease in accumulated Gb3 substrate in kidney peritubular capillaries (PTC) from trial PB-102-F01/F02 was reviewed to determine if there is substantial evidence of effectiveness. Additional data on Plasma Lyso-Gb3 from studies PB-102-F01/F02/F03 and study PB-102-F30 was assessed to provide further support for efficacy of PRX-102. The Agency's efficacy evaluation focused on the following endpoints:

1. Main efficacy endpoints: absolute and percent change from baseline to month 6 in the average number of Gb3 inclusions per kidney PTC
2. Supportive efficacy endpoints: absolute and percent change in plasma lyso-Gb3 from baseline to post-baseline study visits

The Agency's draft guidance on Fabry disease states: "Applicants can use histological reduction of GL-3 (Gb3) inclusion burden in biopsied kidney interstitial capillaries (KIC) as a surrogate endpoint reasonably likely to predict clinical benefit to support accelerated approval." [*Page 6, Fabry Disease: Developing Drugs for Treatment*] Accordingly, the efficacy evaluation (and the proposal for accelerated approval) of PRX-102 is based on reduction in the average number of Gb3 inclusions as the main efficacy endpoint.

The Agency used histological reduction of Gb3 inclusion burden in the kidney as a surrogate endpoint for the accelerated approval of Fabrazyme [https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103979s5135lbl.pdf] and Galafold [https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208623lbl.pdf]. The Fabrazyme trial used an endpoint capturing Gb3 inclusion severity based on the Fabrazyme Scoring System (FSS) with scores ranging from 0 (normal or near normal) to 3 (severe inclusions). The Galafold trial used an endpoint capturing the average number of Gb3 inclusions per kidney PTC based on the BLISS methodology (Barisoni et al, 2012).

Similarly, the Applicant submitted the PRX-102 BLA seeking accelerated approval based on a reduction in renal interstitial capillary Gb3 inclusions. When the PRX-102 BLA was submitted, both Fabrazyme and Galafold still had accelerated approval. However, during the review of this BLA, Fabrazyme received full approval, becoming available therapy for Fabry disease, which has important implications on whether PRX-102 can receive accelerated approval. The Applicant needs to provide a justification and relevant evidence that PRX-102 has a therapeutic advantage over the available therapy. This point is still under review and will be revisited with the applicant in the next review cycle.

Plasma Lyso-Gb3 is a Fabry disease-specific PD biomarker and has been used to provide supportive evidence of efficacy in the accelerated approval of Galafold for the treatment of Fabry disease patients with amenable GLA variants (Multi-disciplinary Review NDA 20862 and

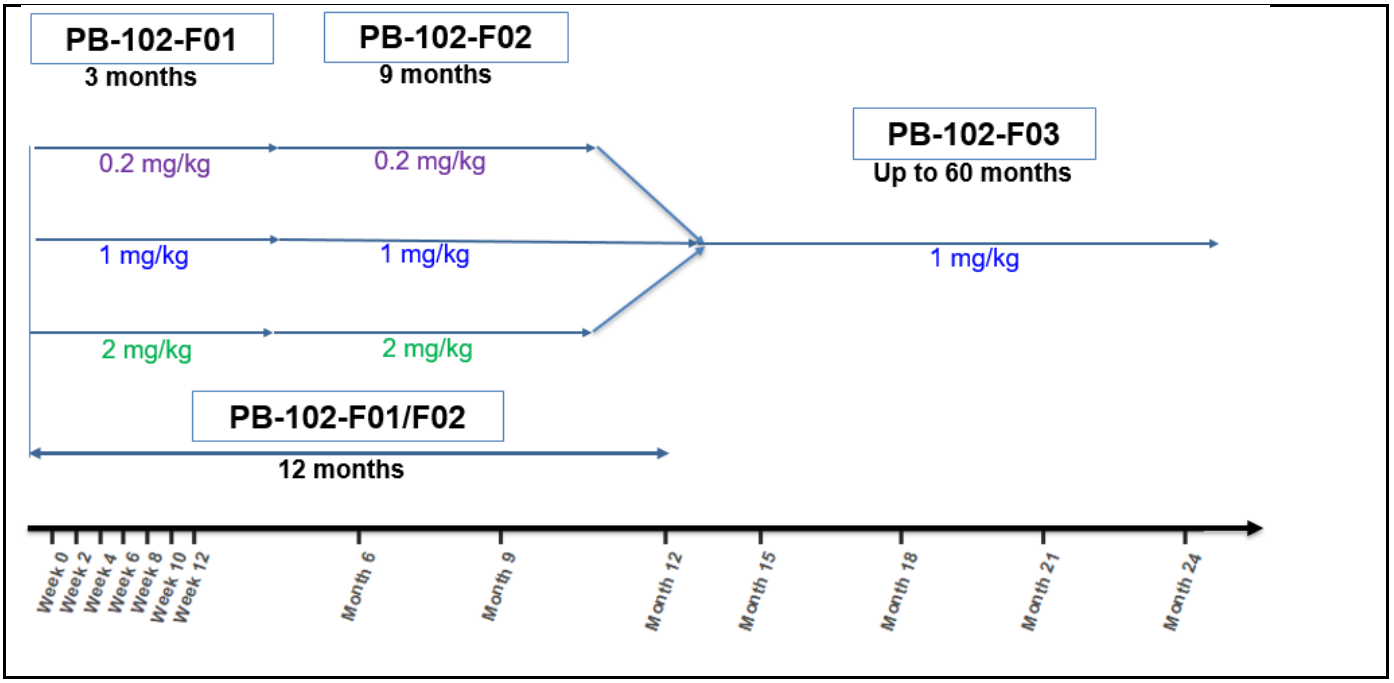
also Galafold Label).

Trials PB-102-F01/F02/F03, PB-102-F30 and PB-102-F60 were reviewed in support of safety. The tables and analyses presented in this review reflect the independent data analyses of the review team except where otherwise noted. Patient narratives of deaths, serious adverse events, and adverse dropouts related to the trials were individually reviewed.

8 Statistical and Clinical and Evaluation

Review of Relevant Individual Trials Used to Support Efficacy

Figure 3: PB-102-F01, PB-102-F02, and PB-102-F03 Trial Design



Study drug is administered intravenously every 2 weeks.
The main efficacy endpoint, Gb3 inclusion per kidney PTC, is assessed at baseline and at 6 months in Study PB-102-F01/F02.
The supportive efficacy endpoint, change in Plasma Lyso-Gb3 is assessed at all time points shown in the figure.

8.1.1. Trial PB-102-F01

Title: A Phase 1/2, Open Label, Dose Ranging Study to Evaluate the Safety, Tolerability,

Pharmacokinetics and Exploratory Efficacy Parameters of PRX-102 Administered by Intravenous Infusion Every 2 Weeks for 12 Weeks to Adult Fabry Patients

Trial Design

PB-102-F01 was an open-label, dose ranging study that evaluated 3 different doses of pegunigalsidase alfa. Patients were enrolled into one of three pegunigalsidase alfa treatment groups (0.2, 1.0 or 2.0 mg/kg) and received IV infusions every 2 weeks for 12 weeks (total of 7 infusions). The first patient was given the lowest dose of 0.2 mg/kg for at least 4 infusions and, only if the dose was well tolerated, the second patient was given 0.2 mg/kg. After all 6 patients tolerated all 7 infusions of 0.2 mg/kg, the 6 patients in next group would receive 1 mg/kg and followed the same stepwise progression. Four patients were given 2.0 mg/kg dose after all 6 patients tolerated the 7 doses of 1.0 mg/kg. Regarding early stopping of patient enrollment into the 2.0 mg/kg group, the Applicant's study report provided the following rationale (page 4): *"At the time of enrollment of the 4thpatient into the 2.0 mg/kg treatment group, the Applicant opted to stop enrollment to the 2.0 mg/kg treatment group and made the decision to use 1.0 mg/kg doses for the pivotal studies. This decision was based on the data obtained thus far from the non-clinical studies, but particularly from the preliminary PK/PD and safety data as an optimal dose between pharmacokinetics, potential efficacy, immunogenicity and infusion-related reactions for the Phase 3 program."*

Key Inclusion Criteria:

- Symptomatic adult Fabry patients ($\geq$ 18 years, males and females)
- Males: plasma and/or leukocyte α galactosidase activity less than lower limit of normal in plasma (3.2 nmol/hr/mL) and/or leukocytes (32 nmol/hr/mg/protein)
- Females: historical genetic test results consistent with Fabry mutations
- Gb3 concentration in urine >1.5 times upper limit of normal
- Patients who have never received ERT in the past, or patients who have not received ERT in the past 6 months and have a negative anti-pegunigalsidase alfa antibody test
- eGFR$\geq$60 mL/min/1.73m^2

Endpoints

1. Safety, tolerability, PK, PD, immunogenicity
2. Efficacy (exploratory):
   - Plasma and urine Gb3 concentrations
   - Plasma lyso-Gb3 concentration
   - eGFR, proteinuria
   - Assessment of gastrointestinal symptoms
   - Short Form Brief Pain Inventory (BPI)

Protocol Amendments

Protocol amendments were reviewed; they were implemented to improve patient safety.

8.1.2. Trial PB-102-F02

Title: An Extension of Phase 1/2, Open Label, Dose Ranging Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Exploratory Efficacy Parameters of PRX-102 Administered by Intravenous Infusion Every 2 Weeks for 38 Weeks (9 Months) to Adult Fabry Patients.

Trial Design

Upon completion of the 12 week treatment period in trial -F01, patients had the option to enroll in an open-label extension study (study -F02) for an additional 9 month treatment period. Patients continued to receive the same dose of pegunigalsidase alfa that they received in PB-102-F01, as an IV infusion every 2 weeks for 38 weeks. An interim analysis was planned to evaluate a subset of pre-defined exploratory efficacy parameters in patients with a total of 6 months of treatment.

Key Endpoints

1. Safety, tolerability, PK, PD, immunogenicity
2. Efficacy (exploratory):
   - Change from baseline (measured in Study PB-102-F01) to six months in the average number of Gb3 inclusions per kidney PTC assessed by the BLISS. The terms *renal Gb3 BLISS score* or *BLISS score* may be used to refer to the average number of Gb3 inclusions per kidney PTC.
   - Plasma Gb3 concentration (mg/mL) and plasma Lyso-Gb3 concentration (ng/mL).
   - Change in eGFR and proteinuria levels.
   - Cardiac function by echocardiography and stress test.
   - Cardiac MRI (left ventricular mass, left ventricular mass index, ejection fraction and myocardial fibrosis)
   - Short Form Brief Pain Inventory (BPI): Pain severity and pain interference
   - Brain MRI: Qualitative assessments for evidence of stroke
   - Gastrointestinal Symptoms Questionnaire.
   - Mainz Severity Score Index (MSSI): Qualitative assessments regarding signs/symptoms in general, neurological, cardiovascular, renal dysfunction.

Assessment of renal Gb3 inclusions (for details, see Sections 15.5-15.8)

Kidney biopsy was performed at baseline of Study PB-102-F01 and 6 months post treatment with pegunigalsidase alfa (at the Month 3 visit of Study PB-102-F02) for study patients. Approximately 300 kidney peritubular capillaries were scored in each specimen. Two scoring

systems, a quantitative Barisoni Lipid Inclusion Scoring System (BLISS) and a semi-quantitative modified Fabrazyme Scoring System (mFSS), were used for the assessment of Gb3 inclusions in kidney peritubular capillary (PTC) biopsy samples. These two scoring systems were implemented by 3 blinded pathologists.

The BLISS counts the number of Gb3 inclusions in each PTC. The final score of each biopsy was the average number of Gb3 inclusions across PTCs. A higher score is indicative of more severe disease on the histologic level. Note: the BLISS was used in Galafold's clinical trial (Barisoni, et al., 2012).

The mFSS assigns a score based on presence/absence of Gb3 inclusions/granules/aggregates and ranges from 0 (no inclusions) to 3 (bulging aggregates) in each PTC. In the original FSS as used in Fabrazyme's clinical trial (Eng et al., 2001; Thurnberg, et al., 2002), the final score for each biopsy slide was the score assigned to the majority of PTCs. In the modified FSS (mFSS) used in Study PB-102-F01/F02, for each severity score (0, 0.5, 1, 2, or 3), the proportion of capillaries receiving the given score was calculated. The following two tables provide a summary for the three systems.

Table 9: Comparative Histological Methodologies of BLISS, FSS, and mFSS

	Comparative Histological Methodology		
	Fabrazyme Score System [a]	**Modified- Fabrazyme Score System [b]**	**BLISS Methodology [c]**
Overall scoring approach	Semi-quantitative	Semi-quantitative	Quantitative
Visualization methodology	Conventional light microscopy (glass slides @ 100x)	Digital pathology (whole slide images scanned @100x)	Digital pathology (whole slide images scanned 100x)
PTC Annotation	No	Yes	Yes
Number of Interstitial capillaries scored	≥50	~300	~300
Metric for each PTC score	Semiquantitative (0-1-2-3)	Semiquantitative (0-0.5-1-2-3)	Quantitative: Number of Gb3 inclusions
Scoring protocol	3 scoring pathologists	1 annotator/adjudicator 2 scoring pathologists	1 annotator/adjudicator 2 scoring pathologists
Score per biopsy per pathologist	Given by the majority of PTC with any given score	N/A	Average of inclusion per PTC
Overall impression per biopsy per pathologist	Pathologist's perception of severity (Gestalt)	N/A	N/A

Final biopsy score	Given by the majority of PTC with any given score. In case of discrepancies on PTC score the three pathologists were supposed to reconvene and give an agreed final score	N/A [d]	The score of the biopsy is the average of the scores given by the two pathologists
Definition of "Score 0"	≥ 50% of PTCs have no GL-3 inclusions AND < 5% of PTCs have a score of ≥ 1 (more that 2 or 3 inclusions) [e]	N/A	Zero GL-3 inclusions in any interstitial capillary

a Barisoni 2012
b Eng 2001
c Barisoni 2015, Barisoni Poster
d The final calculation was not done initially but has since been completed following the Agency guidance
e Galafold Approval Package NDA 208623
Source: Table 1 of the Applicant's responses to the Agency's information request, submitted to BLA761161 (eCTD 0046) on April 6, 2021

Table 10: Comparative Information for the Scoring System Among FSS, mFSS, and BLISS

	Score per PTC						Score per Biopsy				
	0	0.5	1	2	3	4,5,…20	0	1	2	3	4,5,….20
FSS	0-2 inclusions	N/A[a]	>3 inclusions – no aggregates	> 1 Non bulging aggregates	Bulging aggregates	N/A[b]	The majority of PTC have a score of 0	The majority of PTC have a score of 1	The majority of PTC have a score of 2	The majority of PTC have a score of 3	N/A[b]
mFSS	0 inclusion	1 inclusion	>2 inclusions – no aggregates	> 1 Non bulging aggregates	Bulging aggregates	N/A	Individual biopsy scores not generated for mFSS	Individual biopsy scores not generated for mFSS	Individual biopsy scores not generated for mFSS	Individual biopsy scores not generated for mFSS	N/A
BLISS	0 inclusion	N/A[a]	1 inclusion counted	2 inclusions counted	3 inclusions counted	4,5,,…20 inclusions counted	When no inclusions are detected in any of the 300 PTC scored	When an average of 1 inclusion per PTC is calculated using all 300 PTC scored	When an average of 2 inclusions per PTC is calculated using all 300 PTC scored	When an average of 3 inclusions per PTC is calculated using all 300 PTC scored	When an average of 4,5,….20 inclusions per PTC is calculated using all 300 PTC scored

a Not applicable - the option 0.5 is not included in BLISS or FSS
b Not applicable - the semiquantitative scoring systems FSS and mFSS included options between 0 and 3 only
Source: Table 2 of the Applicant's responses to the Agency's information request, submitted to BLA761161 (eCTD 0046) on April 6, 2021

Barisoni et al. (2012) concluded that the BLISS can detect a small amount of Gb3 inclusions and thus it is more sensitive compared to the FSS. This conclusion is further supported by the data from Study PB-102-F01/F02 (see pages 10-11 of the Applicant's histology report). More details on the BLISS, mFSS, and FSS are included in 15.5 and 15.6

For the supportive endpoint of annualized eGFR slope (ml/min/1.73 m^2 per year) eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula provided below:

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

Scr = serum creatinine; $\kappa = 0.7$ for females and 0.9 for males; $\alpha = -0.329$ for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Source: Applicant's statistical analysis plan for PB-102-F01/F02, page 24
Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate

Protocol Amendments

Protocol amendments were reviewed and they were implemented to improve patient safety. As such, these amendments appear to not have affected the efficacy assessments or analyses.

8.1.3. Trial PB-102-F03

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

Trial Design
Study PB-102-F03 is an open-label extension study of PB-102-F02 administering PRX-102 for up to 60 months. The study drug is administered intravenously at a dose of 1.0 mg/kg every 2 weeks (Figure 3). Patients who had received 0.2 mg/kg or 2 mg/kg of PRX-102 in Study PB-102-F02 were gradually switched to 1 mg/kg given intravenously every 2 weeks. Patients who had originally received 1 mg/kg of PRX-102 in Study PB-102-F02 continued to receive the same dosage in this extension study. This is an ongoing study and an interim analysis was planned after all patients completed 12 months of follow-up in this study. When combining across studies (Figure 3), the interim analysis is conducted after patients have completed at least 24 months of treatment with PRX-102 (3 months in study PB-102-F01, 9 months in study PB-102-F02 and 12 months in study PB-102-F03).

Endpoints
Long-term safety, exploratory efficacy (endpoints were similar to study PB-102-F02 except for the lack of assessment of Gb3 inclusions in the kidney).

Statistical Analysis Plans (Studies PB-102-F01, PB-102-F02, PB-102-F03)

For all three studies listed above, the Applicant's SAPs proposed to use descriptive approaches to summarize efficacy data. Specifically, continuous variables would be summarized using mean, standard deviation, standard error, median, minimum, maximum and interquartile range, while categorical variables were summarized using count and percentages. In the Applicant's clinical study reports, p-values were provided based on paired t-tests for the absolute and percent changes in renal Gb3 BLISS score. The review team conducted non-parametric tests given the small sample size of the study.

Analysis of Change in Renal Gb3 BLISS Score at the Patient Level (N-of-1 analysis)

For each patient, the review team conducted analysis to compare the average number of Gb3 inclusions across the approximately 300 capillaries (i.e., the renal Gb3 BLISS score) at baseline and at six months. This comparison was conducted using two-sample t-tests for each of the 14 individual patients. Note: for each patient, the Applicant provided an estimated density function for the difference in the mean BLISS score between the baseline and 6-month visits using a bootstrap approach (see Sections 15.5).

Analysis of Change in Renal Gb3 Inclusions Using mFSS

The Applicant's study report provided summary statistics to examine the Gb3 inclusions as measured by the mFSS and showed an increase from baseline to Month 6 in the percentage of capillaries scoring 0-0.5. The review team conducted the following analyses:

1. Comparison of the change from baseline to six months in **the percentage of capillaries with mFSS score of 0 or 0.5**. This analysis is conducted using a permutation test under the null hypothesis of no treatment effect (i.e. the mean difference from baseline to six-months in the percentage of capillaries with mFSS score of 0 or 0.5 is 0).

2. Comparison of the proportion of patients with **biopsy-level score of 0** at baseline and at six months utilizing an exact version of McNemar's test. The biopsy-level score of zero was defined using the following two approaches:
    a. **majority-rule approach**: this approach assigns a biopsy score of 0 if a majority of the capillaries in that biopsy received a score of 0.
    ~~b.~~ **alternate approach**: this approach assigns a biopsy score of 0 if at most 5% of the capillaries have mFSS score > 1 (i.e. at least 95% have mFSS score ≤ 1) **and** at least 47.5% of the capillaries have mFSS score of 0 (i.e., 0 inclusion).

3. Comparison of the patient-level change from baseline to six months in the **average biopsy-level score**. The review team defined the average biopsy-level score as the weighted average of the capillary-specific scores. For example, if 30% of capillaries have a score of 3, 49% a score of 2, 20% a score of 1, 10% a score 0.5, and 11% a score of 0, the average biopsy-level score will be 2.13 (= 0.3*3 + 0.49*2 + 0.2*1 + 0.1*0.5 + 0.11*0).

Since the Applicant's stated objective considered the evaluation of efficacy to be exploratory, all reported p-values are nominal.

Subgroup analyses were conducted by sex, drug dose group, Fabry disease phenotype (classic vs. non-classic) and ADA status. A patient was classified as having a positive treatment-induced ADA status if:

1. the patient was IgG negative at baseline and positive at any timepoint post-baseline, or,
2. the patient was IgG positive at baseline and experienced IgG titer increase of at least 4-fold from baseline

Definition of Classic Phenotype:

The Applicant's definition of classic phenotype required patients meet the following two criteria and applied to both male and female patients:

- **a.** patients with <30% of the mean of the normal range of alpha-galactosidase A (α-Gal A) activity in the leukocyte (normal range: 33 to 144 nmol/hr/mg) and plasma (normal range: 4 to 21.9 nmol/hr/mL),
- **b.** have at least one of the Fabry disease specific symptoms such as neuropathic pain, cornea verticillata, or clustered angiokeratoma.

The Review team's definition of classic phenotype applies only to male patients, did not use criteria **(b)** above, and used a more stringent threshold of <5% of the mean of the normal range of alpha-galactosidase A (α-Gal A) activity in the leukocyte and plasma. A threshold of <1% was also implemented but there was only 1 patient who met this criterion, and therefore no further analysis is performed using this latter threshold. All relevant efficacy results will be presented using the Review team's definition of classic phenotype.

Sensitivity Analysis Including the Subject With Mislabeled Biopsy Slides

One subject (ID: (b) (6) was removed from the Applicant's efficacy analysis of Gb3 inclusions as a result of the patient's biopsy slides being mislabeled. For this subject, there was a high level of discrepant scores between readers and the patient's biopsy slides could not be matched to the correct visits (i.e. baseline versus six-month visit times could not be identified). Nonetheless, the review team was able to derive the BLISS score based on the Applicant's raw dataset for each visit, and conduct sensitivity analysis for the following two scenarios:

1. Worst case scenario analysis (assumes the BLISS score increased by attributing the higher of the two scores to the six month visit)
2. Best case scenario analysis (assumes the BLISS score decreased by attributing the higher of the two scores to the baseline visit)

The results of the sensitivity analysis including this subject's scores are presented in Table 16 and support the results of the main efficacy analysis.

8.1.4. **Results**: Trial PB-102-F01/PB-102-F02

Compliance with Good Clinical Practices

According to the submission (page 19 of the PB-102-F01/F02 study report), the applicant states "this study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, in compliance with the approved protocol, Good Clinical Practice (GCP) guidelines and applicable regulatory requirements." "An institutional review board (IRB) or Ethics committee (EC) reviewed the study protocol and any amendments. The IRB or EC also reviewed the informed consent forms, their updates (if any), and any written materials given to the subjects."
The applicant provided a signed copy of FDA form 3454 with a list of investigator names from each trial. This certified that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a).

Patient Disposition

Forty-two patients were screened from 13 study sites, of these, only 19 from 11 study sites were considered eligible for enrollment as the other 23 patients did not meet the inclusion or exclusion criteria. Six patients were enrolled in the 0.2 mg/kg treatment group, nine in the 1.0 mg/kg and 4 in the 2.0 mg/kg treatment group. The Applicant stopped enrollment into the 2mg/kg cohort after 4 patients were enrolled after the decision was made that the 1mg/kg was considered the optimal dose for treatment (see clinical pharmacology section). One patient who was in the 1.0 mg/kg treatment group voluntarily withdrew consent from the study prior to receiving any study treatment. At the time of enrollment of the 4th patient into the 2.0 mg/kg treatment group, the Applicant stopped enrollment to this dose based on preliminary PK/PD and safety data to use 1.0 mg/kg as the optimal dose. Two patients who were in the 1.0 mg/kg treatment group discontinued the study, one experienced a hypersensitivity reaction (Grade 3 bronchospasm) during the first infusion and one was found noncompliant to the study and discontinued due to investigator recommendation after the patient received one infusion. Sixteen patients completed study PB-102-F01 and all 16 patients enrolled into study PB-102-F02. All sixteen patients also completed the 9 month extension study PB-102-F02.

Protocol Violations/Deviations

A total of 188 protocol deviations occurred with 84 in PB-102-F01 and 104 in PB-102-F02. Fourteen patients had 37 major protocol deviations. None of the deviations appear to impact the outcome of the study's efficacy or safety analysis.

Table 11: Trial PB 102-F01/F02 Major Protocol Deviations

Deviation Type	Event

Good clinical practice issue	3
Missed visits	4
Infusion Issues	4
Dosing Issues	4
Post-Infusion Safety Period	12
Procedures not Performed	3
Inclusion Criteria	7

Source: reviewer table

Demographics/Baseline Characteristics

Demographic characteristics are notable for 75% of patients being white, 56% of patients were male and 44% of patients were female. Among the 9 male patients, 7 (78%) had the classic Fabry phenotype.

At baseline, there was a large difference between males and females in terms of Gb3 inclusion burden (females have generally lower average number of Gb3 inclusions per PTC compared to males) which is expected due to the x-linked nature of the disease and the tissue mosaicism of the expression of the abnormal X chromosome in females (who are heterozygous). The more extensive substrate deposition in the PTC is indicative of more severe disease on the histologic level and in general, females tend to have lower (and highly variable) Gb3 burden in tissues and typically milder disease manifestations compared to males. This may explain the discrepancy that resulted in the different efficacy responses between males and females. Plasma lyso-Gb3 was also noted to be much larger in the male population than in the females which is consistent with the severity of disease seen in males versus female FD patients. Residual enzyme activity in leukocyte and plasma were much lower among males compared to females.

Table 12: Population Demographic and Baseline Characteristics of the 16 Patients Who Completed Study PB-102-F01/F02

	Female (N=7)	*Male (N=9)*	*Overall (N=16)*
Age (years)			
Mean (SD)	38 (15)	29 (9)	33 (12)
Median (min, max)	34 (20, 54)	27 (17, 50)	30 (17, 54)
Race, n (%)			
White	6 (85.7)	6 (66.7)	12 (75.0)
Black or African American	1 (14.3)	2 (22.2)	3 (18.8)
Other	0 (0.0)	1 (11.1)	1 (6.2)
Ethnicity, n (%)			
Hispanic or Latino	2 (28.6)	1 (11.1)	3 (18.8)
Not Hispanic or Latino	5 (71.4)	8 (88.9)	13 (81.2)
FD Phenotype, n (%)			
Non-classic	7 (100.0)	2 (22.2)	9 (56.2)

Classic[1]	0 (0.0)	7 (77.8)	7 (43.8)
Type of Variant, n (%)			
Nonsense	1 (14.3)	1 (11.1)	2 (12.5)
Missense	3 (42.9)	7 (77.8)	10 (62.5)
Duplication	0	0	0
Duplication and frame shift	0	1 (11.1)	1 (6.3)
Plasma α-Gal A activity (% of mean normal range[2])			
Mean (SD)	[4]—	3.2 (3.0)	—
Median (min, max)	—	2.4 (0.0, 9.3)	—
Leukocyte α-Gal A activity (% of mean normal range[3])			
Mean (SD)	[4]—	1.8 (1.3)	—
Median (min, max)	—	1.3 (0.0, 3.4)	—
Renal Gb3 score (BLISS)[5]			
Mean (SD)	1.7 (1.0)	5.7 (3.1)	4.0 (3.1)
Median (min, max)	1.2 (0.8, 3.3)	6.8 (0.4, 9.0)	3.2 (0.4, 9.0)
Plasma Lyso-Gb3 (ng/mL)			
Mean (SD)	9.6 (5.6)	111.2 (79.3)	66.7 (78.0)
Median (min, max)	7.5 (3.4, 19.2)	84.7 (5.1, 272.9)	40.5 (3.4, 272.9)
eGFR CKD (mL/min/1.73m^2)			
Mean (SD)	108.1 (20.7)	116.0 (23.0)	112.6 (21.6)
Median (min, max)	115.1 (77.7, 131.8)	115.8 (82.4, 156.3)	115.1 (77.7, 156.3)
eGFR MDRD (mL/min/1.73m^2)			
Mean (SD)	97.5 (21.9)	110.5 (30.5)	105.0 (27.0)
Median (min, max)	99.5 (69.7, 131.2)	107.2 (74.8, 166.3)	100.8 (69.7, 166.3)
Creatinine (mg/dL)			
Mean (SD)	0.7 (0.1)	0.9 (0.1)	0.8 (0.2)
Median (min, max)	0.7 (0.6, 0.8)	1.0 (0.7, 1.1)	0.8 (0.6, 1.1)
Protein/Creatinine Ratio (mg/g)			
Mean (SD)	208.0 (127.0)	112.4 (72.9)	150.7 (105.6)
Median (min, max)	195.0 (81.0, 405.0)	105.0 (42.0, 298.0)	106.0 (42.0, 405.0)
Total Protein Random Urine (mg/dL)			
Mean (SD)	25.5 (16.1)	13.3 (3.4)	18.1 (11.7)
Median (min, max)	23.5 (9.9, 44.5)	12.5 (8.7, 19.1)	12.5 (8.7, 44.5)
ACEI/ARB use, n (%)			
No	6 (85.7)	6 (66.7)	12 (75.0)
Yes	1 (14.3)	3 (33.3)	4 (25.0)
NSAID use, n (%)			
No	1 (14.3)	2 (22.2)	3 (18.8)

Yes	6 (85.7)	7 (77.8)	13 (81.3)
History of ERT use, n (%)			
Yes	*1 (14.3)*	*5 (55.6)*	*6 (37.5)*
No	6 (85.7)	4 (44.4)	10 (62.5)
PRX-102 Dose, n (%)			
0.2 mg/kg	2 (28.6)	4 (44.4)	6 (37.5)
1.0 mg/kg	2 (28.6)	4 (44.4)	6 (37.5)
2.0 mg/kg	3 (42.9)	1 (11.1)	4 (25.0)

α-Gal A: alpha-galactosidase A; **ACEi:** Angiotensin-converting-enzyme inhibitors; **ARB:** Angiotensin II receptor blockers

[1] The review team's definition of Classic phenotype was restricted to male patients and required patients to have plasma and leukocyte α-Gal A activity < 5% of the mean of the normal range.

[2] The normal range for α-Gal A activity in the plasma is 33 to 144 nmol/hr/mg.

[3] The normal range for α-Gal A activity in the leukocyte is 4 to 21.9 nmol/hr/mL.

[4] Enzyme activity measurements are not reliable in females.

[5] The BLISS methodology counts the number of GbL-3 inclusions in each renal PTC contained in a biopsy specimen. For each biopsy specimen, approximately 300 renal PTCs were scored, and the final biopsy score for each patient was determined as the average number of GbL-3 inclusions per PTC.

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD0035) on February 8, 2021. Figures on history of ERT use, NSAID use and type of variant were supplied by the Applicant on April 16, 2021 (eCTD 0048).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Fabrazyme, Replagal and any enzyme replacement therapy were prohibited six months prior to screening and any time during study participation. Any other investigational therapy was prohibited 30 days prior to screening or at any time during study participation.

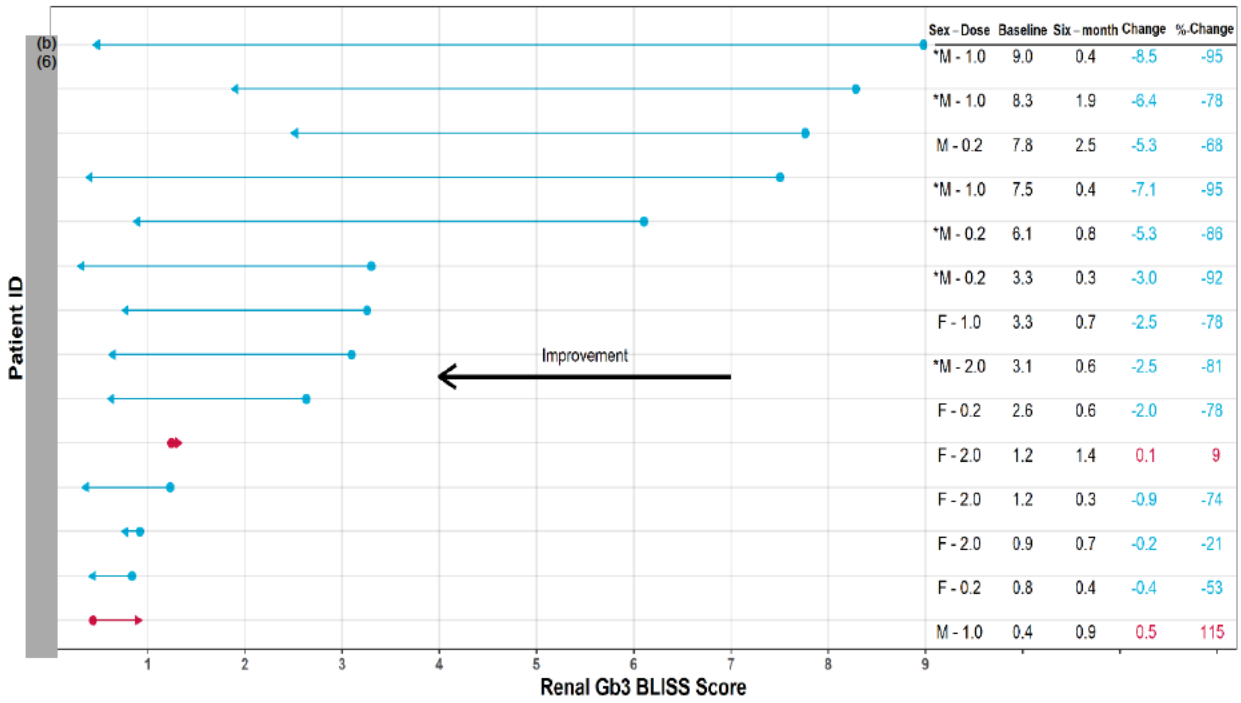
Efficacy Results: Change from Baseline in Renal Gb3 BLISS Score (Average Number of Gb3 Inclusions per PTC)

A total of 14 patients who had Gb3 inclusions assessed at both baseline and 6 months were included in the main efficacy analysis of Gb3 inclusions. Their data are presented in **Figure 4**. Overall, 12/14 (86%) patients had lower renal Gb3 BLISS score at 6 months, while two patients (baseline scores: 0.4 and 1.2) had a minimal increase. For the nine patients who had a baseline renal Gb3 BLISS score above 2, the minimum percent reduction in Gb3 inclusions at six months was 68%. Analysis of change in renal Gb3 BLISS score at the patient level (N-of-1 analysis) showed that 11/14 (79%) patients had a significant reduction ($p<0.001$) at six months (**Figure 4**). This analysis provides compelling evidence of efficacy for PRX-102 because the chance of observing a favorable outcome in 11 out of these 14 patients is 2% if PRX-102 was ineffective.

The median absolute reduction in the renal Gb3 BLISS score was -2.5 (range: -8.5, 0.5; $p = 0.001$), and the median percent reduction was -78% (range: -95%, 115%; $p = 0.017$) (**Table 13**).

The mean absolute reduction in the number of Gb3 inclusions was -3.1 (95% CI: -4.8, -1.4; p < 0.001), and the mean percent reduction was -55% (95% CI: -88%, -22%; p = 0.017).

Figure 4: Changes in Renal Gb3 BLISS Score (Average Number of Gb3 Inclusions per Kidney PTC) by Patient (Study PB-102-F01/F02)



Dots (•): Baseline BLISS score Arrow heads (◄): 6-Month BLISS score (*): Classic Fabry Disease

Increase in BLISS score from baseline to six month indicated in red while decrease in BLISS score is indicated in blue..

The biopsy data for 2 patients (out of the 16 patients enrolled in PB-102-F01/02) could not be used in the main efficacy analysis; 1 female patient had biopsy tissue that could not be scored at baseline as it was taken from the medulla of the kidney; 1 male patient had biopsy slides that were scanned out of focus and mislabeled, and subsequently could not be matched to correct visits (i.e. baseline versus six-month visit times could not be identified).

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025)) on November 11, 2020

Table 13. Changes in Renal Gb3 BLISS Score by Sex (Trial PB-102-F01/F02)

	All Patients (N = 16) [a]	Male (N = 9)	Female (N = 7)
Baseline (n)	14	8	6
Mean (SD)	4 (3.1)	5.7 (3.1)	1.7 (1)
Median (Range)	3.2 (0.4, 9)	6.8 (0.4, 9)	1.2 (0.8, 3.3)
Month 6 (n)	15	8	7

Mean (SD)	0.8 (0.6)	1 (0.8)	0.7 (0.4)
Median (Range)	0.7 (0.3, 2.5)	0.7 (0.3, 2.5)	0.7 (0.3, 1.4)
Change from baseline at Month 6 (n)	14	8	6
Mean (SD)	-3.1 (2.9)	-4.7 (2.9)	-1.0 (1.1)
Median (Range)	-2.5 (-8.5, 0.5)	-5.3 (-8.5, 0.5)	-0.7 (-2.5, 0.1)
95% CI for mean	-3.1 (-4.8, -1.4)	-4.7 (-7.1, -2.3)	-1 (-2.1, 0.1)
P-value[b]	<0.001	0.015	0.058
P-value[c]	0.001	0.016	0.063
% Change from baseline at Month 6 (n)	14	8	6
Mean (SD)	-55 (57)	-60 (71)	-49 (36)
Median (Range)	-78 (-95, 115)	-83 (-95, 115)	-63 (-78, 9)
P-value[b]	0.006	0.068	0.066
P-value[c]	0.017	0.195	0.063

[a]Of the 16 patients enrolled in Study PB-102-F01/F02, 14 patients provided renal tissue that could be assessed using the BLISS methodology.

[b]Permutation test for the mean change.

[c]Exact Wilcoxon signed-rank test for the median change.

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025) on November 11, 2020

Subgroup Analyses

Both male and female patients experienced considerable reductions in renal Gb3 score at six months (**Table 13**). Among the eight male patients, seven of them had relative reductions ranging from 68% to 95%. Among the six female patients, five of them had relative reduction ranging from 21% to 78%. The median absolute reductions were -5.3 (range: -8.5, 0.5; p = 0.016) for males and -0.7 (range: -2.5, 0.1; p = 0.06) for females. The median percent reductions were -83% (range: -95%, 115%; p = 0.20) for males and -63% (range: -78%, 9%; p = 0.06) for females (**Table 13**). As expected, the observed effect on the female patients was lower compared to the male patients because the baseline values of Gb3 inclusions were significantly lower in the females patients (median of 1.1 for females vs. 6.8 for males).

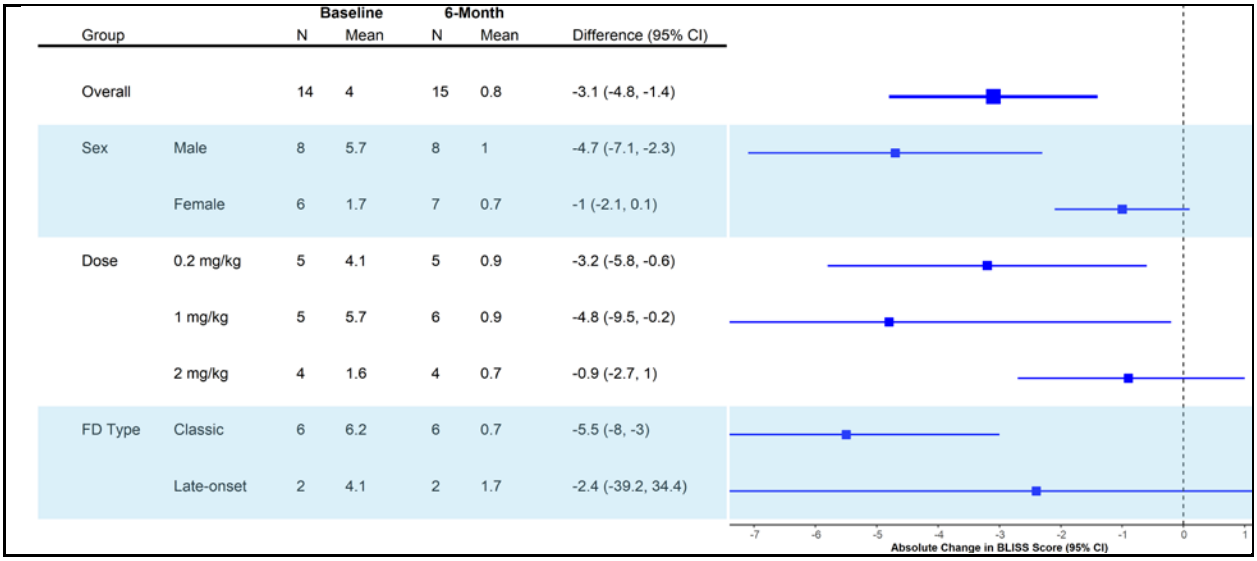
Regarding the three drug doses of 0.2, 1, and 2 mg/kg, the 2 mg/kg arm had lower median values of Gb3 inclusions at baseline: 3.3 and 7.5, and 1.2 for the three dose arms, respectively. The median percent changes were -78%, -78%, and -47% and the median changes were -3.0, -6.4, and -0.5 for the three dose arms (**Table 14**), respectively. For the 2 mg/kg arm, the significantly lower median change and percent change from baseline seemed to be driven by the higher proportion of females who had lower numbers of Gb3 inclusions at baseline. The proportion of females was 74% (3/4) in the 2 mg/kg arm compared to 33% (2/6) in the other two arms. Since the three females in the 2 mg/kg arm had a baseline renal Gb3 BLISS score ranging from 0.9 to 1.2 (Figure 4), the possible maximum reductions at 6 months for these

patients cannot exceed 1.2. Therefore, given the small sample sizes and the imbalance in the baseline values of Gb3 inclusions, it is challenging to compare the treatment effects among the three dose arms. Of note: the Applicant considered 1 mg/kg dose as the optimal dose and evaluated it in their randomized and controlled phase 3 trial (on-going) to demonstrate clinical benefit using the eGFR slope endpoint.

A total of 6 patients met the review team's definition of classic phenotype and they had a 78% or greater reduction in the renal Gb3 BLISS score (**Figure 4**). The mean and median percent reductions were 88% and 89%, respectively; the mean and median absolute reduction were -5.5 and -5.8.

Patients with positive treatment-emergent ADA status (n = 2) had a mean percent reduction of -82% in BLISS scores vs. -51% for patients with negative treatment-emergent ADA status (n = 12). The mean absolute reductions were -6.9 and -2.5 for the ADA positive and negative groups, respectively.

Figure 5: Absolute Change in Renal Gb3 BLISS Score from Baseline to 6 months By Sex, Dose, and FD phenotype



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025) on November 11, 2020

Table 14: Renal Gb3 BLISS Score by Dose (Trial PB-102-F01/F02)

	All Patients (N = 16) [a]	0.2 mg/kg (N = 6)	1 mg/kg (N = 6)	2 mg/kg (N = 4)
Baseline (n)	14	5	5	4
Mean (SD)	4 (3.1)	4.1 (2.8)	5.7 (3.7)	1.6 (1)
Median (Range)	3.2 (0.4, 9)	3.3 (0.8, 7.8)	7.5 (0.4, 9)	1.2 (0.9, 3.1)

Month 6 (n)	15	5	6	4
Mean (SD)	0.8 (0.6)	0.9 (0.9)	0.9 (0.6)	0.7 (0.4)
Median (Range)	0.7 (0.3, 2.5)	0.6 (0.3, 2.5)	0.7 (0.4, 1.9)	0.7 (0.3, 1.4)
Change from baseline at Month 6 (n)	14	5	5	4
Mean (SD)	-3.1 (2.9)	-3.2 (2.1)	-4.8 (3.7)	-0.9 (1.2)
Median (Range)	-2.5 (-8.5, 0.5)	-3 (-5.3, -0.4)	-6.4 (-8.5, 0.5)	-0.5 (-2.5, 0.1)
95% CI for mean	-3.1 (-4.8, -1.4)	-3.2 (-5.8, -0.6)	-4.8 (-9.5, -0.2)	-0.9 (-2.7, 1)
P-value[b]	0.001	0.066	0.125	0.248
P-value[c]	0.001	0.063	0.125	0.25
% Change from baseline at Month 6 (n)	14	5	5	4
Mean (SD)	-55 (57)	-75 (15)	-46 (90)	-42 (43)
Median (Range)	-78 (-95, 115)	-78 (-92, -53)	-78 (-95, 115)	-47 (-81, 9)
P-value[b]	0.005	0.066	0.378	0.25
P-value[c]	0.017	0.063	0.625	0.25

[a]Of the 16 patients enrolled in Study PB-102-F01/F02, 14 patients provided renal tissue that could be assessed using the BLISS methodology.
[b]One-sample comparison of mean change using permutation test.
[c]Exact Wilcoxon signed-rank test p-value.
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD0025) on November 11, 2020

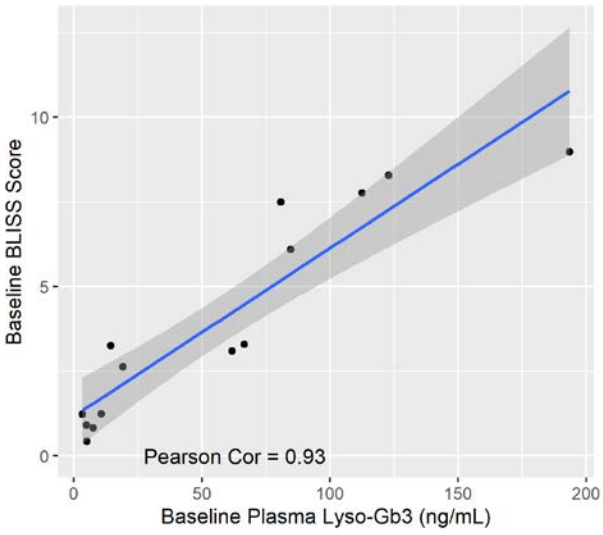
Correlation of Changes in Kidney Gb3 with Changes in Plasma-Lyso Gb3

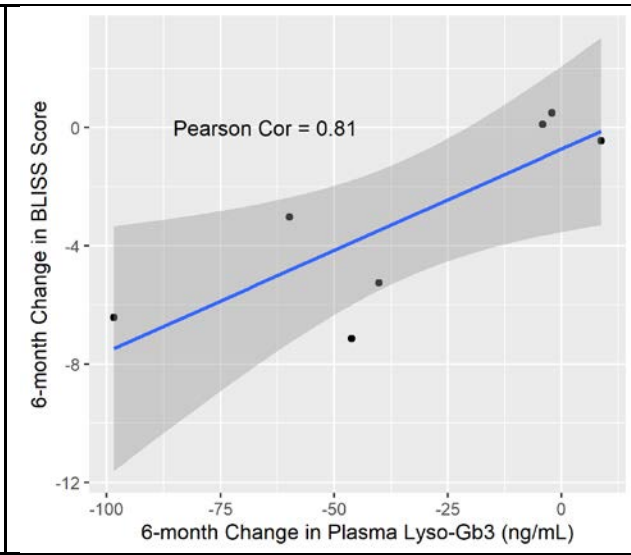
The reduction in kidney Gb3 inclusions was accompanied by a marked reduction in Plasma Lyso-Gb3 with all patients showing a reduction in Plasma Lyso-Gb3 at both 1 year and 2 year visits. Female patients had an average reduction of 31% and 72% at 1 and 2 years, respectively, while male patients had an average reduction of 63% and 86% at 1 and 2 years, respectively (Figure 30).

There was a strong correlation between change in kidney Gb3 inclusions and change in Plasma-Lyso Gb3 (Figure 6) . At six months the correlation between the two biomarkers was 0.81. The correlations between six-month change in kidney Gb3 and change in Plasma-Lyso Gb3 at 12-months (n=14) and 24-months (n=10) were 0.91 and 0.96, respectively.

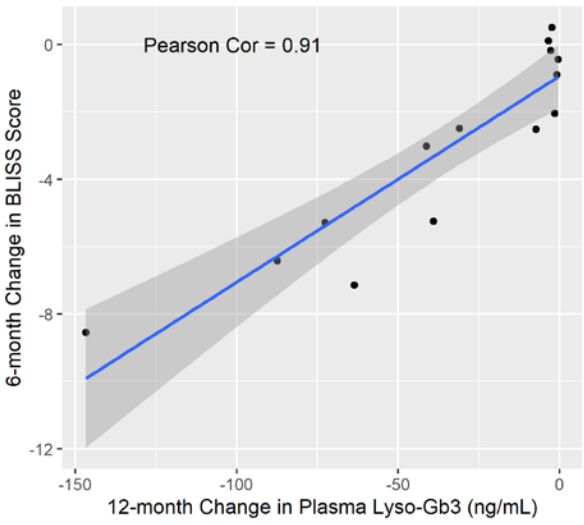
Figure 6: Correlation Between Renal Gb3 BLISS Score and Plasma Lyso-Gb3

A. Baseline BLISS Score vs. Baseline Plasma Lyso-Gb3	**B. 6-Month Change in BLISS Score vs. 6-Month Change in Plasma Lyso-Gb3**

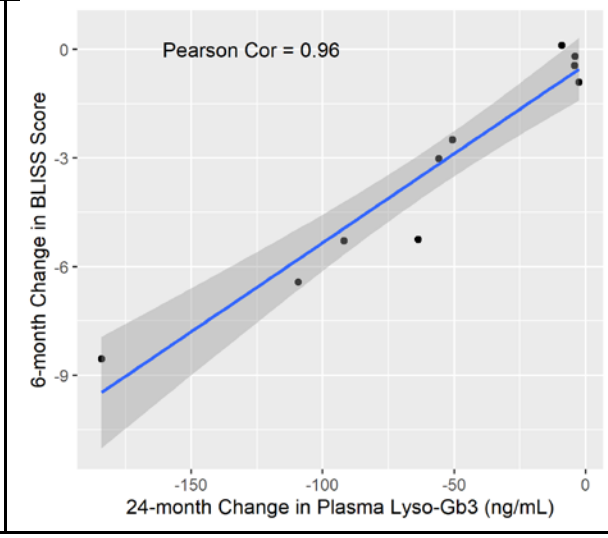




C. 6-Month Change in BLISS Score vs. 12-Month Change in Plasma Lyso-Gb3



D. 6-Month Change in BLISS Score vs. 24-Month Change in Plasma Lyso-Gb3



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0001 on May 27, 2020 and eCTD0025 on November 11, 2020)

Gb3 Inclusions in the kidney measured by modified Fabrazyme Scoring System (mFSS)

Individual level data on Gb3 inclusions in the kidney, measured using mFSS, are presented in Figure 31. Overall, there was a significant reduction in the Gb3 inclusions in absolute and relative terms. The mean absolute change in the weighted mFSS score was -0.8 (95% CI: -1.1, -0.4; p-value <0.001). As shown in Table 15, the mean and median percent reductions were -53% and -70%, respectively.

The average percentage of capillaries with mFSS score of 0-0.5 increased from 47% at baseline to 80% at six-months (p-value = 0.002;

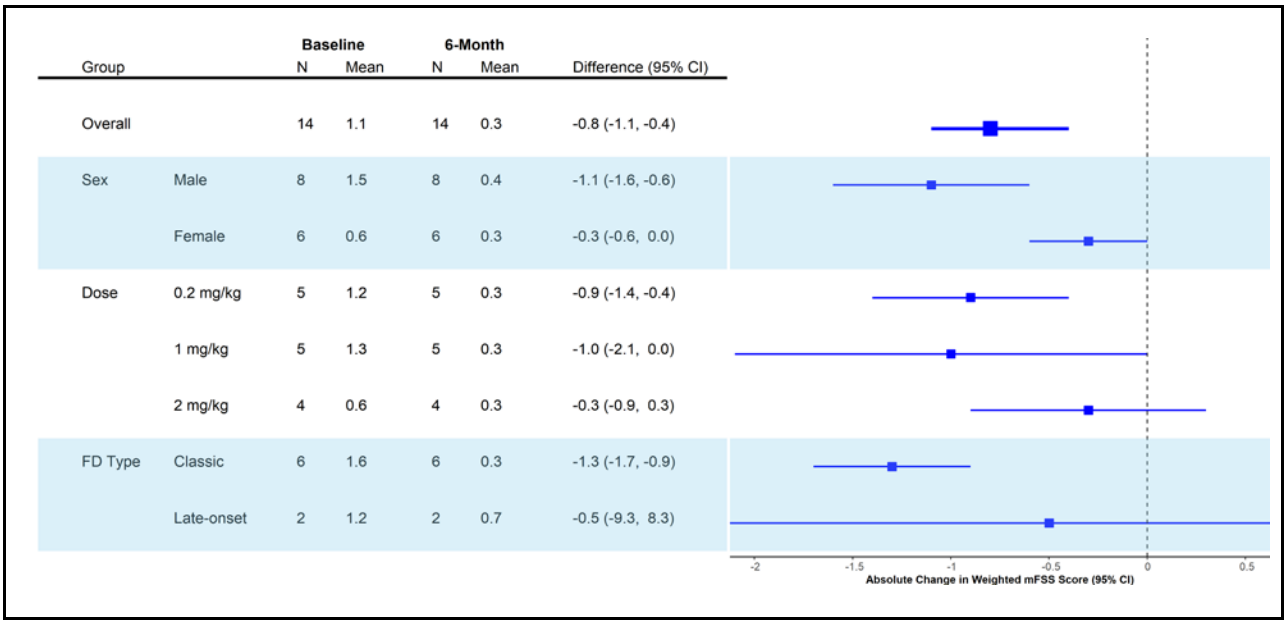
Figure **8**). The average proportion of capillaries receiving scores of 1, 2, and 3 were all reduced by six months. In addition, the proportion of patients with majority-rule mFSS score of 0 (i.e., whose biopsies had a majority of capillaries scored as 0) increased from 57% (8/14) to 100% after six-months of treatment (p-value < 0.03). The proportion of patients with *alternate-approach* score of 0 increased from 7% (1/14) at baseline to 64% (9/14) atsix months (p = 0.008). Subgroup analysis results using the mFSS approach were comparable to those using the BLISS scoring system (Figure 7). Overall, there was a high correlation between mFSS and BLISS methodologies (Figure 9) and both approaches indicate a reduction of Gb3 inclusions at six months.

Table 15: Gb3 Inclusions Based on Weighted mFSS Score (Trial PB-102-F01/F02)

	All Patients (N = 14)	Male (N = 8)	Female (N = 6)
Baseline (n)			
Mean (SD)	1.1 (0.7)	1.5 (0.6)	0.6 (0.2)
Median (Range)	1 (0.2, 2.1)	1.7 (0.2, 2.1)	0.5 (0.3, 0.9)
Month 6 (n)	14	8	6
Mean (SD)	0.3 (0.2)	0.4 (0.3)	0.3 (0.2)
Median (Range)	0.3 (0.1, 0.9)	0.3 (0.1, 0.9)	0.2 (0.1, 0.6)
Change from baseline at Month 6 (n)	14	8	6
Mean (SD)	-0.8 (0.6)	-1.1 (0.6)	-0.3 (0.3)
Median (Range)	-0.8 (-1.7, 0.2)	-1.2 (-1.7, 0.2)	-0.3 (-0.7, 0)
95% CI for mean	-0.8 (-1.1, -0.4)	-1.1 (-1.6, -0.6)	-0.3 (-0.6, 0)
P-value[b]	<0.001	0.017	0.065
P-value[c]	<0.001	0.016	0.063
% Change from baseline at Month 6 (n)	14	8	6
Mean (SD)	-53 (50)	-58 (62)	-47 (33)
Median (Range)	-70 (-91, 92)	-79 (-91, 92)	-64 (-73, 0.8)
P-value[b]	0.005	0.072	0.069
P-value[c]	0.017	0.195	0.063

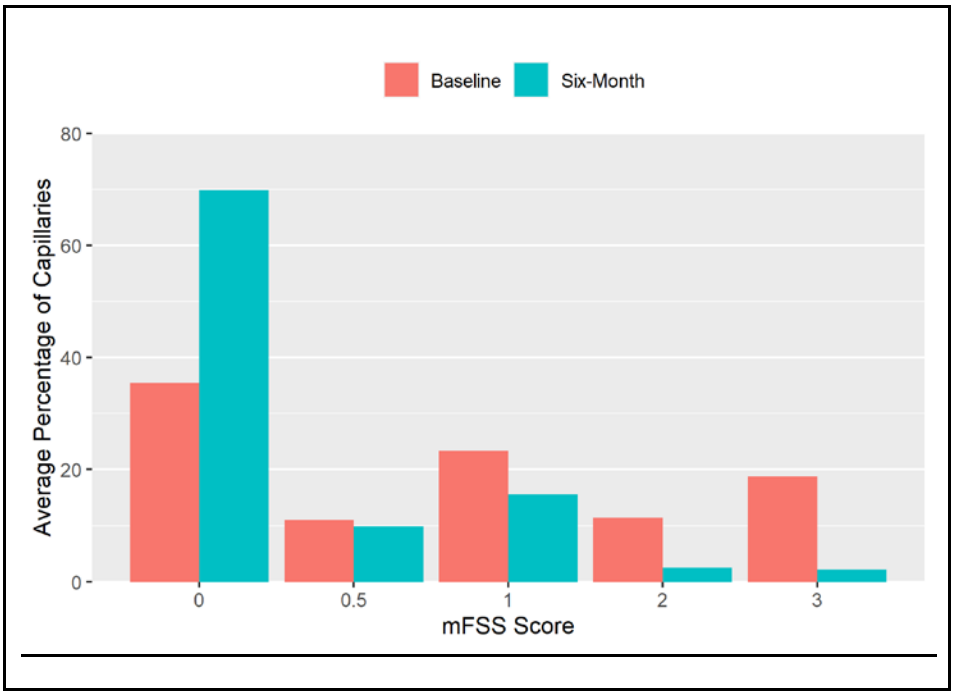
[a]The weighted mFSS score is a biopsy-level score derived by computing the weighted average of the capillary-specific scores. For example, if 30% of capillaries have a score of 3, 49% a score of 2, 20% a score of 1, 10% a score 0.5, and 11% a score of 0, the weighted mFSS score will be 2.13 (= 0.3*3 + 0.49*2 + 0.2*1 + 0.1*0.5 + 0.11*0).
[b]One-sample comparison of mean change using permutation test.
[c]Exact Wilcoxon signed-rank test p-value.
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0001) on May 27, 2020

Figure 7: Absolute Change in Weighted mFSS score from Baseline to 6-months



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0001) on May 27, 2020

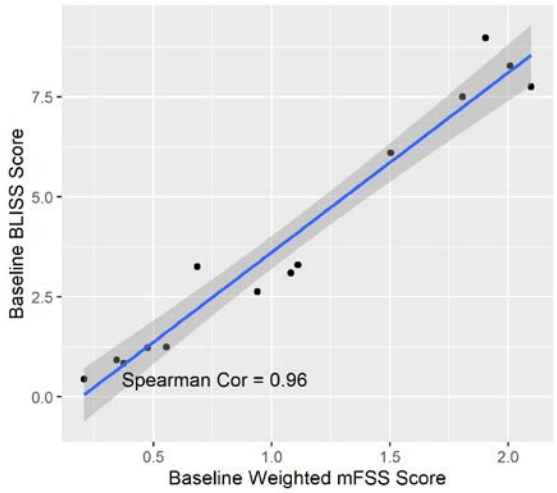
Figure 8: Overall Distribution of the mFSS Score at Baseline and 6 Months (Trial PB-102-F01/F02)



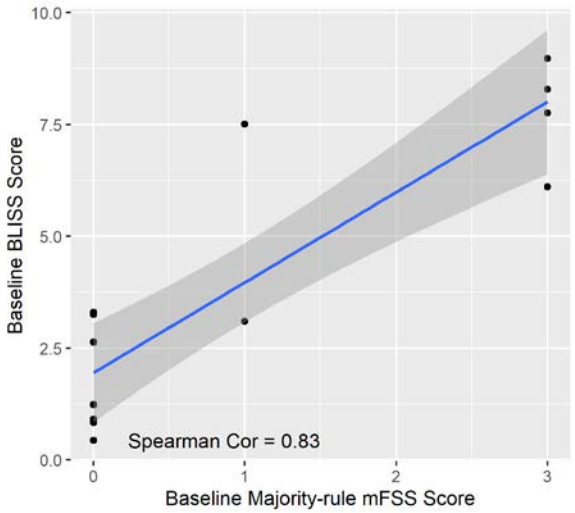
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0001) on May 27, 2020

Figure 9: Correlation of mFSS Scores and BLISS scores

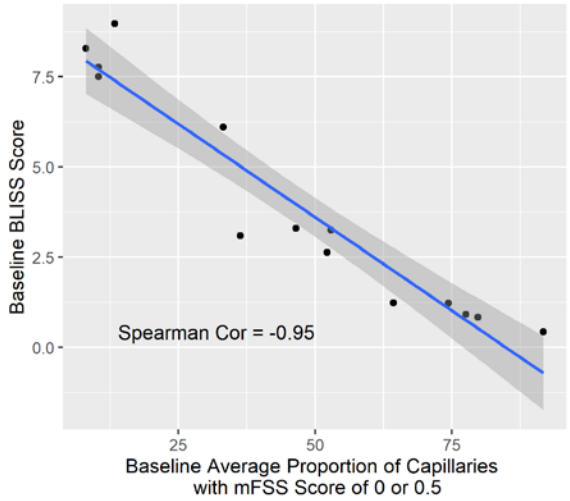
A. BLISS vs. Weighed mFSS Score (Baseline)



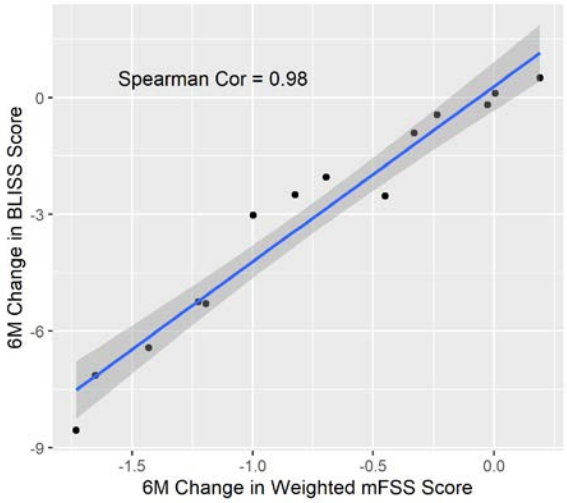
B. BLISS vs. Majority-rule mFSS Score (Baseline)



C. BLISS vs. Average Proportion of Capillaries with mFSS Score of 0 or 0.5 (Baseline)

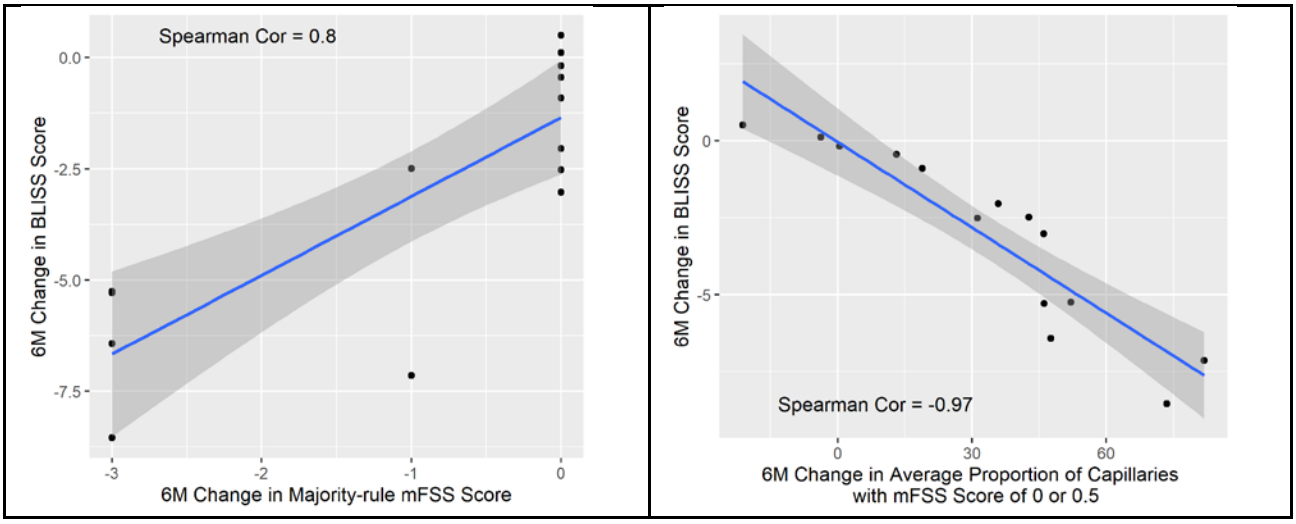


D. BLISS vs. Weighed mFSS Score (Change from Baseline to Six Months)



E. BLISS vs. Majority-rule mFSS Score (Change from Baseline to Six Months)

F. BLISS vs. Average Proportion of Capillaries with mFSS Score of 0 or 0.5 (Change from Baseline to Six Months)



The biopsy-level **weighted mFSS** score is derived by computing the weighted average of the capillary-specific scores. For example, if 30% of capillaries have a score of 3, 49% a score of 2, 20% a score of 1, 10% a score 0.5, and 11% a score of 0, the **weighted mFSS** score will be 2.13 (= 0.3*3 + 0.49*2 + 0.2*1 + 0.1*0.5 + 0.11*0). The biopsy-level **majority-rule mFSS** score corresponds to the score received by the majority of the capillaries. In the above example, the **biopsy-level majority-rule mFSS** score will be 2 since a majority of the capillaries received a score of 2.

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0001 on May 27, 2020 and eCTD 0025 on November 11, 2020)

Sensitivity Analysis Including Subject With Mislabeled Slides

One male subject (ID: (b) (6); classic phenotype) was removed from the main efficacy analysis. For this subject, the biopsy slides were mislabeled and thus could not be matched to the correct visits (i.e., baseline versus six-month visit times could not be identified). The review team derived the BLISS score for each visit based on the Applicant's raw dataset. The two derived BLISS scores were 5.1 and 9.6. The review team conducted sensitivity analysis for the following two scenarios:

1. Worst case scenario analysis (assumes the BLISS score increased by attributing the higher of the two scores to the six month visit)
2. Best case scenario analysis (assumes the BLISS score decreased by attributing the higher of the two scores to the baseline visit)

The results of the sensitivity analysis support the results of the main efficacy analysis (Table 16).

When assuming the baseline score was 5.1 and the 6-month score was 9.6 (i.e., worst-case scenario), the mean change in BLISS scores from baseline was -2.6 (95% CI -4.5 ,-0.7; p = 0.01) (Table 16). The inclusion of this subject under this assumption attenuates the main efficacy result of mean reduction of -3.1 (95% CI -4.8, -1.4) by 0.5 units.

When assuming the baseline score was 9.6 and the six-month score was 5.1, the mean change in BLISS score was -3.2 (95% CI -4.8 ,-1.6; p < 0.001). Although the inclusion of this subject will numerically change the main efficacy results of the mean change in BLISS score, the overall efficacy results are qualitatively unchanged and remain nominally statistically significant.

Under the two scenarios considered above, the median change in BLISS score was the same as that from the main analysis (Table 16).

Of note, this subject had the highest plasma Lyso-Gb3 at baseline (273 ng/ML) and a notable decline in plasma Lyso-Gb3 over the course of the study (48%, 75% and 96% percent reduction at 6, 12 and 24 months, respectively). Given the high correlation between change in plasma lyso-Gb3 and change in BLISS score observed in this study (Figure 9), this subject likely had a reduction in BLISS score at 6 months; consequently, for this subject, the baseline and 6-month BLISS scores were likely 9.6 and 5.1, respectively.

Table 16: Sensitivity Analysis Including Subject With Mislabeled Slides

Population	N	Mean Difference (95% CI)	Exact P-value	Median Difference	Exact Signed-rank P-value
Main Efficacy Population	14	-3.1 (-4.8 ,-1.4)	<0.001	-2.5	0.001
EP + (b) (6) (Worst-case)[1]	15	-2.6 (-4.5 ,-0.7)	0.011	-2.5	0.008
EP + (b) (6) (Best-case)[2]	15	-3.2 (-4.8 ,-1.6)	<0.001	-2.5	<0.001

[1]Since subject (b) (6) scores could not be attributed to a visit, the "worst case" analysis assumed the baseline score is 5.1 and the six-month score is 9.6.
[2]The "best case" analysis assumed the baseline score is 9.6 and the six-month score is 5.1.
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD 0025) on November 11, 2020

Efficacy Results: Mean eGFR and Annualized eGFR Slope

Overall patients had normal renal function at baseline (eGFR >90 mL/min/1.73 m^2), which remained normal during the course of the study. The mean eGFR at baseline, 1 year and 2 years was: 112, 112 and 107 mL/min/1.73 m^2, respectively (Table 17 and Table 18). The mean percent change in eGFR from baseline to 1 year and 2 years were 0% and -1.1%, respectively, indicating minimal reduction in eGFR. The annualized eGFR slope (rate of loss of eGFR per year) at 1 year and 2 years were -2.1 and -1.8 units respectively.

Table 17: eGFR and Annualized eGFR Slope Summary for PB-102-F01/F02

		$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)			$eGFR_{CKD-EPI}$ Slope at Month 12 (mL/min/1.73 m^2/year)
Group	**n**	**Baseline**	**12 Month**	**% Change from Baseline**	
0.2 mg/kg (N=6)	6	116.3 (7.7)	118.0 (9.0)	1.0 (2.7)	-1.1 (1.4)
1.0 mg/kg (N=6)	5 [a]	114.8 (11.6)	117.5 (9.5)	3.2 (3.0)	1.6 (1.9)
2.0 mg/kg (N=4)	4	101.4 (10.9)	96.6 (12.9)	-5.6 (2.7)	-8.2 (3.8)
Male (N=9)	8 [a]	117.5 (7.9)	120.1 (7.9)	2.3 (2.5)	0.5 (1.4)
Female (N=7)	7	105.4 (7.6)	102.9 (8.3)	-2.7 (2.3)	-5.0 (2.7)
Overall (N=16)	15 [a]	111.8 (5.6)	112.1 (6.0)	-0.0 (1.8)	-2.1 (1.6)

a. Patient [redacted] (b) (6) treated intermittently with doxycycline, excluded
Data are presented as mean (SE)

Source: Applicant's *Summary of Clinical Efficacy*, Table 12, page 44

Table 18: eGFR Levels Change from Baseline (subgroup of patients who completed 24 months of treatment)

	eGFR (mL/min/1.73 m^2)						$eGFR_{CKD-EPI}$ SLOPE (mL/min/1.73 m^2/year)
		Baseline	**Month 12**		**Month 24**		**Month 24**
	n	**Value**	**Value**	**% Change from Baseline**	**Value**	**% Change from Baseline**	**Slope**
Male (N=7)	7	112.7 (6.2)	112.2 (8.6)	-1.1 (3.3)	110.2 (6.4)	-2.3 (0.8)	-1.8 (0.8)
Female (N=4)	4	99.9 (10.1)	96.5 (12.9)	-4.4 (3.5)	101.1 (10.9)	1.0 (1.9)	-1.8 (0.7)
Overall (N=11)	11	108.0 (5.5)	106.5 (7.2)	-2.3 (2.4)	106.9 (5.5)	-1.1 (0.9)	-1.8 (0.6)

Data are presented as mean (SE): number with data available

Source: Applicant's *Summary of Clinical Efficacy*, Table 13, page 45

Given the lack of concurrent control, the results on the eGFR endpoint are difficult to interpret.

8.1.5. Assessment of Efficacy Across Trials

The efficacy assessment of pegunigalsidase alfa was based on PB-102-F01 and PB-102-F02, which assessed the histological decrease in substrate deposition in kidney PTC, an endpoint that has been used to support accelerated approval for previous applications.

8.1.6. Integrated Assessment of Effectiveness

The efficacy assessment of pegunigalsidase alfa was based primarily on trial PB-102-F01/F02 which assessed the histological decrease in substrate deposition in kidney PTC which has been used to support accelerated approval for previous applications. Overall, Study PB-102-F01/F02 showed a significant reduction from baseline in the renal Gb3 inclusions at 6 months: the median absolute reduction was 2.5 (nominal p = 0.001), and the median relative reduction was 78% (nominal p-value = 0.017). Given the following observations: (1) no spontaneous reduction in Gb3 inclusions for untreated patients with Fabry disease (Section 15.7), (2) the reliability of the BLISS methodology (Section 15.5), and (3) the significant reductions in the plasma Gb3 over a 2-year period for almost all patients in Study PB-102-F01/F02/F03, the observed mean reduction in the Gb3 inclusions was unlikely due to chance and thus provides compelling evidence of a true drug effect. Additional analysis performed at the patient level showed that 11 out of 14 patients had a significant reduction in Gb3 inclusions (nominal p < 0.001). This "N-of-1" analysis results provide strong supportive evidence of treatment effect given that the chance of observing these favorable results is 2% if pegunigalsidase alfa is ineffective.

However, at the present time, we are unable to conclude that the benefits of pegunigalsidase alfa outweigh its risks. Records inspection of the drug product manufacturing site in (b) (4) led to a withhold recommendation on the facility, and inspection of the drug substance site has not yet occurred. Therefore, we are not assured that the product has sufficient quality for approval, and we will be issuing a Complete Response letter based on the withhold recommendation. In addition, the applicant is seeking accelerated approval but late in the review cycle Fabrazyme received full approval for the treatment for Fabry disease, becoming available therapy. For accelerated approval, the applicant will need to show that pegunigalsidase alfa provides a therapeutic advantage over Fabrazyme. Alternatively, the applicant could show that the reductions in Gb3 renal inclusions predict clinical benefit to support full approval. These late-developing issues have not been resolved in this review cycle and will need to be resolved in the next review cycle before we can conclude that the benefits of the drug outweigh its risks and can be approved.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review approach focuses on trials PB-102-F01/F02/F03, PB-102-F30 and PB-102-F60.

8.2.2. Review of the Safety Database

Overall Exposure

A total of 53 individual patients have been treated with pegunigalsidase alfa every 2 weeks in the open-label studies PB-102-F01/F02/F03 (n=18), PB-102-F30 (n=22), and PB-102-F60 (n=13). There are 69 patients in the blinded PB-102-F20 trial who are receiving pegunigalsidase alfa or Fabrazyme in a 2:1 ratio. A total of 13 patients from PB-102-F20 have transitioned to the open-label extension trial PB-102-F60. A total of 6 patients received 0.2 mg/kg, 52 patients received 1 mg/kg and 4 patients received 2 mg/kg. Per the applicant, mean exposure was 21.3 (± 2.9) months with 17.0 (± 1.9) months in the 1.0 mg/kg group. Thirty-one (60%) of the 52 patients who received the 1 mg/kg dose in open-label studies were treated for at least 12 months. This is adequate long-term exposure in the context of a rare disease. **Table 19** lists the exposure by study and dose level. **Table 20** lists the exposure by months.

Table 19: Total Exposure by Study and Dose Level

Study Number	Dose (mg/kg)	Number (%)[a] of Patients Treated	Total Exposure to PRX-102 (Patient Months)
Open-label Safety Analysis Set (OL-SAS)			
PB-102-F01/F02, PB-102-F03		18 (34.0%)	718
PB-102-F01/F02	Any 0.2 1.0 2.0	18 (34.0%) 6 (11.3%) 8 (15.1%) 4 (7.5%)	
PB-102-F03 (Open-label extension (OLE) of F01/F02)	Any 0.2 1.0 2.0	15 (28.3%) 6[b] (11.3%) 14 (26.4%) 4[b] (7.5%)	
PB-102-F30	1.0	22 (41.5%)	237
PB-102-F60 (OLE of F20 and F30)	1.0	29 (54.7%) n=16 from F30[c] n=13 from F20[c]	176[d]
Total Treated		53[e]	1,131

a. Percentages are based on overall number of patients in the analysis set
b. Patients received 0.2 or 2.0 mg/kg at the start of the study; the dose was adapted gradually to 1.0 mg/kg. One patient receiving 0.2 mg/kg at the start of the study discontinued treatment before moving to 1.0 mg/kg.
c. The patients are also included in study F30 or study F20 as indicated
d. Exposure in run-in studies is not included.
e. Individual patients receiving at least one dose of pegunigalsidase alfa EVERY 2 WEEKS in the OL-SAS
source: Applicant table summary of clinical safety p 13/53

Table 20: Duration of Exposure by Dose

Duration of Exposure (Months)	Open Label – Safety Analysis Set			
	0.2 mg/kg N = 6	1.0 mg/kg N = 52[a]	2.0 mg/kg N = 4	Any dose N = 53
	n (%)	n (%)	n (%)	n (%)
≤3 months	0 (0.0%)	9 (17.3%)	0 (0.0%)	9 (17.0%)
3 -| 12 months	0 (0.0%)	12 (23.1%)	0 (0.0%)	12 (22.6%)
12 -| 18 months	1 (16.7%)	7 (13.5%)	1 (25.0%)	8 (15.1%)
18 -| 24 months	0 (0.0%)	13 (25.0%)	3 (75.0%)	13 (24.5%)
24 -| 36 months	5 (83.3%)	6 (11.5%)	0 (0.0%)	0 (0.0%)
36 -| 48 months	0 (0.0%)	4 (7.7%)	0 (0.0%)	1 (1.9%)
>48 months	0 (0.0%)	1 (1.9%)	0 (0.0%)	10 (18.9%)

N: Number of patients in dose group; n (%): percentage based on N
a. One patient receiving 0.2 mg/kg at the start of the study discontinued treatment before moving to 1.0 mg/kg.
Note: For the PB-102-F60 patients who enrolled after completion of the study PB-102-F20, only the exposure in study PB-102-F60 is included.
In the OL-SAS, exposure within the dose groups was limited to the exposure to the respective dose, i.e., for 0.2 mg/kg and 2.0 mg/kg only the exposure before moving to the 1.0 mg/kg dose was considered. In the 'any dose' analysis, the entire exposure to pegunigalsidase alfa is considered, i.e., if a patient received 12 months of treatment with 0.2 mg/kg and then 10 months treatment with 1.0 mg/kg, he/she would only appear in the 18-24 months category

source: Applicant table summary of clinical safety p14/53

The presentation of safety will focus on the open-label studies PB-102-F01/F02/F03, PB-102-F30, and patients from F20 who have transitioned to the open-label F60 trial. Any serious adverse events, discontinuations due to adverse events (AEs), and deaths from the trials will also be discussed.

Important baseline characteristics of the safety population:

Table 21: Demographics of Safety population

		Open-label Safety Analysis Set			
		0.2 mg/kg N = 6	1.0 mg/kg N = 52	2.0 mg/kg N = 4	Any dose N = 53
Gender	Male, n (%)	4 (66.7%)	35 (67.3%)	1 (25.0%)	35 (66.0%)
	Female, n (%)	2 (33.3%)	17 (32.7%)	3 (75.0%)	18 (34.0%)
Age (years)	Mean (SE)	30.0 (4.4)	42.9 (1.7)	40.0 (8.2)	42.1 (1.7)
Age range (years)		21 to 50	17 to 61	20 to 54	17 to 61
Age at diagnosis (years)	Mean (SE)	22.8 (4.5)	31.4 (2.1)	32.5 (10.2)	31.1 (2.0)
Race	White	4 (66.7%)	48 (92.3%)	4 (100.0%)	49 (92.5%)
	Black	1 (16.7%)	3 (5.8%)	0 (0.0%)	3 (5.7%)
	American Indian or Alaska native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	1 (16.7%)	1 (1.9%)	0 (0.0%)	1 (1.9%)

Source: Applicant table, summary of clinical safety p 19/53

Adequacy of the safety database:

In general, the submitted safety database was adequate in terms of duration of exposure and number of patients in a rare disease population such as FD. However, the representation of different races in the trials may not represent the whole U.S. population as there were a minimal amount of African American, Hispanic and Asian Americans enrolled. More males were also enrolled in the trials than females which is expected as males generally have more severe disease due to the x-linked nature and current guidelines recommend treatment with enzyme replacement therapy in males with classic disease whether or not they are symptomatic whereas females should be considered if there is evidence of organ disease due to FD (Ortiz et al. 2018). As there was no control arm available as a comparator, it will be unclear whether adverse events were related to treatment.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no concerns about data quality and integrity. The datasets were accessible with analytic tools and there was appropriate use of standard terminology.

Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) versions 15.0 (PB-102-F01/F02, PB-102-F03) or 19.0 (PB-102-F30 and PB-102-F60) were used to classify medical history and adverse events (AEs). Coded AEs were displayed by frequency, severity, relationship, and seriousness for each treatment group.

A treatment-emergent AE (TEAE) was defined as any AE that started after the administration of the first study infusion. TEAEs were provided by MedDRA System Organ Class (SOC)/preferred term (PT). Summary statistics were provided for the number of AEs and the number (%) of patients reporting AEs. Severity (mild, moderate, severe) and/or relationship to study medication (unrelated, unlikely, possibly, probably and definitely related) as assessed by the investigator were listed as appropriate. AEs with the causality assessed as unrelated or unlikely were categorized as not related to study medication. AEs with the causality assessed as definite, possible or probable were categorized as related TEAEs. In the summaries of severity and relationship to study drug, the most extreme outcome (highest severity and closest relationship to study drug) was used for patients with multiple occasions of the same PT and SOC. Infusion related reactions were defined as those related TEAEs which occurred during the

infusion or within 2 hours after the completion of the infusion and the causality of the adverse events were determined to be definitely, probably, or possibly related. Infusion related reactions are not identical with reports provided under the MedDRA preferred term 'Infusion related reactions'.
Some PTs were not considered relevant for inclusion in infusion related reactions as they were related to procedures rather than study drug. The applicant's table describes PTs that were excluded, after medical review, from the summary of infusion related reactions. Procedure related complications as an additional combined adverse event that will need to be independently reviewed.

Table 22: Preferred terms excluded from Infusion Related Reactions

MedDRA SOC	MedDRA PT
General disorders and site conditions	Infusion site discomfort Injection site pain Infusion site hematoma
Injury, poisoning and procedural complications	Contusion Procedural site reaction Procedural pain
Vascular disorders	Vein rupture

8.2.4. Safety Results

Deaths

There was only one death reported that was in trial PB-102-F03. The patient was a 35 year old male with a medical history significant for tobacco use, recurrent respiratory infections and emphysema. The patient was originally enrolled into study PB-102-F01 and was rolled over into PB-102-F02 and PB-102-F03. He had been treated with 1.0 mg/kg for 38 months in total when he was admitted to the hospital for pneumonia, requiring a chest drain and transferred to the ICU for respiratory failure. The death was most likely related to his underlying respiratory issues and unrelated to pegunigalsidase alfa.

Serious Adverse Events

There were 10 serious adverse events reported overall across all trials.

Table 23: Serious Adverse Events by Trial

Serious Adverse events	PB-102-F01/F02/F03 N=18	PB-102-F30 N=22	PB-102-F60 N=29[a]	Total N=53
Bacterial Arthritis	0	0	1	1
Pneumonia	1		1	2
Chronic Obstructive Pulmonary Disease	1	0	0	1
Clavicle Fracture	1	0	0	1
Infectious Mononucleosis	0	1	0	1
Anaphylaxis	1	2	0	3
Urinary Tract Infection	0	1	0	1
Total n (%)	4 (22.2)	4(18.2)	2(6.9)	10 (18.9)

a. Patients entered PB-102-F60 came from PB-102-F20(n=13) or from PB-102-F30(n=16)

Source: reviewer's table

In the trials, 3 serious adverse events appear likely related to PRX-102 treatment: one patient with bronchospasm (likely to be a hypersensitivity reaction or anaphylaxis) and two patients with symptoms consistent with anaphylaxis.

1. A 52 year old man (in trial F01) naïve to ERT developed a CTCAE grade 3 bronchospasm (symptomatic interfering with function) 40 minutes into his first infusion. The infusion was interrupted after he received a partial dose of 25 mL (19 mg of 115 mg planned) of study drug. No pre-medication had been given. The patient was hospitalized and recovered the following day. The patient was discontinued from the study. The patient was positive for anti-pegunigalsidase alfa IgG post infusion with a titer of 581 and also positive at the follow-up visit 30 days post-infusion with a titer of 331 and negative at the 90 day follow up visit. The patient was also positive for anti-pegunigalsidase alfa IgE at baseline, visit 1 post-infusion and at the 30 and 90 day follow-up visits.

2. A 29 year old man in trial PB-102-F30 had previously been treated with Replagal for a total of 8 years and 1 month prior to study entry. The patient presented with a CTCAE grade 3 type 1 hypersenstivity soon after the start of his first infusion with the development of nausea, itchy eyes, vomiting, shortness of breath, throat tightness, facial edema, rash over trunk, hives, and tachycardia. No infusion pre-medication had been given. The study treatment was interrupted after 18 minutes with 8.7 mg of treatment given. The patient received intramuscular epinephrine, cetirizine, hydrocortisone and prednisolone as per the local anaphylaxis protocol. The patient was admitted to the short stay unit for overnight observation and was discontinued from the study. The patient was found to have anti-drug IgE antibodies in pre- and post-treatment samples but was negative for anti-drug IgG antibodies.

3. A 24 year old man in study PB-102-F30 had been treated with Replagal for a total of 12 years and 9 months prior to study entry. The patient developed CTCAE type 1 hypersensitivity immediately after the start of the first infusion. The patient developed

nausea, headache, agitation, edema of the hands and periorbital area and tongue with hypotension. No infusion pre-medication had been given. The drug was stopped 5 minutes after the start of infusion with 2.1 mg of pegunigalsidase alfa administered. The patient received methylprednisolone, clemastine and sodium chloride. The patient recovered the same day without sequelae and was discontinued from the study. The patient was found to have pre- and post-treatment anti-drug IgE antibodies and no anti-drug IgG antibodies.

Dropouts and/or Discontinuations Due to Adverse Events

There were four patients who discontinued treatment due to adverse events. All four patients are described above and discontinued treatment due to: death from COPD, bronchospasm or type 1 hypersensitivity. No other discontinuations have occurred.

Adverse Events of Interest

Infusion related reactions occurred in 11 of the 53 patients (21%). An infusion related reaction was defined as any symptom reported during the infusion or within 2 hours after the completion of the infusion and that was related to study treatment rather than to procedures. An AE was considered an IRR if possibly/probably/definitely related to the treatment by the investigator. All patients in the 2 mg/kg cohort in trial PB-102-F01/F02 were given premedication, an H1 blocker plus H2 blocker at standard doses 12 hours and 2 hours before the start of the infusion. Patients in PB-102-F30 who received pre-medication with agalsidase alpha continued on pre-medication with pegunigalsidase alfa. Infusion related reactions were monitored during each pegunigalsidase alfa infusion. Premedication for subsequent pegunigalsidase alfa infusions were considered at the discretion of the investigator and medical director. The algorithm for monitoring and management of infusion related reactions are located in Evaluation and Treatment Algorithm to monitor and manage hypersensitivity reactions (see section 15.9).The Applicant did not provide reasoning for the 2 hour IRR limit and did not provide accurate data regarding information on premedication in the F01/F02 trial. These issues will be addressed at the next review cycle.

Table 24: Infusion Related Reactions (IRRs)

Infusion Related Reaction	PB-102-F01/F02/F03 N=18	PB-102-F30 N= 22	Total N=53 (%)
DIZZINESS	2	1	3 (5.7)
ANAPHYLAXIS*	1	2	3 (5.7)
CHEST PAIN	2	0	2 (3.8)

NAUSEA	2	0	2 (3.8)
NASAL CONGESTION	1	1	2 (3.8)
PRURITUS	1	1	2 (3.8)
ABDOMINAL PAIN	1	0	1 (1.9)
DYSPNEA	1	0	1 (1.9)
ERYTHEMA	0	1	1 (1.9)
EDEMA	1	0	1 (1.9)
RASH MACULO-PAPULAR	1	0	1 (1.9)
RASH PRURITIC	0	1	1 (1.9)
SNEEZING	1	0	1 (1.9)
HYPOTENSION	1	0	1 (1.9)
Total	15 (83.3)	7 (31.8)	22 (41.5)

*also termed type I hypersensivity by the Applicant (see section on SAEs)
Chest discomfort recoded as chest pain
Paranasal sinus hypersecretion recoded as nasal congestion
Infusion related reaction recoded as pruritus
Source: reviewer's table

The applicant also assessed infusion related reactions using the definition of an adverse event that occurred during the infusion and up to 24 hours post infusion. This analysis shows that 15 out of 53 patients (28.3%) had an infusion-related reaction. However, this could not be independently confirmed on our review. Infusion related reactions occurring within 24 hours post infusion will be assessed

Treatment Emergent Adverse Events

Forty-seven patients reported 610 treatment-emergent adverse events (TEAE). The majority of TEAEs 436/610 (71.5%) were assessed by the investigator as unrelated to treatment. The most commonly reported TEAEs occurring in 20% or more patients were musculoskeletal pain (26.4%), respiratory tract infections (24.5%), nasopharyngitis (22.6%), abdominal pain (22.6%), and headache (20.8%). Only four patients were considered to have a TEAE definitely related to treatment. Two patients developed a type 1 hypersensitivity reaction and one patient had bronchospasm which were all considered infusion related reactions and treatment was discontinued. One other patient developed vertigo that was considered related to treatment, which was reported as mild and the patient continued treatment.

Table 25: Treatment Emergent Adverse Events in >5% of patients

Treatment Emergent Adverse Events (>5%)	PB-102-F01/F02/F03 N= 18	PB-102-F30 N=22	PB-102-F60 N=29	Total N=53 (%)
MUSCULOSKELETAL PAIN	12	1	1	14 (26.4)
RESPIRATORY TRACT INFECTION	8	4	1	13 (24.5)

NASOPHARYNGITIS	4	7	1	12 (22.6)
ABDOMINAL PAIN	8	1	3	12 (22.6)
HEADACHE	5	5	1	11 (20.8)
FATIGUE	8	2	0	10 (18.9)
COUGH	5	1	3	9 (17)
BACK PAIN	6	2	1	9 (17)
DIARRHEA	4	1	2	7 (13.2)
DIZZINESS	4	2	1	7 (13.2)
RASH	5	2	0	7 (13.2)
GASTROENTERITIS	6	0	1	7 (13.2)
CHEST PAIN	5	1	0	6 (11.3)
NAUSEA	5	1	0	6 (11.3)
ARTHRALGIA	3	2	1	6 (11.3)
EDEMA	6	0	0	6 (11.3)
OROPHARYNGEAL PAIN	3	2	0	5 (9.4)
VOMITING	5	0	0	5 (9.4)
PRURITUS	3	1	1	5 (9.4)
DYSPNEA	2	3	0	5 (9.4)
PALPITATIONS	3	2	0	5 (9.4)
PARAESTHESIA	5	0	0	5 (9.4)
PAIN	4	0	0	4 (7.5)
TOOTHACHE	2	2	0	4 (7.5)
INFLUENZA	3	1	0	4 (7.5)
VERTIGO	3	0	1	4 (7.5)
ARRYTHMIA	2	2	0	4 (7.5)
NASAL CONGESTION	2	1	0	3 (5.7)
PYREXIA	3	0	0	3 (5.7)
NECK PAIN	2	1	0	3 (5.7)
SNEEZING	2	1	0	3 (5.7)
DEPRESSION	2	1	0	3 (5.7)
EAR PAIN	3	0	0	3 (5.7)
ERYTHEMA	1	2	0	3 (5.7)
INSOMNIA	3	0	0	3 (5.7)
RHINORRHEA	2	1	0	3 (5.7)
URTICARIA	3	0	0	3 (5.7)

Chest discomfort recoded to chest pain
Abdominal pain upper/abdominal discomfort/abdominal distension recoded to abdominal pain
Dizziness postural recoded to dizziness
Ear discomfort recoded to ear pain

Gastroenteritis viral recoded to gastroenteritis
Musculoskeletal stiffness/musculoskeletal spasms/musculoskeletal discomfort/myalgia – recoded as musculoskeletal pain
Peripheral edeam recoded as edema
Lower respiratory tract infection/upper respiratory tract infection/viral respiratory tract infection recoded as respiratory tract infection
Source: reviewer's table

Laboratory Findings

Laboratory parameters assessed in the clinical trials included a complete blood count, prothrombin time (PT), partial thromboplastin time (PTT), metabolic profile, liver enzymes (ALT, AST, GGT), lactate dehydrogenase, creatine phosphokinase, vitamin D and urinalysis. Labwork was assessed every three months. No serious adverse events related to laboratory findings were reported. No discontinuations occurred due to a laboratory adverse event. There were 14 laboratory AEs that were reported in 7 patients. The most commonly reported laboratory AE was anemia or decreased hemoglobin reported in 4 patients. The anemia/decreased hemoglobin were consistent with the baseline values and unlikely related to treatment. No Hy's Law cases were identified.

Vital Signs

In trial PB-102-F01 vitals signs checked included blood pressure, pulse, temperature and respiration. They were checked at each infusion visit every 2 weeks. Vital signs were evaluated every 15 minutes during the first hour of the infusion and then every 30 minutes until 2 hours post infusion, if the subject tolerated the infusion. Otherwise, vitals were evaluated every 15 minutes. In trial PB-102-F02, the extension trial of PB-102-F01, vital signs were evaluated before start of the infusion and every 30 minutes during the infusion and at the end of clinical observation. In trial PB-102-F30, vital signs were measured every 30 minutes for the first hour and then at 120 minutes if the patient tolerated the infusion. The majority of patients had minimal and not clinically significant changes in vital signs. In trial PB-102-F01, one patient developed hypotension with the lowest systolic blood pressure (SBP) of 89 mm/Hg after the start of infusion that was transient and resolved at the end of the infusion. Another patient in that trial had a transient episode of hypertension (HTN) with a SBP of 180 mm/Hg that also resolved at the end of the infusion. In trial PB-102-F30, one patient had bradycardia with a heart rate in the 50s that occurred at the start of the infusion. Another patient had elevated systolic blood pressure in the 150s for only one visit. These cases were single occurrences and without clinical sequelae and unlikely drug related.

Electrocardiograms (ECGs)

Patients had ECGs performed locally at baseline and at months 3, 6, 9, and 12 for studies F01/F02/F30. A total of five (9%) patients had abnormalities seen on ECG. There were two patients in the F01/F02 trial and both patients had nonspecific abnormal T waves that occurred

only at one time point at month 12. One patient in the F30 trial who had an event of a right bundle branch block at the last visit prior to the interim analysis and event outcome is currently unknown but will be followed up in the next review cycle. Two patients in the F60 trial (who had rolled over from F20) at baseline which came from the blinded study and therefore unable to elucidate the treatment. No patients discontinued from the trials due to the ECG changes. Of note, the patients with ECG abnormalities had a past medical history of cardiovascular abnormalities which can typically be seen in Fabry disease. As there is no comparator, it is unclear whether these are secondary to their underlying cardiac history or from the treatment itself and those that occurred only at one time point do not need to be addressed in the label. Overall, there are no apparent cardiac-specific risks that are attributable to the product.

8.2.5. Safety Analyses by Demographic Subgroups

Sex:
There were 18 (34%) females and 35 (66%) males that were part of the safety database. Overall, a total of 193 treatment-emergent adverse events were recorded in females (9%) and 373 adverse events were recorded in males (9%). Infusion related reactions occurred in 17 female patients and in 17 male patients. The most frequently reported adverse events in females versus males were abdominal pain (66.7% vs 45.7%), headache (44.4% vs 40.0%), dizziness (16.7% vs 31.4%) and nasopharyngitis (55.6% vs 31.4%).

Age:
There was one pediatric patient in trial F01/F02 (17 years old) at the start of treatment. No SAEs or ADA were noted on treatment. Muscle spasms, ECG changes noted at baseline and throughout treatment, dyspnea, fatigue, depression and palpitations were reported. The patient discontinued treatment after 15 months due to financial burden of traveling to the investigational site. There were no patients over the age of 65 years enrolled in the study.

Although there was an imbalance between the types of adverse events in males and females, it is unclear how to interpret as there was no comparator group. The assessment of safety by age group is limited as only one patient was <18 years of age and there were no patients that were >65 years of age.

8.2.6. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new cases of a cancer diagnosis were reported during the trials.

Human Reproduction and Pregnancy

One pregnancy was reported in study PB-102-F03. The patient had normal ultrasound findings at week 13 of gestation but decided to terminate the pregnancy at week 14 for personal reasons. Data are limited to make a conclusion regarding the use pegunigalsidase alfa in pregnancy. The long-term safety of pegunigalsidase alfa use during pregnancy as well as effects on the developing fetus and newborn will be assessed in the post marketing setting in a patient registry.

Pediatrics and Assessment of Effects on Growth

Assessment of safety in the pediatric population is limited as only one patient aged 17 years entered the PB-102-F01 trial.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable

8.2.7. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

Many subpopulations were not well represented in the safety database, including pediatric patients (including adolescents), patients older than 65 years of age, and patients of different ethnicities. Anaphylaxis will be labeled accordingly and will be further evaluated in the post marketing setting with routine pharmacovigilance. However, important differences in the safety profile are not anticipated in the post marketing setting.

8.2.8. Integrated Assessment of Safety

A total of 53 individual patients with Fabry Disease have been treated with pegunigalsidase alfa every 2 weeks. There were 18 patients treated in trial PB-102-F01/F02/F03, 22 patients in trial PB-102-F30, and 13 patients in PB-102-F60. Six patients received 0.2 mg/kg, 52 patients received 1 mg/kg and four patients received 2 mg/kg. The mean duration of exposure was 21.3 months with 17.0 months seen in the 1.0 mg/kg group. The overall safety database appears adequate for assessment of safety of pegunigalsidase alfa in the patient population studied given the rarity of the disease. Anaphylaxis with positive IgE antibodies was noted in three patients. Infusion related reactions defined as AEs that occurred within 2 hours of infusion occurred in 11 patients. The most common treatment-emergent adverse events were musculoskeletal pain, respiratory tract infection, nasopharyngitis, abdominal pain, and headache. As there was no control arm available as a comparator, it is unclear whether most of the adverse events were related to treatment, however, the timing of severe reactions (e.g., anaphylaxis, bronchospasm) close to the infusion are presumably drug-related. There were no clinically significant laboratory or vital sign changes noted in the phase 3 trials.

Limited data are available on the use of pegunigalsidase alfa during pregnancy and any effects on the developing fetus and newborn. Despite the lack of safety signals observed on fertility in the nonclinical studies and given that women with Fabry disease who are of reproductive age will be treated with pegunigalsidase alfa, safety data from the use of pegunigalsidase alfa during pregnancy and data on its potential effects on the developing fetus and newborn are still needed. This will be accomplished as a required post marketing pregnancy safety study. A lactation study will not be required as the physical characteristics of pegunigalsidase alfa, namely its size of 120kDa, make it unlikely to be present in milk or reach the infant in a significant quantity after oral ingestion.

In summary, the available safety database in patients exposed to pegunigalsidase alfa 1mg/kg IV every 2 weeks provides a sufficient basis for the conclusion of safety for pegunigalsidase alfa for the granted indication. In general, anaphylaxis and hypersensitivity reactions (including IRRs) appear to be related to pegunigalsidase alfa as it is a foreign protein product inducing immunogenicity. Anaphylaxis and the most frequent adverse events reported with pegunigalsidase alfa will be communicated through prescriber labeling. Continued safety monitoring in treated patients in the post marketing setting is recommended through routine pharmacovigilance.

8.3. **Conclusions and Recommendations**

The determination for efficacy in pegunigalsidase alfa in adults with Fabry disease was primarily based on the phase 1/2 open label dose finding trial that assessed the histological effect of the reduction of Gb3 in the peritubular capillaries of the kidney, with confirmatory evidence from

the biomarker, plasma lyso-Gb3. Overall a significant reduction was seen in the reduction of Gb3 in the kidney. The effect was more pronounced in males which is expected as males have a larger substrate burden due to the greater severity of disease typically found in male patients due to the x-linked nature of Fabry Disease. Although there was no comparator, it was unlikely that these reductions of the substrate would be related to variability of testing or spontaneous reduction in this patient population. The long term reduction of plasma lyso-gb3 is supportive of a continued treatment effect of pegunigalsidase alfa and correlation was also noted between reduction of Gb3 in the kidney and plasma lyso-Gb3. The available safety database showed an acceptable safety profile in pegunigalsidase alfa in the population studied with known adverse events seen in enzyme replacement therapies.

However, at the present time, we are unable to conclude that the benefits of pegunigalsidase alfa outweigh its risks. Records inspection of the drug product manufacturing site in (b) (4) led to a withhold recommendation on the facility, and inspection of the drug substance site has not yet occurred. Therefore, we are not assured that the product has sufficient quality for approval, and we will be issuing a Complete Response letter based on the withhold recommendation. In addition, the applicant is seeking accelerated approval but late in the review cycle Fabrazyme received full approval for the treatment for Fabry disease, becoming available therapy. For accelerated approval, the applicant will need to show that pegunigalsidase alfa provides a therapeutic advantage over Fabrazyme. Alternatively, the applicant could show that the reductions in Gb3 renal inclusions predict clinical benefit to support full approval. These late-developing issues have not been resolved in this review cycle and will need to be resolved in the next review cycle before we can conclude that the benefits of the drug outweigh its risks and can be approved.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened. We determined that the application did not raise efficacy or safety issues needing input from external experts. A reduction in GB3 inclusions and plasma lyso-GB3 have been used to establish efficacy for other Fabry products, and the safety concerns are typical of those seen with other enzyme replacement therapies.

10 Pediatrics

The granted indication is for only adult patients with Fabry disease. Pegunigalsidase alfa does not have orphan designation and therefore has triggered PREA regulations. The applicant has submitted an initial pediatric study plan (iPSP) which has been agreed to by the Agency. The Agency agreed with the Applicant's proposal for a partial waiver of pediatric studies in the pediatric FD subpopulation of 0 to 23 months (who are generally asymptomatic and, thus, a pediatric study would not be feasible or practical). The agreed-upon pediatric clinical trial will be a (b) (4) to evaluate the safety, efficacy, pharmacokinetic, and pharmacodynamic effects of pegunigalsidase alfa-iwxj in pediatric patients aged 2 to <18 years with confirmed Fabry disease.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The labeling discussions were paused and will continue in the next review cycle.

12 Risk Evaluation and Mitigation Strategies (REMS)

The risks are typical of those seen with enzyme replacement therapies and do not warrant mitigation approaches beyond labeling.

13 Postmarketing Requirements and Commitments

PMR and PMC discussions will continue in the next review cycle.

Draft PMRs:

1. Randomized, double-blind, concurrently controlled clinical trial to evaluate the efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) effects of pegunigalsidase alfa-iwxj in patients with confirmed Fabry disease. This trial will aim to verify and describe the clinical benefit of pegunigalsidase alfa-iwxj in Fabry disease as part of the accelerated approval regulatory pathway (21 CFR 601 subpart E). The trial will be of at least 2 years duration. The trial will also assess the product's immunogenicity and include correlative analyses between antibody formation (and titers if appropriate) and safety, efficacy, PK, and PD of the product in treated patients

2. Clinical trial under PREA to evaluate the safety, efficacy, pharmacokinetic, and pharmacodynamic effects of pegunigalsidase alfa-iwxj in pediatric patients aged 2 to <18 years with confirmed Fabry disease. The trial will evaluate patients over at least 1 year from the time of enrollment and will include assessments of immunogenicity and correlative analyses between antibody formation (and titers if appropriate) and safety, efficacy, PK, and PD in treated patients.

3. An international, single-arm, observational study collecting prospective and retrospective data in women exposed to pegunigalsidase alfa-iwxj during pregnancy to assess the risks of pregnancy and maternal complications and adverse effects on the fetus, neonate, and infant. Infant outcomes will be assessed through at least the first year of life. The study will collect these data for a minimum of 10 years.

4. Develop and validate an assay for detection of neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa-iwxj.

5. Develop and validate an anti-PEG IgE antibody assay.

6. Improve the current anti-pegunigalsidase alfa-iwxj IgG antibody assay or develop a new assay to improve the drug tolerance. Validate the assay.

7. Revise and re-validate the anti-pegunigalsidase alfa-iwxj IgM antibody assay with anti-pegunigalsidase alfa-iwxj IgM antibodies to be used as positive controls.

(b) (4)

9. Evaluate neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa-iwxj in clinical samples from studies PB-102-F01/02, PB-102-F03, and PB-102-F30 using the assay developed and validated under PMR XXXX-4. Assess the impact of cellular uptake neutralizing antibodies on the pharmacokinetics, pharmacodynamics, efficacy and safety of pegunigalsidase alfa-iwxj in a representative sample of patients with Fabry disease treated with the product in clinical trials.

10. A pre- and postnatal development study in rats treated with pegunigalsidase alfa-iwxj.

Draft PMCs:

(b) (4)

4. Conduct a drug product (DP) shipping validation study using (b) (4) the first three commercial shipments of finished DP vials from Chiesi Farmaceutici (Parma, Italy) to Chiesi USA (Cary, NC, USA). Include at minimum the following testing on DP samples at release and post-shipping: appearance by visual inspection, particulate matter, non-denatured and denatured SE-HPLC, peptide map purity assay, enzyme kinetics assay, protein content and container closure integrity.

5. Improve and revalidate the peptide mapping purity method for the drug substance and drug product to quantify the relative concentrations of product-related substances. Characterize oxidized product-related substances and identify those that may be critical quality attributes or stability-indicating; update the drug substance and drug product specifications accordingly with quantitative acceptance criteria for the relevant substances.

(b) (4)

(b) (4)

14 Office Director Comments

I concur with the review team's recommendation of a Complete Response action on this BLA based on the product manufacturing deficiencies (discussed in previous sections) which preclude approval.

15 Appendices

15.1. References

1. Kizhner T, Azulay Y, Hainrichson M, Tekoah Y, Arvatz G, Shulman A, et al. Characterization of a chemically modified plant cell culture expressed human α-Galactosidase-A enzyme for treatment of Fabry disease. Molecular genetics and metabolism. 2015;114(2):259-67.

15.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): PB-102-F01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 47		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		

Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): PB-102-F02

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 41		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): PB-102-F03

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 31		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): PB-102-F30

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 32		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): PB-102-F60

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 83		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.2. Nonclinical Pharmacology/Toxicology

No additional information.

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. Individual Study Summary

The Applicant submitted clinical pharmacology data from four clinical trials in patients with Fabry disease: studies PB-102-F01, PB-102-F02 and the open-label extension study PB-102-F03 in ERT-naïve patients and study PB-102-F30 in ERT-experienced patients. The PK, PD and immunogenicity data are summarized in Section 6 of this review. This section provides additional data based on individual study assessment.

Studies PB-102-F01/F02 and Its Open-Label Extension Study PB-102-F03 in ERT-naïve Patients

Pharmacokinetics

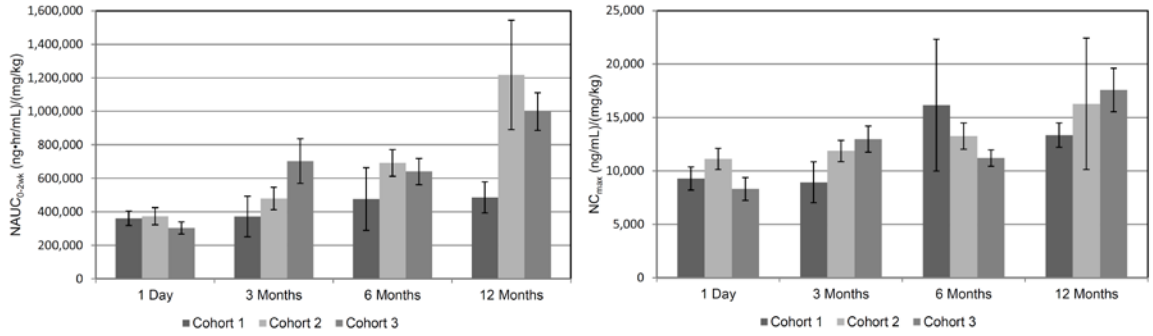
PK of pegunigalsidase alfa was evaluated at different treatment times (Day 1, Months 3, 6 and 12) in studies PB-102-F01/F02 following IV infusions of 0.2, 1 or 2 mg/kg EVERY 2 WEEKS. PK assessment was conducted on Day 1 and after 3, 6, and 12 months of treatment. At each PK assessment, blood samples were collected at pre-infusion, 1 hour after the beginning of infusion, at the end of infusion, and at 1, 4, 8, 24, 48, 72, 96 hours and 2 weeks post-infusion. The PK parameters are summarized in Table 30. Based on dose-normalized AUC and Cmax, pegunigalsidase alfa exhibited approximately dose-proportional PK on Day 1 following single dose administration, while dose-proportional PK was not observed at Months 3, 6 and 12 following multiple dose administration (Figure 12).

Table 26. PK Parameters of Pegunigalsidase alfa in ERT-naïve Patients in Study PB-102-F01/F02

Treatment Group	Patients Number (M;F)	Protocol Visit Day	Mean Infusion Length (hr)	Mean ± SD					
				AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	Cl (mL/hr/kg)	V_z (mL/kg)	T_{max} (hr)
0.2 mg/kg IV EOW	6 (2 F; 4M)	Day 1	4.04	62,835 ± 28,944	1,858 ± 531	60.3 ± 19.6	2.96 ± 0.81	246 ± 68	4.40 ± 0.56
		Month 3	2.02	68,940 ± 60,554	1,787 ± 935	60.3 ± 44.5	16.1 ± 22.5	282 ± 99	2.38 ± 0.49
		Month 6	2.01	86,121 ± 82,585	3,230 ± 2,761	53.4 ± 36.6	5.07 ± 5.36	212 ± 98	2.45 ± 0.54
		Month 12	1.50	68,750 ± 21,769	2,670 ± 557	63.0 ± 27.2	2.44 ± 1.04	219 ± 114	1.52 ± 0.02
1 mg/kg IV EOW	6 (2 F; 4M)	Day 1	5.49	375,625 ± 127,323	11,123 ± 2,409	78.9 ± 10.3	2.85 ± 0.66	321 ± 71	5.84 ± 1.83
		Month 3	4.36	478,466 ± 164,702	11,870 ± 2,447	85.7 ± 28.4	2.30 ± 0.79	271± 89	5.04 ± 1.86
		Month 6	3.87	688,489 ± 191,101	13,265 ± 3,022	96.5 ± 31.4	1.58 ± 0.59	226 ± 116	4.39 ± 1.49
		Month 12	3.28	1,333,955 ± 830,014	17,320 ± 6,058	121 ± 22	1.12 ± 0.65	186 ± 91	3.83 ± 1.84
2 mg/kg IV EOW	4 (3 F; 1M)	Day 1	6.37	575,488 ± 176,086	16,625 ± 4,299	70.7 ± 18.0	3.41 ± 0.68	345 ± 105	6.41 ± 0.37
		Month 3	6.03	1,392,917 ± 508,760	25,975 ± 4,875	83.1 ± 16.5	1.57 ± 0.53	179 ± 33	6.34 ± 0.50
		Month 6	5.12	1,309,647 ± 334,484	22,425 ± 3,041	117 ± 8	1.63 ± 0.39	274 ± 58	5.36 ± 0.37
		Month 12	3.13	1,885,929 ± 400,544	35,150 ± 8,137	111 ± 14	1.05 ± 0.26	169 ± 54	3.28 ± 0.37

AUC_{0-t}, Area under the plasma concentration-time curve from 0 hours to the last measurable concentration;
Cmax, Maximum observed concentration; $t_{1/2}$, Half-life in the terminal elimination phase;
Cl, Clearance from plasma; Vz, Volume of distribution during elimination phase;
Tmax, Maximum concentration within a dosing interval; SD, Standard Deviation; EVERY 2 WEEKS, every 2 weeks.
Source of data: Table 1, Summary of Clinical Pharmacology Studies

Figure 10. Dose-normalized Exposures (NAUC0-2wk and NCmax) (Mean ± SE) of Pegunigalsidase Alfa in Study PB-102-F01/F02



NAUC0-2wk, Dose normalized area under the plasma concentration time curve from 0 hours to 336 hours, which is a 2-week interval; NCmax, Dose-normalized maximum observed concentration; SE, Standard Error.
Patients in Cohorts 1, 2 and 3 received pegunigalsidase alfa treatment 0.2, 1 and 2 mg/kg EVERY 2 WEEKS, respectively.
(*Source of data: Fgure 1, Study PB-102-F01/02 PK Report.)*

Immunogenicity

Antibody incidence in the ERT-naïve population (Phase 1/2 studies PB-102-F01/F02 at 0.2, 1 and 2 mg/kg EVERY 2 WEEKS and PB-102-F03 at 1 mg/kg EVERY 2 WEEKS) is summarized in Table 31. The presence of IgM ADA was also evaluated. Samples tested positive for IgG ADA were analyzed for neutralizing antibodies (NAbs), antibodies to polyethylene glycol (PEG) cross-linker, and antibodies to plant specific glycans. In addition, in the event of a hypersensitivity reaction, IgE ADA was tested.

Table 27. Immunogenicity Incidences in Studies PB-102-F01/F02/F03

Antibody Specificity	Baseline Prevalence	Post-treatment Incidence
IgG ADA	16.7% (3/18)	18.8% (3/16)
Persistent ADA [a]	--	18.8% (3/16)
NAb ADA	--	12.5% (2/16)
IgM ADA	0% (0/18)	0% (0/16)
Anti-Glycan [b]	16.7% (3/18)	6.3% (1/16)
Anti-PEG	0% (0/18)	6.3% (1/16)
IgE ADA [c]	1/1 positive	1/1 positive

a. Persistent ADA was defined as a positive result in the ADA assay remained positive through Month 12, regardless of any missing sample.
b. One was discontinued and 1 became ADA negative during treatment.
c. IgE test was only performed on one patient.
(Source of data: Table 38, Immunogenicity Report.)

Impact of Immunogenicity

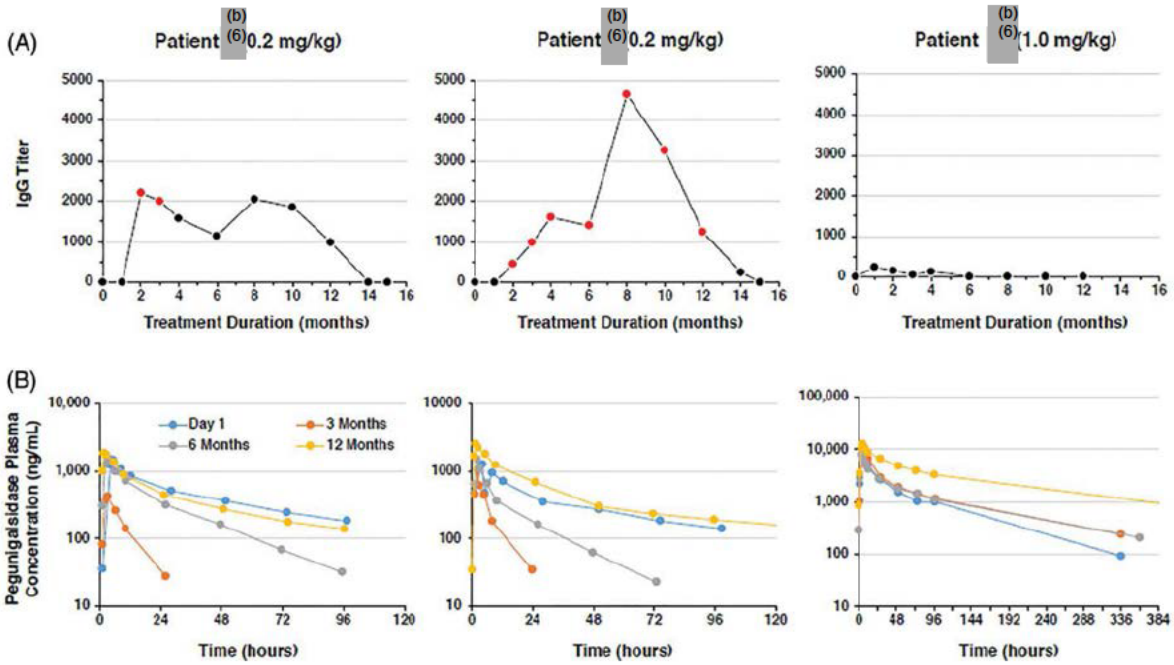
Among the 3 subjects who developed antibodies to pegunigalsidase alfa, lower plasma pegunigalsidase alfa concentrations were observed in two patients who received the 0.2 mg/kg dose and no clear antibody effect was observed in the third subject who received 1 mg/kg dose (Figure 13 and Figure 14). Note that the antibody titer in the patient who received 1 mg/kg dose was lower than the antibody titers in the two patients who received the 0.2 mg/kg dose, which may be a factor causing the differences in the ADA impact on PK between the two doses.

The two ADA positive subjects in the 0.2 mg/kg treatment groups showed a trend of continuous reduction of plasma Lyso-Gb3 concentrations even at timepoints before Month 12 when relatively higher antibody titers were observed. No significant impact of ADA on plasma Lyso-Gb3 was observed in the one ADA positive subject treated with 1.0 mg/kg (Figure 16). The overall data indicated that ADA did not have a significant impact on PD of pegunigalsidase alfa.

There was no identified significant effect of ADA on kidney Gb3 inclusions (Table 30) or efficacy as assessed by kidney function, eGFR and eGFR Slope (Table 33).

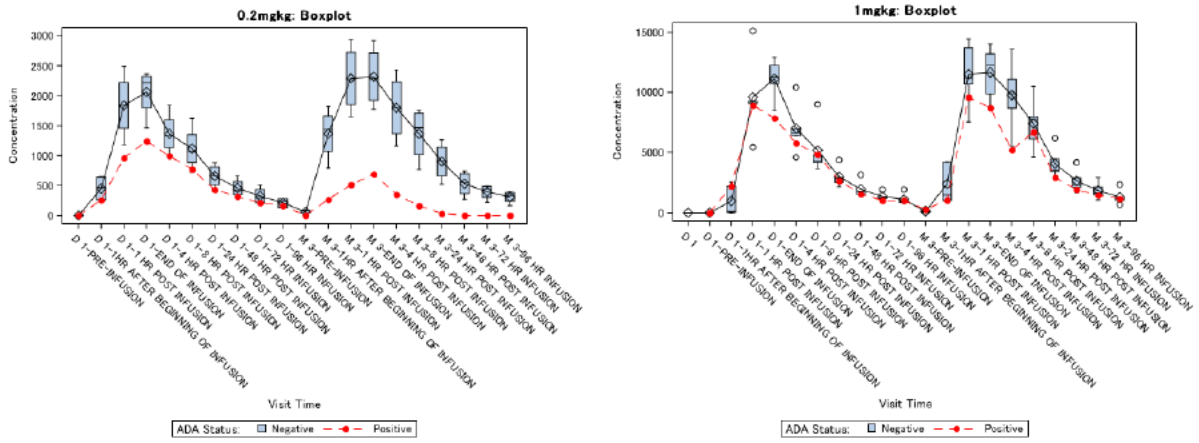
Due to the low numbers of ADA positive patients and imbalance in patient numbers and doses administered between the ADA positive (N =3, 2 in 0.2 mg/kg dose, 1 in 1.0 mg/kg dose, 0 in 2 mg/kg dose group) and antibody negative (N = 13, 4 in 0.2 mg/kg dose, 5 in 1.0 mg/kg, 4 in 2.0 mg/kg dose group), it is not feasible to conclude whether TEAEs are different between ADA positive and negative patients in the post-treatment period (Table 32). Infusion related reactions (IRRs) were reported in 2 patients with pre-existing antibodies but no other IRRs were reported in the treatment-emergent ADA patients.

Figure 11. Plasma Pegunigalsidase Alfa PK Profiles in ADA Positive Patients in Studies PB-102-F01/F02



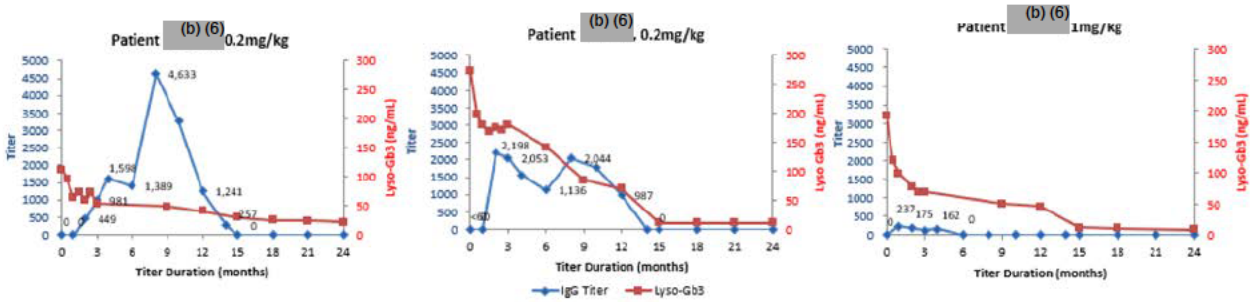
A) IgG titer for the ADA positive subjects. Red diamonds represent NAb-positive time points.
B) Pegunigalsidase alfa PK profiles at Day 1 and Months 3, 6, and 12
(Source of data: Figure 19, Immunogenicity Report.)

Figure 12. Comparision of Pegunigalsidase Alfa Mean (SD) Plasma PK Profiles in ADA Positive and Negative Patients in Studies PB-102-F01/F02



Red line and symbol are for ADA-positive; Blue line and symbol are for ADA-negative patients.
(Source of data: Reviewer's analysis.)

Figure 13. Antibody Titers and and Plasma Lyso-Gb3 Profiles in ADA Positive Patients in Studies PB-102-F01/F02/F03



Blue line and symbol represent IgG titer; Red line and symbol represent plamsa Lyso-Gb3
(Source of data: Figure 22, Immunogenicity Report.)

Table 28. Kidney Gb3 in ADA-Positive and ADA-Negative Patients –by Gender and Phenotype (Studies PB-102-F01/F02 Efficacy Population)

Kidney Gb_3 Score (BLISS)	IgG Anti-Pegunigalsidase Antibody Status									
	All Patients		By Gender				By Phenotype			
			Male	Female	Male	Female	Classic	Non-Classic	Classic	Non-Classic
	N= 3	N = 13	N = 3	N = 0	N = 6	N= 7	N = 3	N = 0	N = 5	N = 8
	Positive	Negative	Positive		Negative		Positive		Negative	
	n=2*	n=11	n=2	n = 0	n=5	n= 6	n = 2	n = 0	n = 5	n = 6
MEAN (SE) Baseline	8.3 (0.7)	3.5 (0.8)	8.3 (0.7)	na	5.7 (1.1)	1.7 (0.4)	8.3 (0.7)	na	5.7 (1.1)	1.7 (0.4)
MEAN (SE) Week 26	1.4 (1.0)	0.7 (0.1)	1.4 (1.0)	na	0.8 (0.3)	0.7 (0.2)	1.4 (1.0)	na	0.8 (0.3)	0.7 (0.2)
Change from Baseline	-6.9 (1.6)	-2.8 (0.8)	-6.9 (1.6)	na	-5.0 (1.0)	-1.0 (0.4)	-6.9 (1.6)	na	-5.0 (1.0)	-1.0 (0.4)
% Change from Baseline	-82.0 (13.2)	-65.2 (10.3)	-82.0 (13.2)	na	-86.3 (3.3)	-47.7 (15.6)	-82.0 (13.2)	na	-86.3 (3.3)	-47.7 (15.6)

c. *The kidney biopsy of the ADA positive Patient (b) (6) was unavailable.
(Source of data: Table 47, Immunogenicity Report.)

Table 29. Kidney eGFR and eGFR Slope in ADA Positive and Negative Patients (Study PB-102-F01/F02 Efficacy Population)

Subgroup	All Patients		By Gender				By Phenotype			
			Male	Female	Male	Female	Classic	Non-Classic	Classic	Non-Classic
	Positive	Negative	Positive		Negative		Positive		Negative	
ADA Status of Patients	N=3	N=13	N=3	N=0	N=6	N=7	N=3	N=0	N=5	N=8
eGFR [Mean (SE)]										
eGFR at Baseline [c] ($mL/min/1.73\ m^2$)	115.1 (8.5)	n=11 111.9 (7.1)	115.1 (8.5)	n/a	n=5 116.4 (12.8)	n=6 108.1 (8.5)	115.1 (8.5)	n/a	n=4 121.4 (15.2)	n=7 106.5 (7.3)
eGFR at 3M (Week 12) ($mL/min/1.73\ m^2$)	117.2 (7.8)	111.6 (6.1)	117.2 (7.8)	n/a	114.8 (10.9)	108.8 (6.9)	117.2 (7.8)	n/a	116.6 (13.2)	108.4 (6.0)
Change from baseline to Week 12 ($mL/min/1.73\ m^2$)	2.1 (1.3)	1.2 (2.2)	2.1 (1.3)	n/a	-1.3 (3.2)	3.4 (3.0)	2.1 (1.3)	n/a	-3.3 (3.0)	4.1 (2.7)
% Change from baseline to Week 12	1.9 (1.1)	1.4 (2.2)	1.9 (1.1)	n/a	-1.3 (3.4)	3.8 (2.7)	1.9 (1.1)	n/a	-3.5 (3.3)	4.4 (2.5)
eGFR at 3M (Week 26) ($mL/min/1.73\ m^2$)	117.5 (10.4)	108.6 (6.1)	117.5 (10.4)	n/a	118.0 (8.9)	100.5 (7.7)	117.5 (10.4)	n/a	117.7 (10.8)	102.8 (7.0)
Change from baseline to Week 26 ($mL/min/1.73\ m^2$)	2.3 (4.1)	-1.8 (2.4)	2.3 (4.1)	n/a	1.9 (4.5)	-4.9 (1.6)	2.3 (4.1)	n/a	-2.2 (2.4)	-1.5 (3.7)
% Change from baseline to Week 26	1.9 (3.8)	-1.4 (2.4)	1.9 (3.8)	n/a	2.6 (4.4)	-4.8 (1.6)	1.9 (3.8)	n/a	-1.5 (1.9)	-1.3 (3.7)
eGFR at 12M (52 W) ($mL/min/1.73\ m^2$)	113.1 (13.8)	n=12 109.5 (7.3)	113.1 (13.8)	n/a	117.9 (10.6)	n=6 101.1 (9.6)	113.1 (13.8)	n/a	119.6 (12.8)	n=7 102.3 (8.2)
Change from baseline to Week 52 ($mL/min/1.73\ m^2$)	-2.0 (7.6)	-0.2 (2.0)	-2.0 (7.6)	n/a	1.9 (3.2)	-2.3 (2.4)	-2.0 (7.6)	n/a	-0.4 (2.8)	-0.1 (3.0)
% Change from baseline to Week 52	-2.3 (7.2)	-0.5 (2.1)	-2.3 (7.2)	n/a	1.6 (3.2)	-2.7 (2.7)	-2.3 (7.2)	n/a	-0.8 (2.6)	-0.4 (3.2)
eGFR Slope [Mean (SE)]										
eGFR Annualized Slope at Week 52 [a] ($mL/min/1.73\ m^2$/year)	-7.6 (5.8)	-2.0 (1.8)	-7.6 (5.8)	n/a	1.5 (1.5)	-5.0 (2.7)	-7.6 (5.8)	n/a	0.5 (1.3)	-3.6 (2.7)

Male, Classic, ADA positive (b) (6) patient, who was treated intermittently with doxycycline was excluded from the analysis in PB-102-F01/F02, but is included as part of the current analysis
Inclusion criteria eGFR ≥60 mL/min/1.73 m^2
eGFR was calculated as Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
(Source of data: Table 48, Immunogenicity Report.)

Table 30. Number of TEAE Through Month 12 in ADA Positive and Negative Patients Overall, by Gender and by Fabry Disease Phenotype (Study PR-102-F01/02)

Number of TEAE Reported per Group										
Subgroup	All Patients		By Gender				By Phenotype			
			Male	Female	Male	Female	Classic	Non-classic	Classic	Non-classic
ADA Status	Positive	Negative	Positive		Negative		Positive		Negative	
Number of Patients	N = 3	N = 13	N = 3	N = 0	N = 6	N = 7	N = 3	N = 0	N = 5	N = 8
Total N = 222	25	197	25	na	98	99	25	na	92	105
Mild or moderate N= 219	25 (100%)	194(98.5%)	25	na	95	99	25	na	89	105
Severe N =3	0% (0.0%)	3 (1.5%)	0	na	3	0	0	na	3	0
Serious N = 1	0% (0.0%)	1 (0.5%)	0	na	1	0	0	na	1	0
Unrelated or unlikely related to study drug N = 169	24 (96.0%)	145(73.6%)	24	na	71	74	24	na	66	79
Possibly, probably, or definitely related to study drug N = 53	1 (4.0%)	52 (26.4%)	1	na	27	25	1	na	26	26

(Source of data: Table 54, Immunogenicity Report.)

Study PB-102-F30 in ERT-experienced Patients

Pharmacodynamics

In the ERT-experienced patients, the baseline plasma Lyso-Gb3 concentration was still elevated despite being previously treated with ERT. After switching to pegunigalsidase alfa treatment at 1 mg/kg EVERY 2 WEEKS for 12 months, all patients showed a reduction in plasma Lyso-Gb3 concentration with the mean %reduction from baseline of 36% (Table 35). As seen in ERT-naïve patients, greater reduction was also observed in males (41%) than in females (30%) in ERT-experienced patients.

Table 31. Plasma Lyso-Gb_3 Concentrations, Change from Baseline, and %Change from Baseline by Gender and Overall (Study PB-102-F30)

	Male Patients N=9	Female Patients N=7	Overall N=16
Plasma Lyso-Gb_3 Concentration (nM)			
Baseline			
n	9	7	16
Mean (SE)	53.6 (19.3)	13.8 (2.3)	36.2 (11.8)
Median (min; max)	48.6 (1.2; 189.4)	12.9 (7.4; 23.2)	19.0 (1.2; 189.4)
Month 6 (Visit 14)			
n	9	7	16
Mean (SE)	37.8 (12.5)	12.2 (1.5)	26.6 (7.6)
Median (min; max)	26.2 (1.1; 122.4)	13.1 (7.2; 17.4)	16.3 (1.1; 122.4)
Month 12 (Visit 27)			
n	9	7	16
Mean (SE)	28.4 (9.8)	9.2 (1.1)	20.0 (5.6)
Median (min; max)	26.9 (0.9; 90.0)	10.6 (4.7; 12.6)	11.2 (0.9; 90.0)
Change in Plasma Lyso-Gb_3 Concentration from Baseline to Month 12 (nM)			
n	9	7	16
Mean (SE)	-25.2 (10.3)	-4.6 (1.4)	-16.2 (6.3)
Median (min; max)	-19.6 (-99.4; -0.3)	-2.7 (-10.6; -1.4)	-6.6 (-99.4; -0.3)
% Change in Plasma Lyso-Gb_3 Concentration from Baseline to Month 12 (nM)			
n	9	7	16
Mean (SE)	-41.1 (3.0)	-29.8 (4.7)	-36.2 (2.9)
Median (min; max)	-40.3 (-52.5; -25.0)	-23.3 (-45.7; -17.3)	-37.8 (-52.5; -17.3)

SE, Standard Error.
(*Source of data: Table 7 in Pharmcodynamics Report)*

Immunogenicity

The antibody incidences in the ERT-experienced population in study PB-102-F30 at 1 mg/kg EVERY 2 WEEKS are summarized in Table 36.

Table 32. ADA Incidences in Study PB-102-F30

Baseline Prevalence	Baseline Prevalence	Post-treatment Incidence
IgG anti-Replagal	5.9% (1/17)	NA [a]
IgG ADA	5.9% (1/17)	37.5% (6/16)
Persistent ADA [b]	n/a	18.8% (3/16)
NAb ADA	5.9% (1/17)	6.3% (1/16)
Anti-Glycan	0% (0/17)	6.3% (1/16)
Anti-PEG	0% (0/17)	0% (0/16)
IgE ADA [c]	1/1 positive	1/1 positive [b]

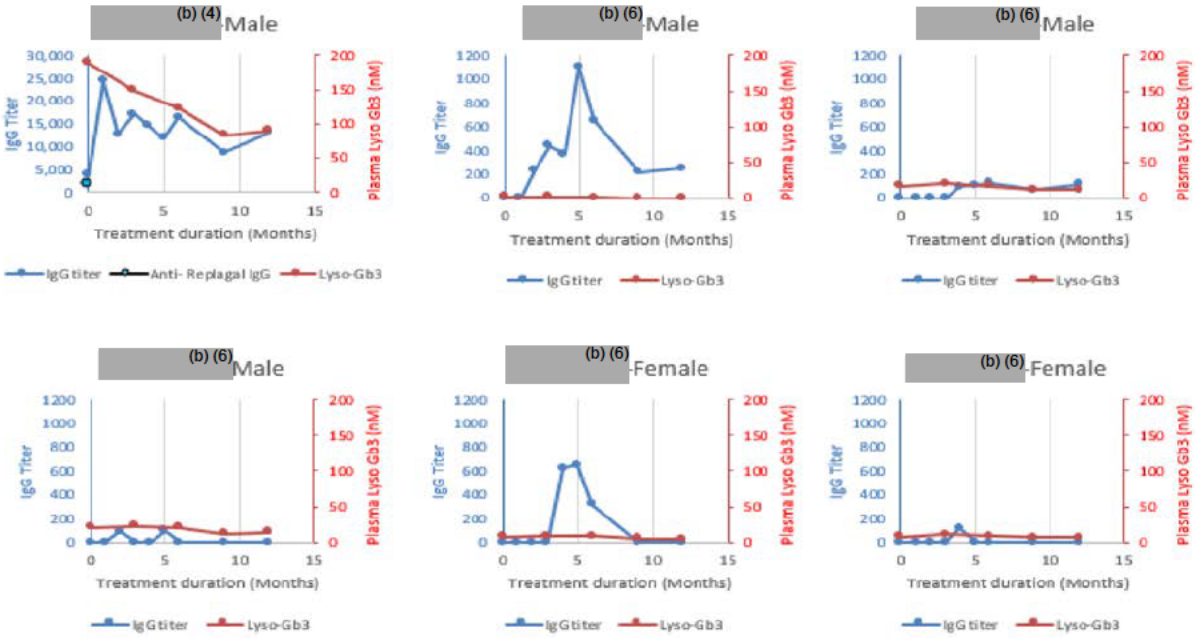
a. Not evaluable as no post-treatment samples were tested for anti-Replagal antibodies

b. Persistent ADA was defined as a positive result in the ADA assay that remained positive through Month 12, regardless of any missing sample.
c. IgE test was only performed on one patient.
(Source of data: Table 65, Immunogenicity Report.)

Impact of Immunogenicity

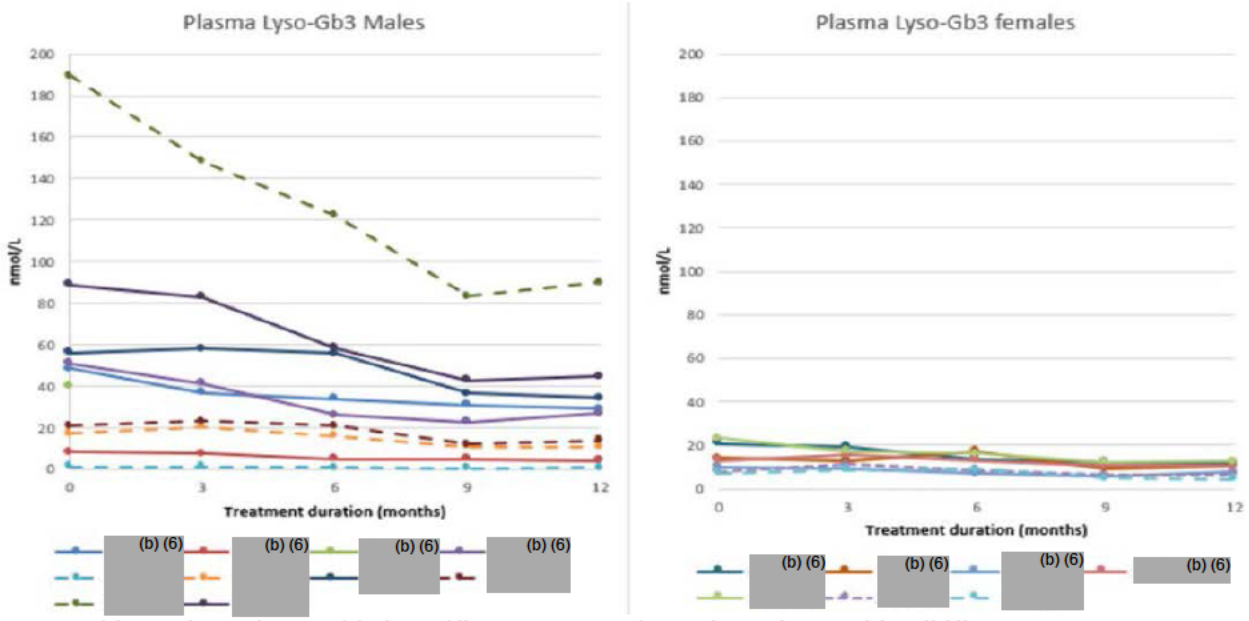
ADA had no apparent impact on the PD effect of pegunigalsidase alfa on reduction of plasma Lyso-Gb3 concentrations (Figure 16). Among patients with higher plasma Lyso-Gb3 levels, both ADA-positive and ADA-negative patients showed declining Lyso-Gb3 levels. Patients with lower initial plasma Lyso-Gb3 concentrations had low concentrations throughout the study regardless of whether they were ADA positive or negative (Figure 17). The development of antibodies by classic and non-classic Fabry disease phenotypes also did not show an effect on reduction of plasma Lyso-Gb3 concentration (Table 37). In addition, ADA positive patients did not show significant differences in response to pegunigalsidase alfa treatment as measured by eGFR and eGFR Slope, compared to the ADA negative subpopulations (Table 38). Furthermore, there was no identified significant effect of ADA on the safety of pegunigalsidase alfa (Table 39). Two of the 6 treatment emergent IgG ADA positive patients (one with classic and one with non-classic Fabry disease) experienced IRRs. However, a definitive conclusion of the effect of anti-pegunigalsidase alfa antibodies on PD, efficacy or safety could not be made due to the small number of subjects.

Figure 14. IgG ADA and Plasma Lyso-Gb3 Concentrations in ADA Positive Patients (Study PB-102-F30)



(Source of data: Figure 24, Immunogenicity Report.)

Figure 15. Plasma Lyso-Gb3 Profiles in Study PB-102-F30-by Gender



ADA-positive patients shown with dotted lines, ADA-negative patients shown with solid lines.
(Source of data: Figure 25, Immunogenicity Report.)

Table 33. Plasma Lyso-Gb3 Concentrations in ADA-Positive and Negative Patients –by Gender and Phenotype (Study PB-102-F30 Efficacy Population)

		IgG Anti-Pegunigalsidase Antibody Status									
				By Gender				By Phenotype			
		All Patients		Male	Female	Male	Female	Classic	Non-classic	Classic	Non-classic
		Positive	Negative	Positive		Negative		Positive		Negative	
Plasma Lyso-Gb3	Parameter	N= 6 [a]	N = 10	N = 4	N = 2	N = 5	N= 5	N = 3	N = 3	N = 5	N = 5
Baseline N = 1 Ab Pos [b]	Mean nM (SE)	40.72 (29.88)	33.45 (8.42)	57.20 (44.27)	7.75 (0.35)	50.66 (12.85)	16.24 (2.46)	75.87 (56.78)	5.57 (2.19)	50.66 (12.85)	16.24 (2.46)
Visit 7 (12W/3M) [c] N = 2 Ab Pos	Mean nM (SE)	35.53 (22.79)	30.13 (7.80)	48.30 (33.69)	10.00 (1.30)	45.42 (12.40)	14.84 (1.79)	64.00 (42.16)	7.07 (3.03)	45.42 (12.40)	14.84 (1.79)
Visit 14 (26W/6M) N = 4 Ab Pos	Mean nM (SE)	29.77 (18.73)	24.72 (6.01)	40.18 (27.73)	8.95 (0.05)	35.90 (9.85)	13.54 (1.77)	53.20 (34.63)	6.33 (2.62)	35.90 (9.85)	13.54 (1.77)
Visit 20 (38W/9M) N = 3 Ab Pos	Mean nM (SE)	19.78 (12.83)	18.97 (4.28)	26.85 (19.02)	5.65 (0.65)	27.72 (6.53)	10.22 (1.16)	35.50 (23.95)	4.07 (1.63)	27.72 (6.53)	10.22 (1.16)
Visit 27 (52W/12M) N = 3 Ab Pos	Mean nM (SE)	21.23 (13.88)	19.26 (4.25)	29.00 (20.53)	5.70 (1.00)	27.86 (6.62)	10.66 (0.77)	38.37 (25.83)	4.10 (1.70)	27.86 (6.62)	10.66 (0.77)
Change from baseline to 52 Weeks	Mean nM (SE)	-19.48 (16.02)	-14.19 (4.27)	-28.20 (23.78)	-2.05 (0.65)	-22.80 (6.47)	-5.58 (1.82)	-37.50 (30.95)	-1.47 (0.69)	-22.80 (6.47)	-5.58 (1.82)
% Change from baseline to 52 Weeks	Mean % (SE)	-33.36 (4.87)	-37.83 (3.77)	-36.60 (5.78)	-26.89 (9.60)	-44.69 (2.12)	-30.97 (5.98)	-40.46 (6.08)	-26.26 (5.58)	-44.69 (2.12)	-30.97 (5.98)

a. Number of patients with positive or negative ADA in Study PB-102-F30.
b. Number of patients positive for anti-pegunigalsidase alfa antibody at same time point as plasma Lyso-Gb3 measurement.
c. Study visit (times for plasma Lyso-Gb3 measurements/times for antibody measurements).
(Source of data: Table 66, Immunogenicity Report.)

Table 34. Kidney eGFR [b] and eGFR Annualized Slope in ADA Positive and Negative Patients (Study PB-102-F30 Efficacy Population)

	All Patients		By Gender				By Fabry Disease Phenotype			
			Male	Female	Male	Female	Classic	Non-classic	Classic	Non-classic
ADA Status	Positive	Negative	Positive		Negative		Positive		Negative	
Number of Patients	N=6	N=10	N=4	N=2	N=5	N=5	N=3	N=3	N=5	N=5
eGFR (mL/min/1.73 m^2) Mean (SE)										
eGFR at Baseline[b]	69.788 (7.017)	86.509 (7.168)	69.28 (9.10)	70.80 (15.50)	80.75 (13.29)	92.27 (6.16)	75.78 (9.01)	63.80 (11.36)	80.75 (13.29)	92.27 (6.16)
Visit 3 (4W/1M)[c]	n=5 66.481 (8.155)	n=9 89.573 (7.738)	70.09 (9.44)	n=1 52.04 (.)	n=3 89.71 (17.07)	89.47 (6.38)	77.10 (8.94)	n=2 50.55 (1.49)	n=4 89.71 (17.07)	89.47 (6.38)
Visit 5 (8 W/ 2M)	n=4 57.524 (3.936)	n=8 88.513 (7.225)	n=3 60.22 (4.05)	n=1 49.43 (.)	83.19 (18.97)	91.71 (5.60)	n=2 64.27 (0.03)	n=2 50.77 (1.35)	n=3 83.19 (18.97)	91.71 (5.60)
Visit 7 (12 W/ 3M)	n=5 65.100 (9.071)	n=9 83.306 (9.417)	69.14 (10.48)	n=1 48.93 (.)	78.42 (15.64)	n=4 89.42 (10.10)	75.21 (12.09)	n=2 49.93 (1.00)	78.42 (15.64)	n=4 89.42 (10.10)
Visit 9 (16 W/4M)	69.325 (6.338)	88.932 (7.051)	69.65 (9.16)	68.68 (9.92)	84.27 (13.61)	93.59 (5.26)	77.32 (7.09)	61.34 (9.31)	84.27 (13.61)	93.59 (5.26)
Visit 11 (20 W/ 5M)	69.019 (6.770)	88.525 (7.916)	68.96 (8.83)	69.14 (14.83)	83.03 (14.63)	94.02 (7.27)	75.94 (7.63)	62.09 (11.09)	83.03 (14.63)	94.02 (7.27)
Visit 14 (26W/M6)	70.194 (7.220)	87.837 (7.464)	68.73 (8.75)	73.12 (17.60)	81.34 (13.91)	94.33 (6.01)	76.09 (6.69)	64.30 (13.46)	81.34 (13.91)	94.33 (6.01)
Visit 16 (30 W)	n=5 75.171 (7.865)	n=9 89.515 (9.229)	n=3 78.81 (10.80)	69.72 (14.81)	83.02 (15.12)	n=4 97.63 (9.52)	78.81 (10.80)	n=2 69.72 (14.81)	83.02 (15.12)	n=4 97.63 (9.52)
Visit 18 (34W)	69.780 (7.689)	n=9 90.032 (8.140)	72.29 (10.11)	64.76 (15.34)	81.60 (13.56)	n=4 100.57 (4.96)	79.26 (10.36)	60.30 (9.92)	81.60 (13.56)	n=4 100.57 (4.96)

	All Patients		By Gender				By Fabry Disease Phenotype			
			Male	Female	Male	Female	Classic	Non-classic	Classic	Non-classic
ADA Status	Positive	Negative	Positive		Negative		Positive		Negative	
Number of Patients	N=6	N=10	N=4	N=2	N=5	N=5	N=3	N=3	N=5	N=5
Visit 20 (38W/9M)	66.431 (6.852)	84.909 (8.198)	67.14 (8.88)	65.02 (15.09)	80.76 (15.53)	89.06 (7.25)	75.39 (4.67)	57.48 (11.52)	80.76 (15.53)	89.06 (7.25)
Visit 22 (42 W)	68.950 (6.771)	86.900 (9.419)	70.22 (8.06)	66.40 (16.98)	n=4 72.06 (14.09)	n=4 101.74 (8.29)	77.63 (4.51)	60.27 (11.56)	72.06 (14.09)	101.74 (8.29)
Visit 24 (46W)	71.957 (8.064)	87.189 (7.838)	74.61 (10.44)	66.65 (16.72)	80.35 (14.10)	94.03 (7.37)	82.87 (9.02)	61.04 (11.17)	80.35 (14.10)	94.03 (7.37)
Visit 27 (52 W/12M)	65.935 (8.276)	83.806 (7.674)	65.21 (8.94)	67.38 (23.34)	80.04 (15.36)	87.57 (4.70)	71.29 (9.28)	60.58 (15.09)	80.04 (15.36)	87.57 (4.70)
Change from Baseline to 52 W	-3.853 (2.054)	-2.703 (3.498)	-4.07 (0.53)	-3.42 (7.83)	-0.70 (5.75)	-4.70 (4.48)	-4.49 (0.45)	-3.22 (4.53)	-0.70 (5.75)	-4.70 (4.48)
eGFR Annualized Slope (mL/min/1.73m^2/year) Mean (SE)										
eGFR Annualized Slopepre-switch	-5.47 (3.36)	-4.94 (1.51)	-6.44 (4.80)	-3.54 (4.99)	-4.25 (2.66)	-5.63 (1.71)	-8.62 (6.05)	-2.31 (3.13)	-4.25 (2.66)	-5.63 (1.71)
eGFR Annualized Slope Post-switch	-0.93 (1.76)	0.01 (2.37)	-0.17 (2.17)	-2.46 (3.85)	-0.67 (4.75)	0.70 (1.54)	0.80 (2.75)	-2.67 (2.23)	-0.67 (4.75)	0.70 (1.54)
Change from pre-switch	4.54 (3.40)	4.96 (3.05)	6.26 (5.08)	1.08 (1.14)	3.58 (6.36)	6.33 (0.63)	9.42 (5.62)	-0.35 (1.57)	3.58 (6.36)	6.33 (0.63)

a. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
b. Study inclusion criteria eGFR ≥60 mL/min/1.73 m^2.
c. Study visit (times for eGFR measurements/times for antibody measurements).
(Source of data: Table 67, Immunogenicity Report.)

Table 35. Number of TEAEs through Month 12 in ADA Positive and Negative Patients Overall, by Gender and by Fabry Disease Phenotype (Study PB-102-F30)

Subgroup	All Patients		By Gender				By Fabry Disease Phenotype			
ADA Status	Positive	Negative	Positive		Negative		Positive		Negative	
Gender	Total	Total	Male	Female	Male	Female	Classic	Non-Classic	Classic	Non-Classic
Number of Patients	N=6	N=10	N=4	N=2	N=5	N=5	N=3	N=3	N=5	N=5
Number of TEAE	38	51	32	6	26	25	11	27	26	25
Mild or Moderate TEAE	38 (100.0%)	50 (98.0%)	32 (100.0%)	6 (100.0%)	25 (96.2%)	25 (100.0%)	11 (100.0%)	27 (100.0%)	25 (96.2%)	25 (100.0%)
Severe TEAE	0% (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)
Serious TEAE	0% (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)
TEAE Unrelated or Unlikely Related to Study Drug	29 (76.3%)	51 (100.0%)	23 (71.9%)	6 (100.0%)	26 (100.0%)	25 (100.0%)	5 (45.5%)	24 (88.9%)	26 (100.0%)	25 (100.0%)
TEAE Possibly, Probably, or Definitely Related to Study Drug	9 (23.7%)	0 (0%)	9 (28.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (54.5%)	3 (11.1%)	0 (0.0%)	0 (0.0%)

(Source of data: Table 73, Immunogenicity Report.)

15.3.2. Pharmacometrics Review

15.3.2.1. Applicant's PPK and PKPD Analysis

Objectives: To develop a population PK model for PRX-102, and to develop population PKPD models for the PRX-102 exposures and two biomarkers associated with efficacy, Lyso-Gb3 (globotriaosylsphingosine), and Gb3 (globotriaosylceramide) inclusions.

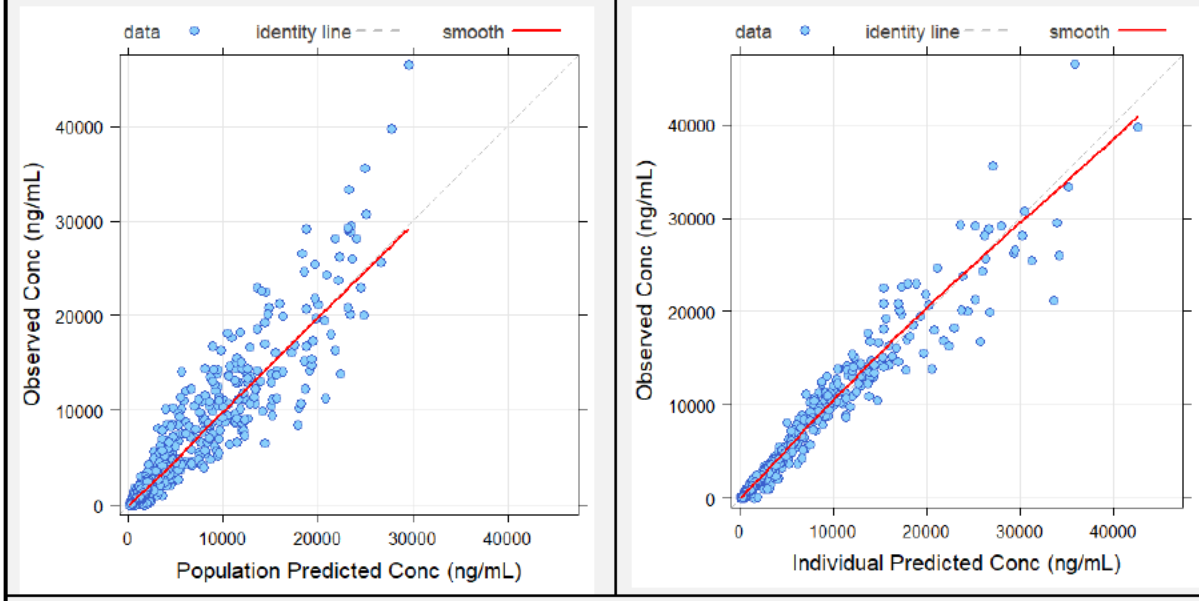
Data: The analyses are based on PK and biomarker (Lyso-Gb3 and Gb3 inclusions) data from Studies PB-102-F01 and PB-102-F02. PK profiles were determined on Day 1, and at 3, 6, and 12 months. For each PK profile, blood samples were collected at pre-dose, 1 hour after the start of the infusion, at the end of the infusion, and at 1, 4, 8, 24, 48, 72, and 96 hours after the end of the infusion. Lyso-Gb3 concentrations in plasma were collected at baseline and prior to every study drug infusion during Study PB-102-F01, and then every 3 months during Study PB-102-F02. Gb3 inclusion was assessed via kidney biopsy during Study PB-102-F01 baseline and then at Month 3 of Study PB-102-F102 (that is the total treatment of 6 months from the start of PB-102-F101) using the BLISS (Barisoni Lipid Inclusion Scoring System) method.

Methods: (b) (4) models with zero-order infusion were evaluated to characterize the PK profiles of PRX-102 in patients with Classic Fabry. Inter-individual variability (IIV) was investigated on all PK parameters. Weight, lean body mass (LBM), age, sex, total PRX-102 amount given at each administration, dose group, creatinine clearance (CrCL), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were tested for their influence on PRX-102 PK. Goodness-of-Fit (GOF) plots were used to assess whether the model described the data adequately. The final population PK model was used to predict Cmax, Cmin, Cave and AUCτ following each dose administration for each patient.
Generalized linear models were used to develop PKPD models for the two biomarkers associated with efficacy: Lyso-Gb3 and Gb3 inclusions measured by BLISS scores. Whether or not a patient had Classic Fabry disease was used as a covariate during the modeling.

Results: The final PPK analysis for PRX-102 was based on 680 plasma concentrations of PRX-102 collected from 16 patients for up to 12 months. A three-compartment mammillary population PK model with zero-order absorption and first-order elimination, with IIV terms estimated on central and peripheral compartments (CL, V1, Q3, V3) and a covariance term on CL and V1 provided the best fit to the observed PRX-102 plasma concentrations (**Figure 18**). Residual error was best described by additive and proportional terms. Inter-occasion variability (IOV) on bioavailability term F significantly improved the overall model fit. No covariate was determined to be statistically significant on any PK parameter. The parameters for the final population PK model were estimated (**Table 40**). The final PPK model was used to predict exposure parameters (individual Cmin, Cmax and AUCτ) as independent variables in PKPD analyses of Lyso-Gb3 and Gb3 inclusions.

PKPD Modeling of Lyso-Gb3: PKPD modeling of Lyso-Gb3 was based on the data collected from 16 patients. There was a statistically significant relationship identified between Lyso-Gb3 and PRX-102 exposure in male patients. PRX-102 0.2 mg/kg, 1 mg/kg and 2 mg/kg doses were associated with Lyso-Gb3 reductions of 39%, 71%, and 74%, respectively, in male patients (**Figure 19**). Female patients had few or no elevated levels of Lyso-Gb3 at baseline and accordingly there was no reduction in Lyso-Gb3 with increase in exposure (**Figure 20**).

Figure 16: Observed versus model predicted pegunigalsidase concentration for final population PK model



Source: Figure 12-4 of Applicant's PPK and PKPD report

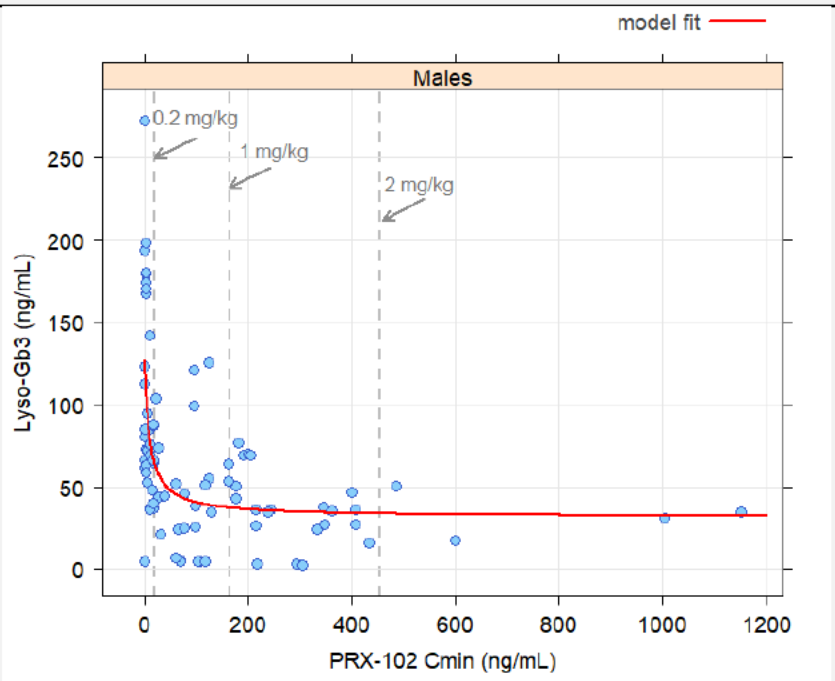
Table 36: Final population PK model parameter estimates with bootstrap estimates

Parameter (Unit)	Estimate	Shrinkage	RSE (%)	CV(%)	Bootstrap Median (90% Percentile Interval)
Fixed Effects					
θ_1: CL (L/hr)	0.0479		19.83	70.43	0.0477 (0.0318, 0.0746)
θ_2: V_1 (L)	5.399		5.23	18.33	5.356 (4.957, 5.886)
θ_3: Q_2 (L/hr)	0.217		12.47		0.214 (0.169, 0.285)

θ_4: V_2 (L)	6.437		7.59		6.414 (5.479, 7.513)
θ_5: Q_3 (L/hr)	0.0986		2.10	0.42	0.0979 (0.0965, 0.0986)
θ_6: V_3 (L)	2218.61		0.25	0.38	2211.74 (2194.33, 2226.07)
Inter-Individual Variability					
η_1(CL)	0.496	5.66	18.61		0.443 (0.117, 0.851)
η_{12}(CL,V_1)	0.109		27.72		0.09 (0.006, 0.207)
η_2(V_1)	0.0336	10.6	30.70		0.0248 (0.001, 0.0655)
η_3(V_3)	1.75×10^{-5}	96.24	489.84		6.1×10^{-8} (0.3×10^{-8}, 113.8×10^{-8})
η_4(V_3)	1.43×10^{-5}	96.65	779.66		1×10^{-9} (0, 19.0×10^{-9})
Inter-Occasion Variability					
η_5(F IOV$_1$-IOV$_4$)	0.122		1.70		0.118 (0.062, 0.195)
Residual Variability					
σ_1 (prop)	0.0490	6.77	8.07		0.0481 (0.0378, 0.0617)
σ_2 (add)	2009.47	6.77	37.59		1970.38 (803.20, 5259.46)

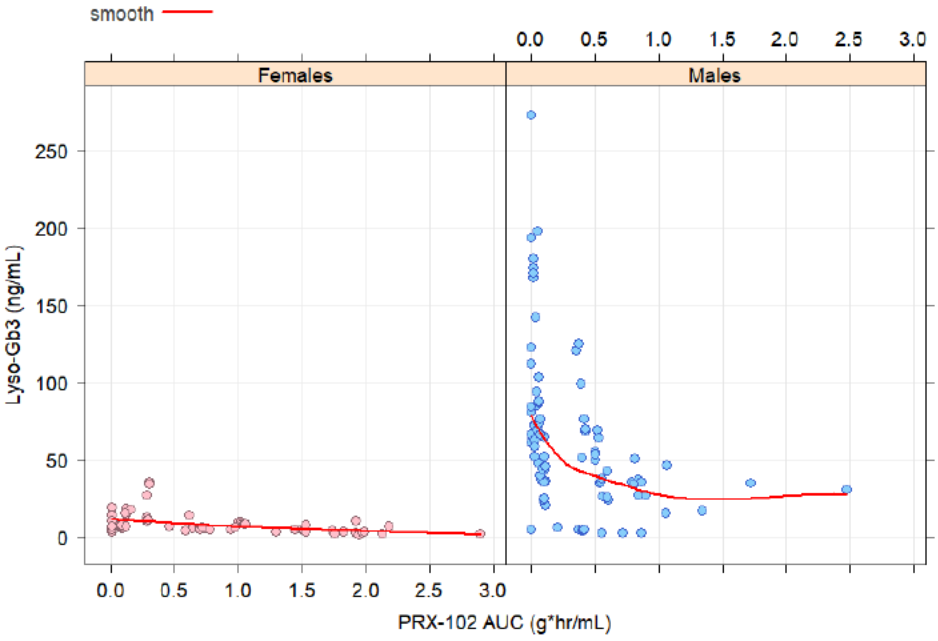
Source: Table 12-1 of Applicant's PPK and PKPD Report

Figure 17: Relationship between population PK model predicted Cmin and Lyso-Gb3 for male patients (patients with classic Fabry) overlaid with fitted PKPD relationship (red line)



Note: The dash line marks the median trough concentration (Cmin) of each dose group
Source: Figure 12-10 of Applicant's PPK and PKPD report

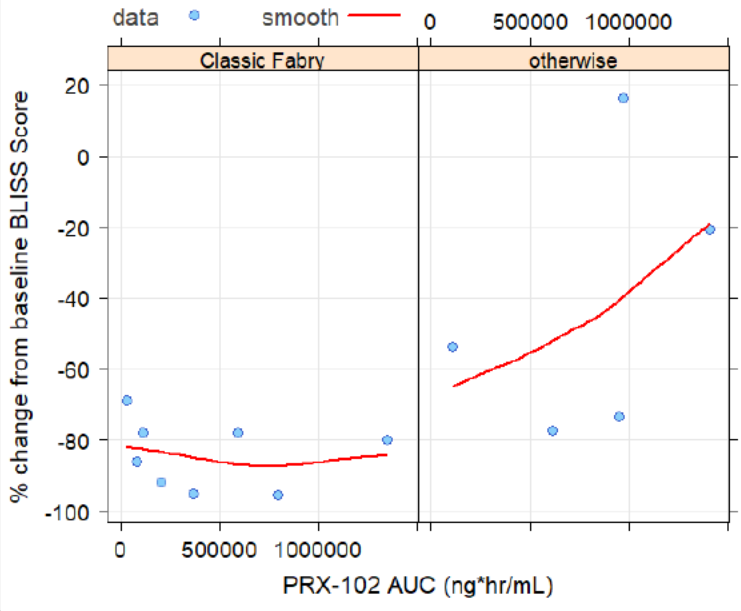
Figure 18: Relationship between population PK model predicted AUCτ at each plasma Lyso-Gb3 visit and Lyso-Gb3 in males and females



Note: The x-axis is the area under plasma drug concentration vs time curve (AUC) for a dose interval at steady-state
Source: Figure 12-7 of Applicant's PPK and PKPD report

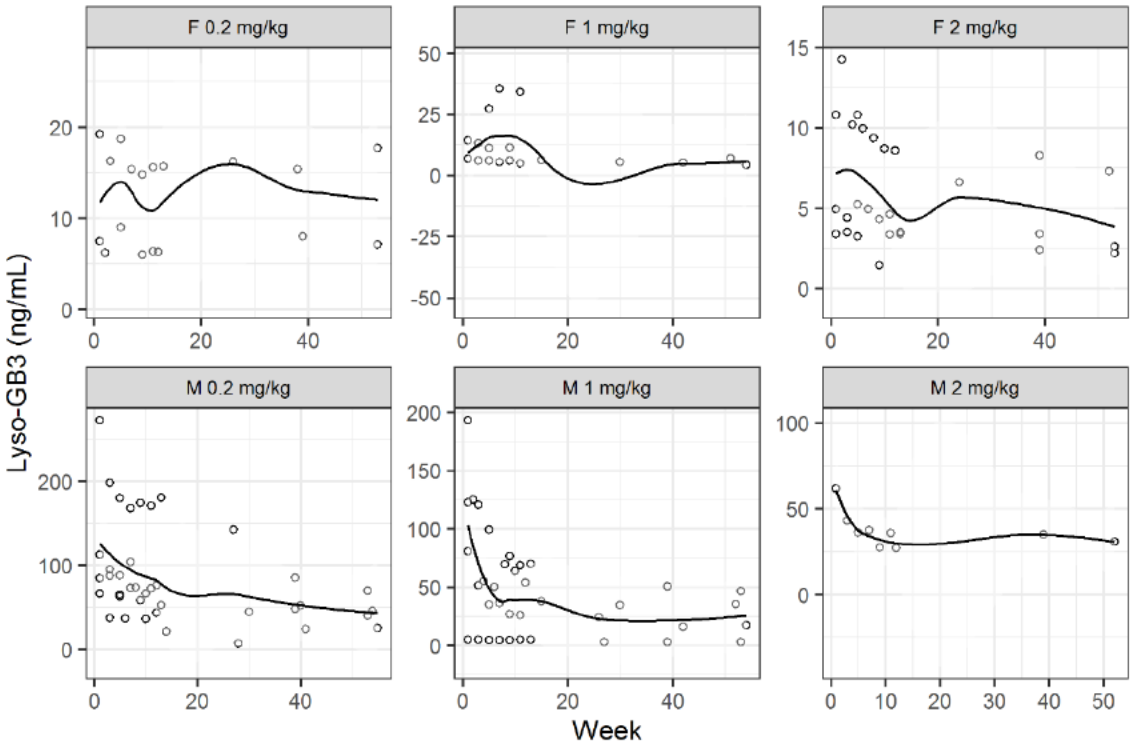
PKPD Modeling of Gb3 Inclusions: PKPD analysis of Gb3 inclusions was based on the data collected from 13 patients. Exploratory plots of the percent change from baseline in BLISS score for Gb3 inclusions versus PRX-102 AUCτ showed a difference between Classic Fabry patients and others; however, there was no statistically significant relationship between change in Gb3 inclusion and PRX-102 exposure (AUCτ) (**Figure 21**).

Figure 19: Percent change from baseline in BLISS score for Gb3 inclusions vs. PRX-102 AUCτ stratified by whether patients had Classic Fabry disease



Note: The x-axis is the area under plasma drug concentration vs time curve (AUC) for a dose interval at steady-state
Source: Figure 12-12 of Applicant's PPK and PKPD report

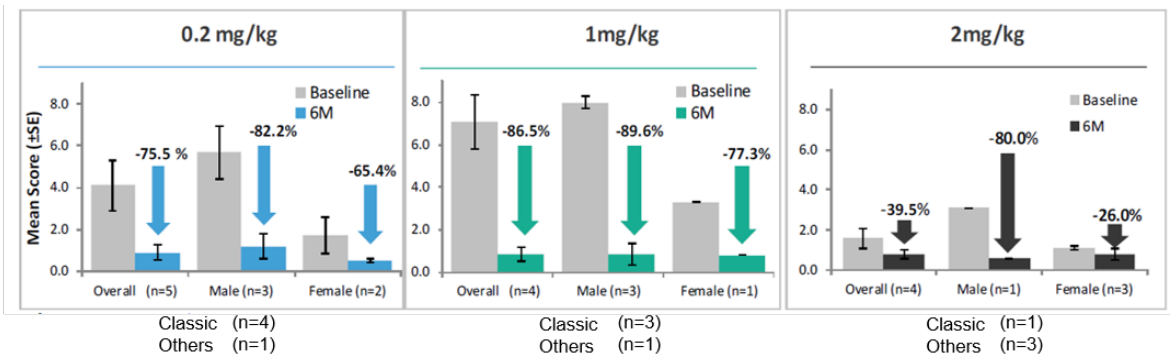
Figure 20: Plasma Lyso-Gb3 over 12 Months of Treatment by Dose Group and Gender



Source: FDA reviewer's analysis based on icx-b152-pkpd-lyso-gb3.xpt

The applicant's PPK model captured the central tendency of observed pegunigalsidase alfa concentration data. The lack of body weight effect on PK does not immediately support the proposed mg/kg dosing regimen, however, the conclusion could be limited by the small number of subjects (N=16 weighing 52-90 kg) in the dataset. The Applicant's PK/PD analysis is also limited by small number of subjects, and varying baseline values across dose levels potentially due to imbalanced distribution in sex and FD phenotype (**Figure 23**). In addition, the applicant's analysis for Lyso-Gb3 was based on absolute values (not accounting for difference at baseline), and pooled data over time which includes multiple datapoints per subject. As such, the overall dose-response and exposure-response relationships for efficacy based on available data are considered inconclusive.

Figure 21: Mean BLISS Score Reduction in Gb3 Inclusions following 6 Months of Treatment by Dose Group and Gender



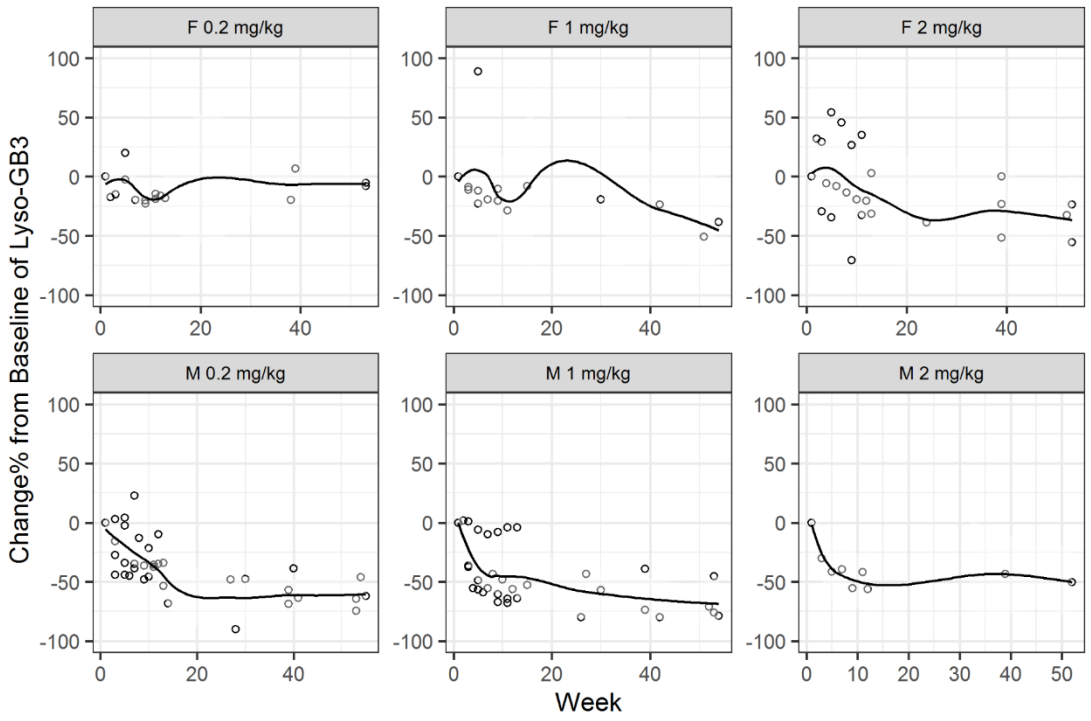
Source: Figure 3 of Applicant's Summary of Clinical Efficacy

15.3.2.2. FDA Analysis

As noted, the applicant's PK/PD analysis for Lyso-Gb3 was based on absolute values and pooled data over time which did not account for the variability in the baseline Lyso-Gb3 levels and the differences in time course. Using R graphics function, we further explored the dose-response and exposure-response relationships for Lyso-Gb3 in female and male patients based on percent change from baseline as the efficacy endpoint. The analysis was conducted using Lyso-Gb3 data collected from Studies PB-102-F01 and PB-102-F02.

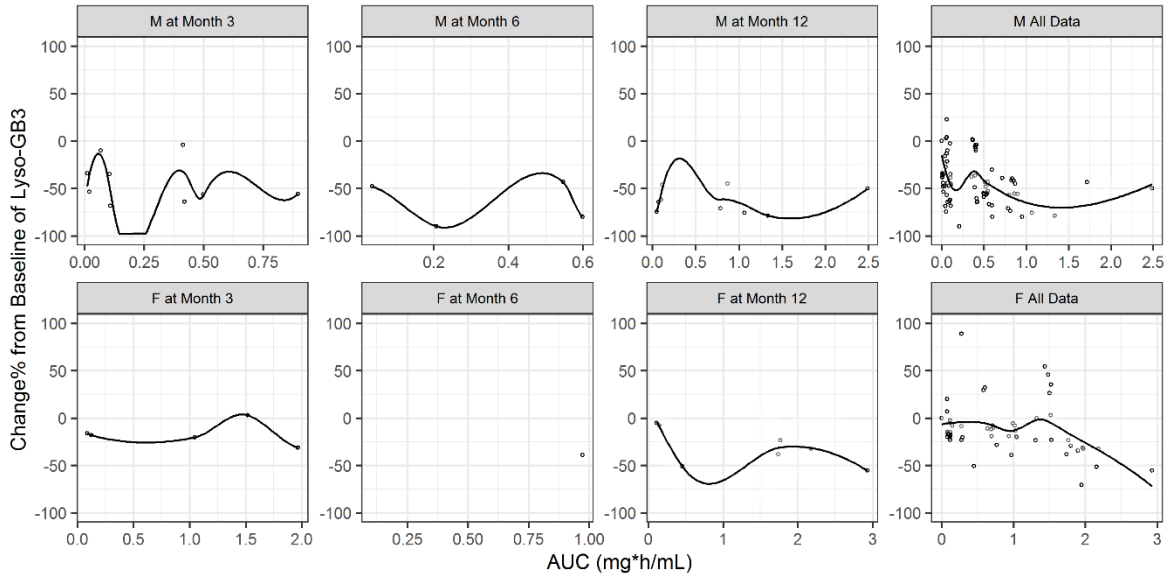
In contrast to **Figure 22** where absolute plasma Lyso-Gb3 levels are plotted over 12 months by dose and gender, **Figure 24** shows the percent change from baseline in plasma Lyso-Gb3 over 12 months of Treatment in PB-102-F01/F02 by dose and gender. In addition, the exposure-response relationships at Month 3, 6 and Month 12 were explored in **Figure 25**. Overall, no clear dose-response or exposure-response relationship for Lyso-Gb3 was observed, except for a slight trend of greater reduction at 2 mg/kg compared to low doses in female subjects. However, this observation may also be confounded by imbalanced baseline values and FD phenotypes across dose groups.

Figure 22: Percent Change from Baseline in Plasma Lyso-Gb3 over 12 Months of Treatment by Dose Group and Gender



Note: The lines represent loess smooth curves of the data points
Source: FDA Reviewer's Analysis Based on Dataset icx-b152-pkpd-lyso-gb3.xpt

Figure 23: Percent Change from Baseline in Plasma Lyso-Gb3 at Months 3, 6 and 12 and All Times up to Month 12 vs. AUC by Gender



Note: The lines represent loess smooth curves of the data points. Data collected during Weeks 12-14, 23-29, and 49-55 are included for Month 3, 6, and 12, respectively
Source: FDA Reviewer's Analysis Based on Dataset icx-b152-pkpd-lyso-gb3.xpt

15.3.3. Bioanalytical Methods

PK assay: bioanalytical method for determination of pegunigalsidase alfa concentrations in human plasma

The Applicant developed and validated an ELISA assay to determine the concentrations of pegunigalsidase alfa (PRX-102) in human plasma PK samples collected in studies PB-102-F01 and PB-102-F02. The validation parameters and performance of the ELISA assay are summarized in Table 41.

Table 37 Validation Parameters and Performance of the ELISA Assay Used to Determine the Concentrations of Pegunigalsidase Alfa in Human Plasma.

Bioanalytical method review summary	The analytical method (Method 30-50-006)(PCL-14-006/R) for pegunigalsidase alfa (PRX-102) in human plasma met acceptance criteria in general, with respect to sensitivity, precision, accuracy, linearity, and dilution integrity, spanning a theoretical concentration range of 0.20 ng/mL to 12.5 ng/mL. The stability evaluations in matrix exceeded the recommended acceptance criteria, with the accuracy (%bias) up to 31.2% for overnight at 2-8°C, up to 44.7% on ice 4 hours, ranging from -21.2% to 16.8% at -20°C for 2 months, and 2.4% to 48% at -70°C for 26 months.		
Method description	Sandwich ELISA format using anti-PRX-102 murine monoclonal antibodies as capture antibodies and anti-PRX-102 rabbit antibody as the sandwich antibody; with alkaline phosphatase (AP)-conjugated donkey anti-rabbit-IgG antibody.		
Materials used for calibration curve & concentration	PRX-102 drug product spiked in normal human plasma pool at the following concentrations (ng/mL): 0.20, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5.		
Validated assay range	0.2 to 12.5 ng/mL (due to minimum required dilution [MRD] of 1:100, 19.95-1250 ng/mL in the plasma)		
Material used for QCs & concentration	PRX-102 drug product spiked in normal human plasma pool. QCs: 750, 250, 62.5 ng/mL (diluted 1:100 to 7.5, 2.5 and 0.625) Dilution control (DC): 50,000 ng/mL diluted 1:20,000		
Minimum required dilutions (MRDs)	1:100		
Source & lot of reagents (LBA)	Reference drug pegunigalsidase alfa SDP00003, Lot 030213, exp. date Jul/2014, Jan/2015, Jul/2015 SDP00005, Lot PRX 102-040615, exp. date Jul/2015, Nov/2017		
Regression model & weighting	Five-parameter logistic model		
Validation parameters	**Method validation summary**		**Acceptability**
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ	7	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-8.7 to -30.0%	Acceptable
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 34.8%	Acceptable

QCs performance during accuracy & precision	Number of QCs	3	Acceptable
	Cumulative inter-run accuracy (%bias)	HQC: -6.7 to 22.9% MQC: -18.8 to 20.4% LQC: -31.2 to 32.8%	Acceptable
	Inter-run precision(%CV)	HQC: 9.9% MQC: 10.6% LQC: 14.8%	Acceptable
	Total error (%TE) [a]	HQC ≤32.8% MQC ≤31.0% LQC ≤42.9%	
Selectivity & matrix effect	10 lots tested, the range of observed bias -10.9 to 25.0%.		Acceptable
Interference & specificity	Not evaluated		
Dilution linearity & hook effect	The highest concentration tested was 50,000 ng/mL, evaluated at 10,000-fold and 20,000-fold. The range of observed bias was ≤ 18%.		Acceptable
Bench-top/process stability	Three aliquots of HQC and LQC tested overnight at 2-8°C, and 4 hours on ice Overnight 18 hours and 23minutes at 2-8°C: HQC ≤24.3% CV and ≤15.5% RE LQC ≤6.9% CV and ≤31.2% RE On ice 4 hours: HQC ≤15.5% CV and ≤44.7% RE LQC ≤5.3% CV and ≤28.0 % RE		Acceptable
Freeze-Thaw stability	6 freeze thaw cycles: HQC ≤8.4% CV and ≥-27.5% RE LQC ≤8.8% CV and ≤15.2 %RE		Acceptable
Long-Term storage	-70°C for up to 26 months HQC ≤4.6 %CV and ≤48.3% RE MQC ≤6.7 % CV and ≤30.8% RE LQC ≤2.6% and ≤37.6% RE At -20°C, tested up to 2 months HQC ≤8.3 %CV and ≤16.0% RE MQC ≤2.0 % CV and ≥-21.2% RE LQC ≤5.5% and ≤16.8% RE		Acceptable
Parallelism	Parallelism was demonstrated by testing the calibration curve with increasing plasma levels (0.0%, 0.1%, 1.0%, 10%, and 100%plasma). The maximal bias observed was 31% for the LLOD (with 100% plasma). With 10% and 1% plasma the bias was ≤15% and ≤3%, respectively		Acceptable
Carry over	Not applicable		
Method performance in study PB-102-F01 (PCL-12-015/R)			
Assay passing rate	ISR was done as part of the PCL-12-015 study. From a total of 350 samples, 39 underwent the ISR test (11%), and 37 samples (95%) met the pre-specified criteria.		Acceptable

Standard curve performance	Standard calibrators from LLOQ to ULOQ (ng/mL): 0.20, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5 Cumulative bias range: -10.2 to 25.0%	Acceptable
QC performance	Cumulative bias: -28.0 to 37.6%	Acceptable
Method reproducibility	• Total Number of samples in the ISR test: 39 (11 % of total 350 samples analyzed) using the same dilution as in the original test • Total Number of incurred samples reproducible (within ± 30% difference from the original result): 37 (95% of total reproducible samples)	Acceptable
Study sample analysis/ stability	The long-term stability study evaluated samples (assay QCs) for 26 months at a storage temperature of -70°C. In study PB-102-F01, the study samples with the longest storage duration were collected on [redacted] (b) (6) (Patient [redacted] (b) (6), visit 1) and tested on [redacted] (b) (6) (Storage Duration of ~23 months).	
Method performance in study PB-102-F02 (PCL-14-013/R)		
Assay passing rate	ISR was done as part of study PB-102-F01 (PCL-12-015/R)	Acceptable
Standard curve performance	Standard calibrators from LLOQ to ULOQ (ng/mL): 0.20, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5 Cumulative bias: -20.8 to 70%	Acceptable
QC performance	Cumulative bias: -44 to 18.8%	Acceptable
Method reproducibility	ISR was done as part of study PB-102-F01 (PCL-12-015/R) • Total Number of samples in the ISR test: 39 (11 % of total 350 samples analyzed) using the same dilution as in the original test • Total Number of incurred samples reproducible (within ± 30% difference from the original result): 37 (95% of total reproducible samples)	Acceptable
Study sample analysis/ stability	The long-term stability study evaluated samples (assay QCs) for 26 months at a storage temperature of -70°C. In study PB-102-F02, the study samples with the longest storage duration was collected on [redacted] (b) (6) (Patient [redacted] (b) (6), visit 7), and tested on [redacted] (b) (6) (~14 months)	

[a] %TE was calculated as the maximal %bias + maximal %CV; it was not calculated as part of the validation report; CV-Coefficient of Variation; LLOQ-Lower Limit of Quantification; ULOQ-Upper Limit of Quantification; High Quality Control (HQC) = 750 ng/mL; Medium Quality Control (MQC) = 250 ng/mL; Low Quality Control (LQC) = 62.5 ng/mL

PD assays: bioanalytical methods for determination of Lyso-Gb3 concentrations in human plasma

The Applicant used LC-MS/MS and UPLC-MS/MS methods for determination of plasma Lyso-Gb3 concentrations in pegunigalsidase alfa clinical studies.

- The plasma Lyso-Gb3 concentrations in Studies PB-102-F01/F02, and F03 were analyzed in the [redacted] (b) (4)

[redacted] using the analytical method based on the method described in Boutin 2012, et al. The validation of this assay was performed by [redacted] (Validation Report [redacted] VR003). The validation parameters and assay performance are summarized in Table 42. Of note, the Applicant did not submit in-study validation report for the assay performance in studies PB-102-F01/F02 or study PB-102-F03, which indicates a limitation of the PD data.

- The bioanalytical method for the PD assay for Study PB-102-F30 was validated at [redacted] (Validation report SOP-WCECCMS-002). The validation parameters and assay performance are summarized in Table 43. The in-study analytical report (PB-102-F30-001) from study PB-102-F30 was also submitted.

Table 38. Validation Parameters and Performance of the LC-MS/MS Assay for Determination of Plasma Lyso-Gb3 Concentration in Studies PB-102-F01/F02/F03

Bioanalytical method review summary	The analytical method for Lyso-Gb3 in human plasma was based on literanture reported Method (Boutin 2012, et al). The analytical method validation report: [redacted]_VR003) for palsma Lyso-Gb3 met acceptance criteria in general, with respect to sensitivity, precision, and accuracy, spanning a theoretical concentration range of 0.1 ng/mL to 500 ng/mL. However, specificity, linearity, dilution integrity, and stability were not evaluated. In-study method performance in studies PB-102-F01/F02/F03 was also not conducted.		
Method description	Plasma Lyso-Gb3 was extracted using an organic mixture of solvents containing the internal standard of [redacted] After extraction of the plasma Lyso-Gb3 and the internal standard, which is used for quantitation, the sample is analyzed using an LC-MS/MS mass spectrometer (Waters, Aquity Xevo TQS). Plasma Lyso-Gb3 and the internal standard are separated from salts and interfering compounds using a ACQUITY UPLC BEH C8 Column (reverse phase chromatography) before analysis by mass spectrometry. Mass detection is performed using the instrument run in multiple reaction monitoring mode (MRM). Plasma Lyso-Gb3 is quantified absolutely by utilizing a calibration curve made from externally sourced Lyso-Gb3 standard and [redacted] internal standard. After establishing the plasma concentrations all values are reported as ng/mL [Boutin 2012; Heywood 2019]..		
Materials used for calibration curve & concentration	Pooled plasma from healthy volunteers; [redacted] Lyso-Gb3 (0.1 – 500 ng/mL)		
Validated assay range	Control range: 0.4-1.8 ng/mL; Fabry range: 2.3 – 234.9 ng/mL		
Material used for QCs & concentration	Low Fabry QC → Pooled plasma taken from patients with low levels of plasma lyso-Gb3. (LQC: 11.899 ng/mL) High Fabry QC → Pooled plasma taken from patient		
Minimum required dilutions (MRDs)	not applicable		
Source & lot of reagents (LBA)	Methanol [redacted], Acetone [redacted] Formic Acid [redacted] Trifluoroacetic acid [redacted] sopropanol [redacted] Acetonitrile [redacted]		
Regression model & weighting	Linear regression modelling		
Validation parameters	**Method validation summary**		**Acceptability**
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ (0.50, 5.00, 50.00, 100, 150, 200, 300, 500 ng/mL)	8	Acceptable

	Cumulative accuracy (%bias) from LLOQ to ULOQ	ULOQ -4.21 to -2.49% LLOQ-14.84 to 13.27%	Acceptable
	Cumulative precision (%CV) from LLOQ to ULOQ	ULOQ ≤ 4.8% LLOQ not reported	Acceptable
QCs performance during accuracy & precision	Number of QCs	2	Acceptable
	Inter-run accuracy (%bias)	High 5.24% Low 1.77%%	Acceptable
	Inter-run precision(%CV)	High 8.51% Low 12.72%	Acceptable
Selectivity & matrix effect	Up to 30% matrix suppression observed.		

Table 39 Validation Parameters and Performance of the UPLC-MS/MS Assay for Determination of Plasma Lyso-Gb3 Concentration in Study PB-102-F30

Bioanalytical method review summary	The analytical method for Lyso-Gb3 in human plasma (validation report: SOP-WCECCMS-002) met acceptance criteria in general, with respect to sensitivity, precision, and accuracy, spanning a theoretical concentration range of 0.2 nM to 400 nM. Linearity, dilution integrity, interference, and selectivity were not evaluated. Stability evaluations in matrix and solutions met acceptance criteria in general.		
Method description	A UPLC-MS/MS assay that uses for the quantification of globotriaosylsphingosine (lyso-Gb3) in plasma. Briefly, plasma samples are mixed with the internal standard (IS), then a solid phase extraction (SPE) procedure using Oasis MCX (Mixed-mode Cation eXchange) cartridges is performed. Lyso-Gb3 is analyzed using an ultra-performance liquid chromatography (UPLC) system hyphenated with electrospray-tandem mass spectrometry detection (ESI-MS/MS). Lyso-Gb3 is quantified according to a calibration curve, using the response factor (area of the molecule/area of the internal standard). Plasma lyso-Gb3 concentrations are reported in nmol/L. Detailed information and parameters regarding this assay were previously published UPLC-MS/MS assay that we use for the quantification of globotriaosylsphingosine (lyso-Gb3) in plasma specimens.		
Materials used for calibration curve & concentration	The calibration curve, ranging from 0.2 to 400 nM (0.2, 2, 10, 40, 140, 400), is prepared in 4X depleted charcoal plasma.		
Validated assay range	Concentration range: 0.2-400 nM		
Material used for QCs & concentration	Pooled plasma samples from Fabry patients having low (30 nM) and high (200 nM) concentrations of lyso-Gb3. For accuracy, using charcoal-stripped plasma spiked with a lyso-Gb3 standard to obtain concentrations of 5 nM (n = 2) and 200 nM (n = 2).		
Minimum required dilutions (MRDs)	not applicable		
Source & lot of reagents (LBA)	Not provided		
Regression model & weighting	The 1/x weighing is an automated curve-fitting algorithm, provided as part of the quantification software		
Validation parameters	**Method validation summary**		**Acceptability**
	No of standard calibrators from LLOQ to ULOQ	6	Acceptable

Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) from LLOQ to ULOQ	NA	
	Cumulative precision (%CV) from LLOQ to ULOQ	NA	
QCs performance during accuracy & precision	Number of QCs	2	Acceptable
	Inter-run accuracy (%bias)	0.6% to 2.2%	
	Inter-run precision(%CV)	Not provided	
Bench-top/process stability	• Fabry patient plasma samples were aliquoted and aliquots (n=3) were stored at room temperature (22°C) and in a refrigerator (4°C) for 72 hours. Aliquots were analyzed every 24 hours to assess the stability. Bias was ≤14.6% for plasma Lyso-Gb3 samples at both temperatures (22°C and 4°C) for at least 72 hours. • Prepared samples (N=15; ranging from 9.9 to 233.8 nM) left in the autosampler at 10°C for 24 hours, then in the refrigerator at 4°C for 24 hours, and 48 hours. Bias ≤ 10.0%for plasma Lyso-Gb3 in processed plasma specimens left for 24 h in the UPLC autosampler, then in the refrigerator at 4°C for 48 hours.		Acceptable
Freeze-Thaw stability	Not evaluated		
Long-Term storage	Plasma samples stored for a known period of time, 1.6 year (n=5, ranging from 7.9 to 199.8 nM), 2.0 years (n=5, ranging from 12.4 to 224.8 nM), and 3.2 years (n=5, ranging from 16.5 to 133 nM), in a freezer (-20°C). Bias was ranging from -9.9 to 24.4%, 4.0 to 23.3%, and 4.4 to 25.1%, respectively, for the store duration of 1.6, 2 and 3.2 years.		Acceptable
Method performance in study PB-102-F30 (Analytical study report: PB-102-F30-001)			
Assay passing rate	(including incurred sample reanalysis [ISR]) 100%		Acceptable
Standard curve performance	Cumulative bias range: -11 to 6.2% Cumulative precision: ≤ 4.54% CV		Acceptable
QC performance	2 QCs (LQ and HQ) Cumulative bias range: -12.5 to 17.9% Cumulative precision: ≤ 11.1% CV		Acceptable
Method reproducibility	Incurred sample reanalysis was performed in 10 of 124 study samples and 100% of ISR samples met the prespecified criteria.		Acceptable
Study sample analysis/ stability	None of the samples storage period (<15 months) exceeded the 3 years long term stability period		

15.4. Additional Clinical Outcome Assessment Analyses

None.

BLISS Methodology

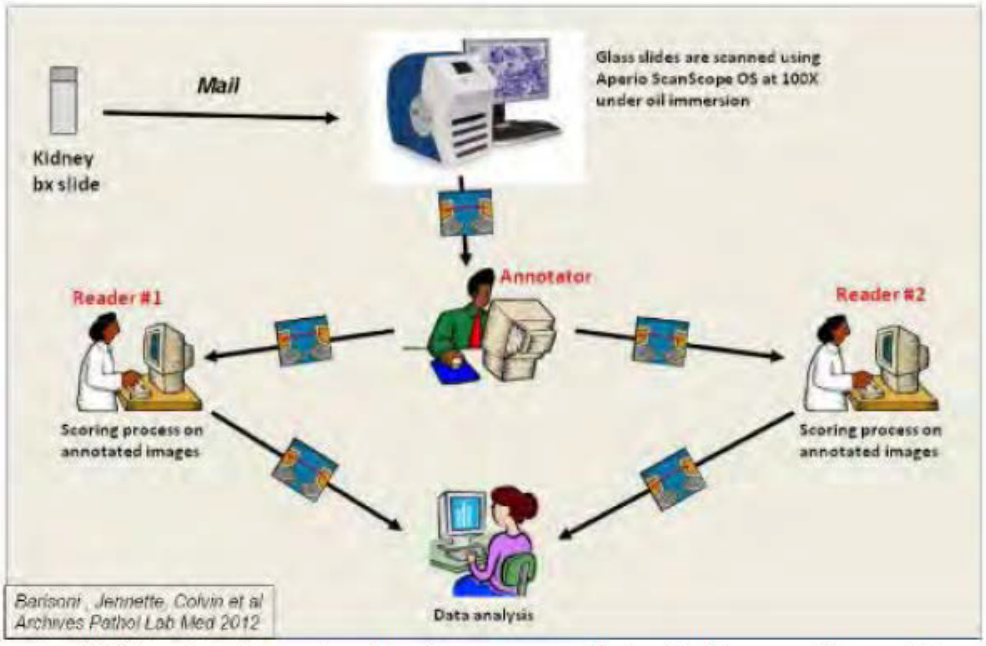
15.5.1 BLISS Scoring Algorithm

The implementation of the BLISS protocol requires three pathologists: one pathologist who serves as the annotator and two pathologists who serve as readers. The annotator and reader roles were assigned to the pathologists on a rotation basis and therefore, each pathologist

served as the annotator for 1/3 of the kidney biopsies and as the reader for the remaining 2/3 of the kidney biopsies. All pathologists are blinded to each other's scores, the treatment assignment and biopsy collection timepoints (i.e. baseline vs. 6-month visit).

The annotator-pathologist identifies approximately 300 capillaries on the Whole Slide Images (WSI) and marks each with an arrow. Once the annotation is complete, two identical copies of the WSI are distributed to the reader-pathologists (Figure 26), and each pathologist will independently count the number of Gb3 inclusions at each capillary (these are the capillary-level scores). Regarding the selection of the capillaries and differential tissue sampling, the applicant states:
"Criteria for the selection of capillaries for digital annotation were established so that the size of the peritubular capillaries was consistent across all specimens as previously described. The selection of the 300 capillaries was random across all blocks processed for each biopsy. This protocol was created to assure a broad and standardized representation of peritubular capillaries across all areas of the cortical renal tissue available (Barisoni 2012). This process served to minimize any possible variation in results due to differential tissue sampling."
Applicant's Late-Cycle Meeting Discussion Supplement, page 6

Figure 24: Flowchart of the BLISS Scoring Procedure



Glass slides are mailed to an imaging center where they are scanned into virtual images. The annotator pathologist annotates PTC on WSI. Annotated WSI are triplicated and distributed to two reader-pathologists for scoring and one copy was maintained in the database at the image coordinating center. Abbreviation: bx, biopsy.

Source: Figure 1, Applicant's Histology Report, Page 9

15.5.2 Adjudication Process

To improve the reliability of the scoring system and reconcile large disagreements between the readers, the following adjudication process was pre-specified. As stated in the Applicant's Histology Report, the adjudication process was to be implemented in the following two scenarios:

- For capillary-level scores ≤ 10 (by both readers): if there is a difference > 5 units between the two readers' scores
- For capillary-level scores >10 (by one or both of the readers): if there's ≥50% difference between the two readers' scores

Once the capillaries that meet the above adjudication rules are identified, the data-management center will provide the adjudicator pathologist (original annotator) with a list of the capillaries that need to be re-scored. The adjudicator, who is blinded to the scores from the two original readers, will then count the number of Gb3 inclusions at each of the capillaries in question. Once adjudication is complete, the two closest (of the three scores) will be assigned as the capillary-level scores. In case the differences between the scores were equal (e.g., 0, 5, 10), the middle score will be taken as the final capillary-level score.

15.5.3 Derivation of the Renal Gb3 BLISS Score (Average Number of Gb3 Inclusions per Kidney PTC)

The biopsy-level score was determined as the average number of Gb-3 inclusions per kidney PTC (i.e. total number of Gb3 inclusions summed across all annotated-capillaries divided by the number of capillaries scored). The final score used for primary efficacy assessment is obtained by averaging the biopsy-level score from each reader-pathologist (i.e. [Reader 1 Biopsy-level Score + Reader 2 Biopsy-level Score]/2).

We examined sensitivity of the primary efficacy analysis to the Applicant's scoring strategy whenever adjudication was done. In addition to the Applicant's scoring strategy of picking two closest (of three scores), the review team implemented the following scoring strategies:

1. Capillary-level scores determined as the average score of the three readers
2. Capillary-level scores determined as the median score of the three readers

For each of the scoring strategies shown in (1) and (2) above, the biopsy-level score is determined as the average number of inclusions per PTC defined as the total sum of capillary-level scores divided by the total number of capillaries. Results of this sensitivity analysis are described in section 15.5.6 (Figure 29).

15.5.4 Reliability of the BLISS Approach for Renal Gb3 BLISS Score (Average Number of Gb3 Inclusions per Kidney PTC)

The Applicant examined agreement between readers in the overall trial population using a Bland-Altman plot. In addition, to minimize variability due to female tissue mosaicism, we examined the inter-reader variability in the population of male patients (Figure 27).

15.5.5 BLISS Assay Variability: FDA's Assessment of Inter-reader agreement, intra-reader agreement and sampling variability

The mean inter-reader difference was 0.0002 (95% CI: -0.35, 0.35) for the overall population and 0.06 (95% CI: -0.45, .57) for male patients indicating a high level of agreement between readers (Figure 27). The mean inter-reader differences were much smaller than the mean observed reductions at six months (-3.1 units for the overall population and -4.7 units for male patients), suggesting that the observed reductions were unlikely to be due to inter-reader variability.

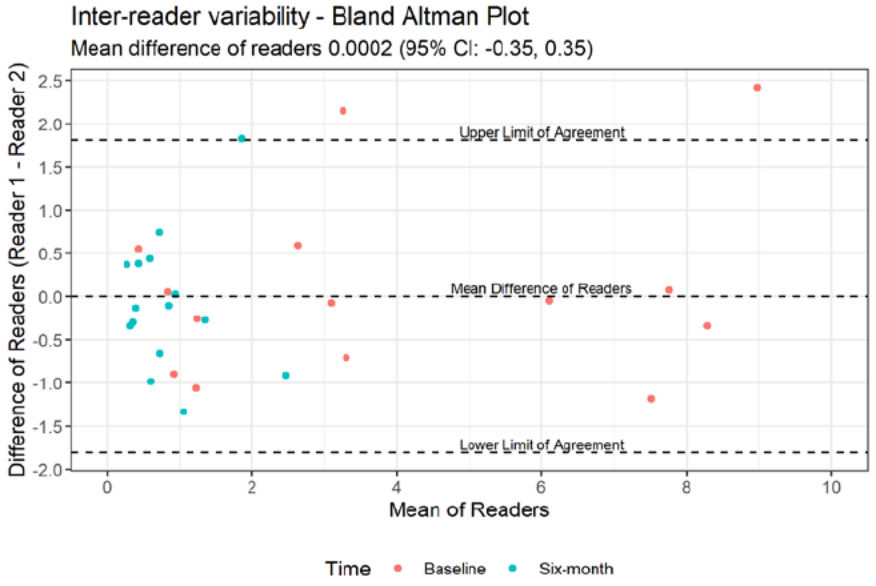
The review team notes that intra-reader variability of the BLISS procedure could not be assessed in this study. However, since the pathologists who implemented the BLISS methodology in this study of PRX-102 also implemented it in the Galafold trial in the same manner, it is reasonable to borrow information on intra-reader variability from the Galafold trial (Barisoni et al. 2012) . According to Barisoni et al. (2012), the mean intra-reader difference is 0.07 (95% CI: -0.34 to 0.49). This intra-reader variability is much lower than the mean reduction in Gb3 inclusions at six months (-3.1 with 95%CI: -4.8, -1.4) and suggests that the observed reduction is not a result of intra-rater variability.

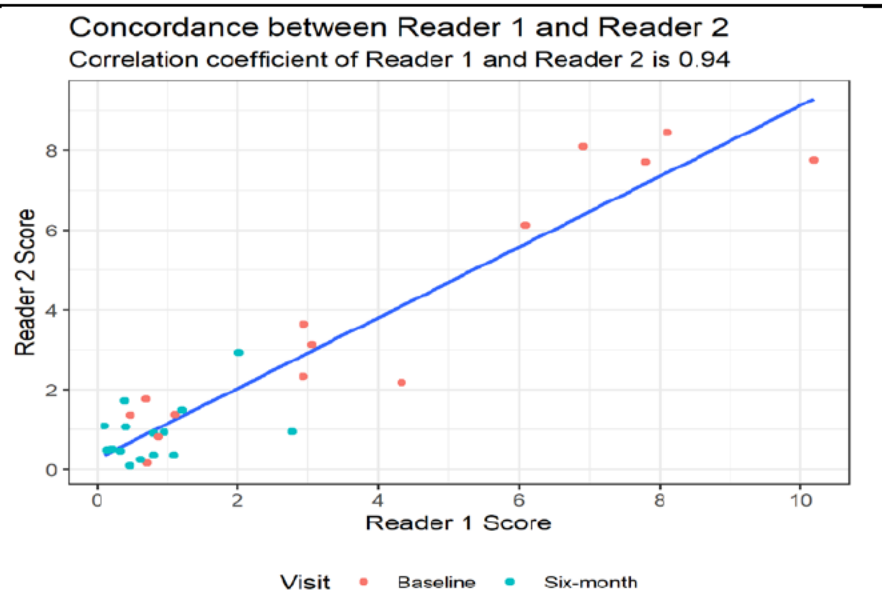
The bootstrap analysis showed that 11 out of 14 (79%) subjects showed significant reductions that were more than what would have been expected due to sampling variability (Figure 28). Of the remaining three patients, one subject had a minimal (from 0.4 at baseline to 0.9 at six-months) yet nominally statistically significant increase, while the other two patients had small changes that were within the range of what would have been expected due to sampling variability.

Overall, given the small inter-reader and intra-reader variability, and the small sampling variability of the BLISS methodology, the reductions observed in this study are not likely to be attributed to variability in the BLISS methodology.

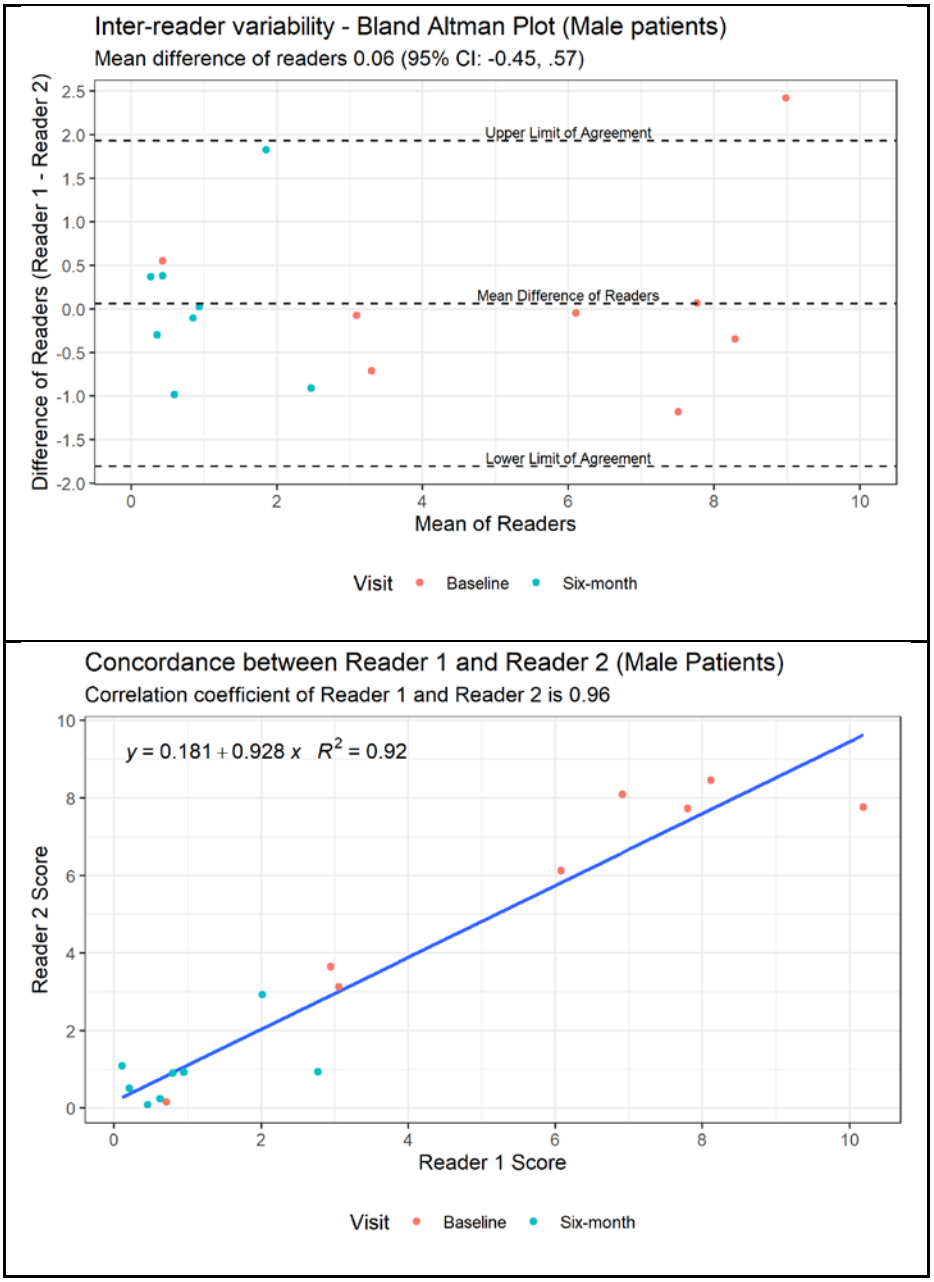
Figure 25: Inter-reader Variability (Study PB-102-F01/F02)

All patients



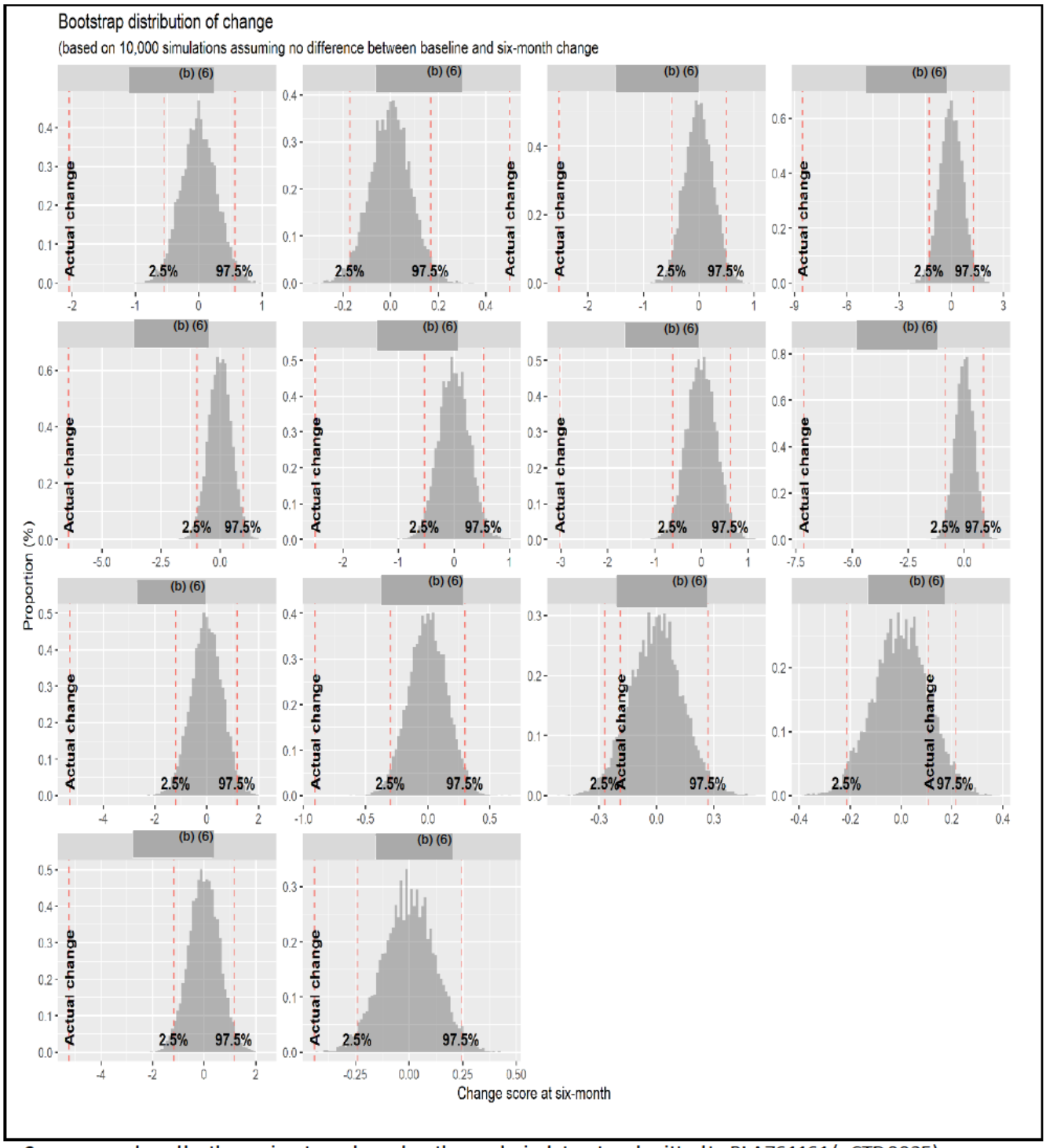


Male Patients



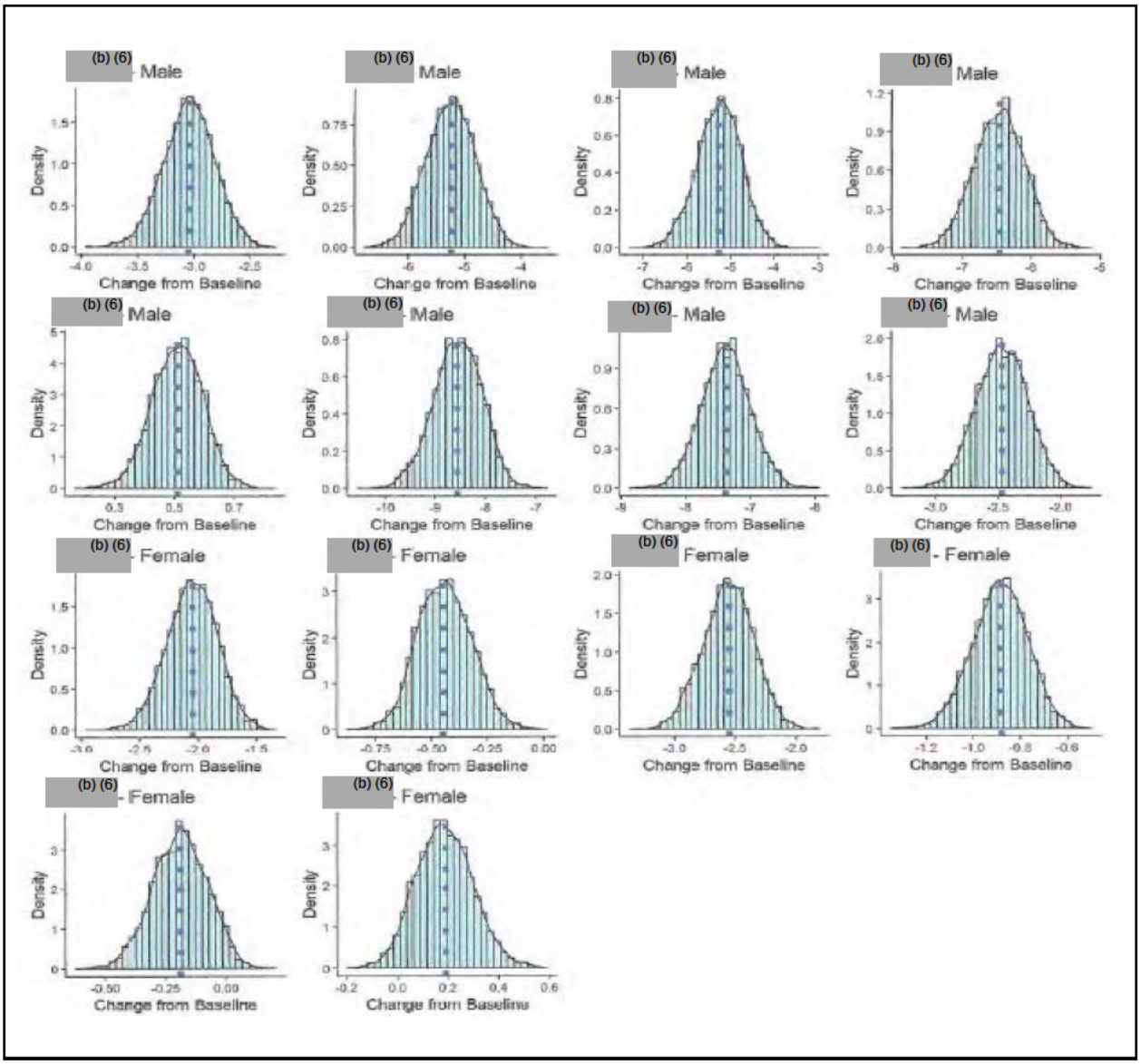
Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD0025) on November 11, 2020

Figure 26: Bootstrap Analysis: Scaled Histogram of Six-month Change in BLISS Score Assuming the Distribution of Six-month Gb3 Score is Identical to the Distribution of Baseline Gb3 Score



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD0025) on November 11, 2020

Figure 29: Bootstrap Analysis: estimated density fuction of the difference in average BLISS score between baseline and 6 months



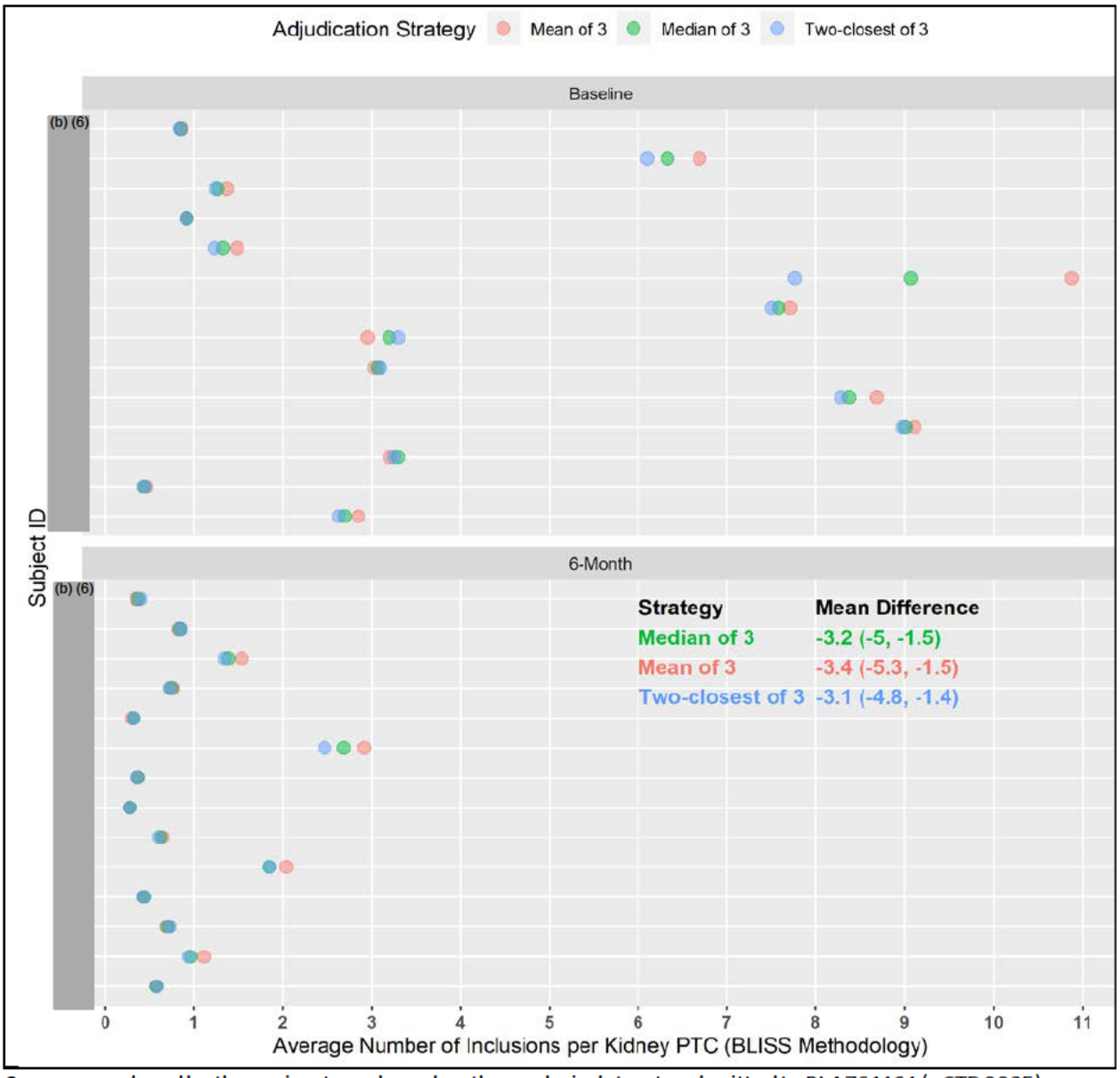
Source: Figure 2 of Applicant's histology report

All but three patients (b) (6) had a significant reduction in Gb3 inclusions.

15.5.6 BLISS Protocol: FDA Assessment of Applicant's Adjudication Procedure

Overall, 13% of the capillary-level scores needed adjudication. When the mean of the scores from each of the three pathologists was used to derive the capillary-level score, the mean reduction in BLISS scores was -3.4 (95% CI: -5.3, -1.5). When the median of the scores from each of the three pathologists was used to derive the capillary-level score, the mean reduction in BLISS scores was -3.2 (95% CI: -5.0, -1.5). Both of these results were similar to the primary efficacy result which was based on the Applicant's adjudication strategy of taking the two-closest of the three scores (Figure 29).

Figure 27: Comparison of Strategies for BLISS Score Determination in the Presence of Adjudication



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD0025) on November 11, 2020

15.6. Modified Fabrazyme Scoring System (mFSS)

The following text is extracted from the Applicant's Histology Report:

FSS is semi-quantitative scoring system first introduced by the Fabrazyme® clinical trial, and initially applied using conventional light microscopy. In the FSS scoring method each capillary received a score based on inclusions/granules/aggregates ranging from 0 (no inclusions) to 3 (bulging aggregates). FSS semi-quantitative score is based on the presence, size, and distribution of Gb_3 granules in endothelial cells of PTC: 0 = ≤ 2granules; 1 = ≥ 3 granules; 2 = ≥1 non-bulging aggregate; 3 = ≥1 bulging aggregate (Thurberg, et al., 2002).

For PB-102-F01/F02 studies, the FSS method was modified as followed: a) the FSS was applied to the annotated PTCs from the WSI, b) an overall biopsy score was based on the majority of capillaries with a given score was not implimented and c) the biopsy FSS score was reported as the average number of capillaries scored 0, 0.5, 1, 2, or 3, with 0 representing no deposition and 3 representing severe deposition.

Source: Applicant's Histology Report, pages 9-10

15.7. Absence of Spontaneous Reduction in Kidney Gb3

The Applicant has argued that concerns regarding the single arm design of study PB-102-F01/F02 are mitigated by the lack of evidence for spontaneous decrease of Gb3 concentrations in the kidney. The following text is extracted from the Applicant's Summary of Clinical Efficacy Document:

By design, a placebo arm was not included in the PB-102-F01/F02 study, since reduction of Gb_3 in kidney biopsies is considered an objective measurement of treatment effect (see PB-102-F01/F02 Histology Report). As reported in published placebo-controlled studies with Fabrazyme [Eng 2001; Thurberg 2002] and Galafold [Germain 2016] spontaneous reductions in this biomarker have not been observed in Fabry disease patients, and no improvement in renal Gb_3 clearance was observed in the placebo arm. Given the nature of the disease and considering the objectivity of kidney Gb_3 accumulation assessment, a spontaneous reduction is not expected.

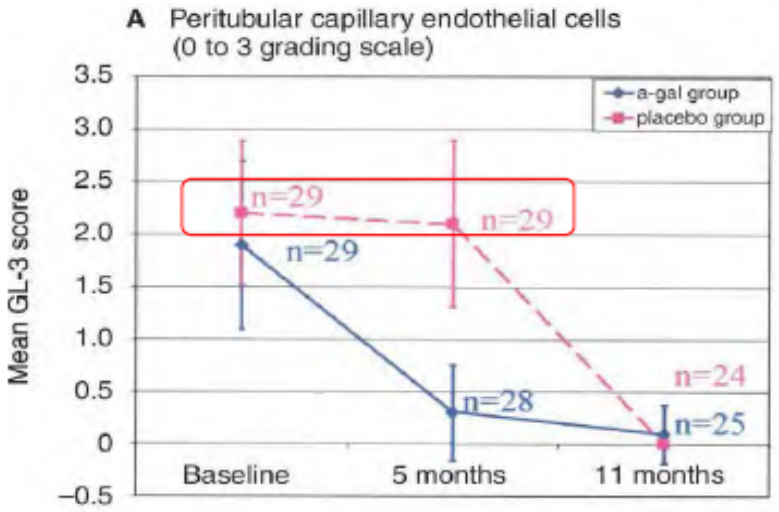
Source: Summary of Clinical Efficacy Document, Page 13

The following text is extracted from from the Applicant's Histology Report:

6.3. Comparison of Pegunigalsidase Alfa to Relevant Published Data with Treated and Untreated Fabry Disease Patients

In the Phase 3 program for Fabrazyme® (agalsidase beta), kidney PTC in biopsies from previously untreated patients were assessed for Gb_3 inclusion bodies at baseline and after 5 months of treatment with either agalsidase beta or placebo, using a semi-quantitative scoring methodology (Eng, et al., 2001; Thurberg, et al., 2002).

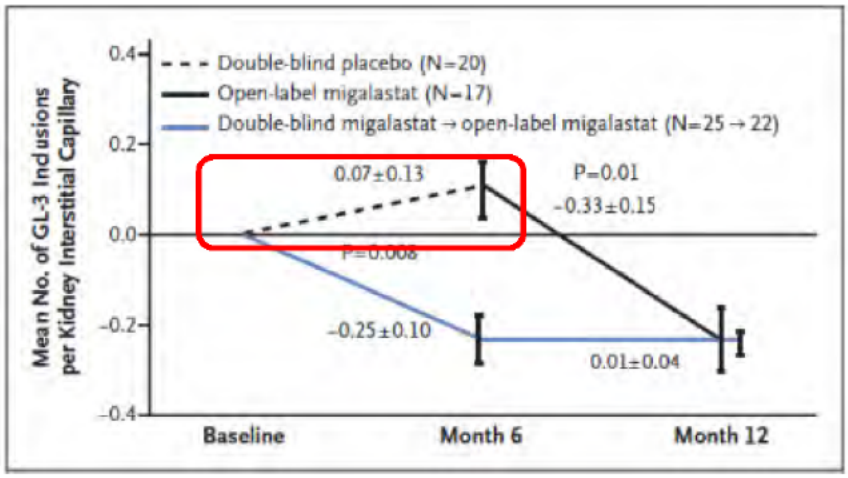
Figure 15: Kidney Biopsy Data from the Published Phase 3 Development Program for Fabrazyme® (Thurberg et al., 2002)



The results from the placebo arm, kidney biopsies demonstrated no spontaneous improvement in the 5 months study period (Figure 15). After 5 months of placebo treatment, all patients were switched to receive agalsidase beta and evaluated at 11 months. The results show that patients treated for 6 months with agalsidase beta after 5 months of placebo treatment phase, resulted with a reduction in Gb_3 inclusions, further supporting that Gb_3 reduction accrued only following ERT. Regardless of the scoring methodology, these results evidently show that there is no spontaneous reduction in Gb_3 burden following placebo treatment.

The Phase 3 Galafold™ (migalastat) study (AT-1001-11), in which the BLISS quantitative scoring system was used to evaluate Gb_3 in kidney PCTs (Figure 16), further demonstrated that placebo patients experienced no reduction in kidney Gb_3 after 6 months. Similar to the agalsidase beta results described above, after switching to active treatment (Galafold™) placebo patients had a decline in mean number of Gb_3 inclusions per kidney PTC at 6 months from starting active treatment (Germain, et al., 2016).

Figure 16: Change from Baseline of Gb_3 Inclusions in Kidney PTC in Patients with Mutations That Were Suitable for Migalastat Therapy (Germain et al., 2016)



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Both studies demonstrated that there is no spontaneous improvement of Gb_3 kidney burden in untreated (placebo arm) Fabry patients as assessed by various scoring systems. The patients in the placebo arm of Fabrazyme® and Galafold™ were followed for duration of 5 and 6 months, respectively, a similar period as pegunigalsidase alfa treatment duration in the PB-102-F01/F02 study. This finding was further supported by Fabry disease physician input; therefore, the Sponsor considers that a placebo control arm is not necessary to interpret the results observed for the PB-102-F01/02 study.

Source: Applicant's Histology Report, Page 29-33

From a statistical perspective, the Applicant's rationale for lack of evidence of spontaneous reduction in kidney Gb3 appears reasonable.

15.8. Supplementary Tables, Listings and Figures

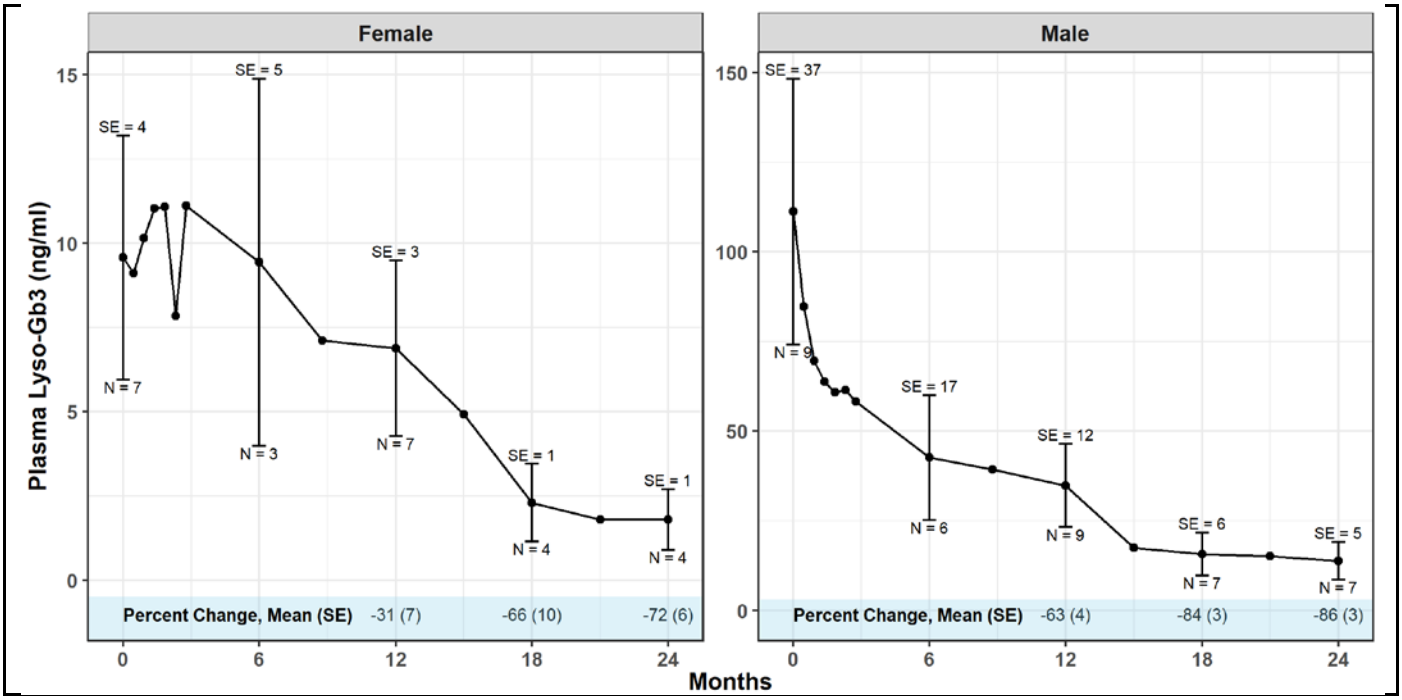
Table 40: Individual Renal Gb3 BLISS Score and Plasma Lyso-Gb3 Levels in Study PB102-F01/F02

Subject ID	Treatment (mg/kg)	Sex	Renal Gb3 BLISS Score			Plasma Lyso-Gb3 (ng/mL)				
			Baseline	Month 6	% Change at Month 6	Baseline	Month 6	Month 12	% Change at Month 6	% Change at Month 12
(b) (6)	0.2	F	2.6	0.6	-77.8	19.2	NA	17.7	NA	-7.8
	1	M	0.4	0.9	114.9	5.1	2.9	2.8	-43.1	-45.1

(b) (6)										
	1	F	3.3	0.7	-77.6	14.4	NA	7.1	NA	-50.7
	1	M	9.0	0.4	-95.2	193.4	NA	46.7	NA	-75.9
	1	M	8.3	1.9	-77.6	123.0	24.5	35.6	-80.1	-71.0
	2	M	3.1	0.6	-80.7	61.8	NA	30.8	NA	-50.2
	0.2	M	3.3	0.3	-91.7	66.5	6.7	25.2	-89.9	-62.1
	1	M	7.5	0.4	-95.2	80.8	34.7	17.2	-57.1	-78.7
	1	F	NA	1.1	NA	6.8	5.5	4.2	-19.1	-38.2
	0.2	M	7.8	2.5	-68.2	112.5	NA	40.0	NA	-64.5
	2	F	1.2	0.3	-74.0	3.4	NA	2.6	NA	-23.5
	2	F	0.9	0.7	-20.7	5.0	NA	2.2	NA	-55.6
	0.2	M	NA	NA	NA	272.9	142.3	69.5	-47.9	-74.5
	2	F	1.2	1.4	8.8	10.8	6.6	7.3	-38.9	-32.4
	0.2	M	6.1	0.8	-86.1	84.7	44.5	45.7	-47.5	-46.0
	0.2	F	0.8	0.4	-52.9	7.5	16.2	7.1	116.0	-5.3

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD0025) on November 11, 2020

Figure 28: Average Absolute and Percent Change in Plasma Lyso-Gb3 by Sex in Study PB102-F01/F02/F03



Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD0025) on November 11, 2020

Figure 29: Individual Level Distribution of the mFSS Score, Majority-rule Based mFSS Score, Weighted mFSS Score and BLISS Score

mFSS: modified Fabrazyme Scoring System; **Majority:** Majority rule mFSS score; **Weighted:** weighted mFSS score; The biopsy score for each scoring system is represented using the notation x → y, where x represents the baseline score, and y represents the six-month score.

Source: produced by the review team based on the analysis datasets submitted to BLA761161 (eCTD0001) on May 27, 2020

The above figure shows each patient's Gb3 burden using the semi-squantitative mFSS and quantitative BLISS methodology. In the mFSS, each capillary receives a severity score of 0, 0.5, 1, 2, or 3 and, the proportion of capillaries receiving the given score is calculated. The biopsy-level **weighted mFSS** score is derived by computing the weighted average of the capillary-specific scores. For example, if 30% of capillaries have a score of 3, 49% a score of 2, 20% a score of 1, 10% a score 0.5, and 11% a score of 0, the **weighted mFSS** score will be 2.13 (= 0.3*3 + 0.49*2 + 0.2*1 + 0.1*0.5 + 0.11*0). The biopsy-level **majority-rule mFSS** score corresponds to the score received by the majority of the capillaries. In the above example, the **biopsy-level majority-rule mFSS** score will be 2 since a majority of the capillaries received a score of 2. Compared to the BLISS methodology, the semi-quantitative mFSS is less sensitive to small changes in the number of Gb3 inclusions. For example, the individual shown in the top right panel has a majority-rule score of 0 both at baseline and at six-month, however, the BLISS score for this individual are 0.8 and 0.4 at baseline and six-month, respectively.

15.9. Evaluation and Treatment Algorithm to monitor and manage hypersensitivity reactions

During and after infusion of PRX-102, the following algorithm will be followed to monitor and manage the occurrence of hypersensitivity, anaphylaxis, or anaphylactoid reactions.

Clinical signs

Early

- Sensation of warmth and itching
- Feelings of anxiety

Moderate

- Pruritus
- Flushing
- Urticaria
- Chest discomfort
- Mild Hypotension

Progressive

- Erythematous or massive urticarial rash
- Edema of face, neck, soft tissues

Severe

- Hypotension
- Bronchospasm (wheezing)
- Laryngeal edema (dyspnea, stridor, aphonia, drooling)
- Arrhythmias

Treatment algorithm:

With the onset of any of the above clinical signs, immediately discontinue study medication administration and initiate the following monitoring.

- Continuous electrocardiographic monitoring
- Continuous pulse oximetry
- Measure blood pressure every 5 minutes
- Perform chest auscultation every 5 minutes
- Collect blood samples for Tryptase (29-33), antibodies and C3, C4. Tryptase samples need to be withdrawn at:
    - 1st sample taken 0.25-3 hours after onset of symptoms
    - 2nd sample taken between 3-6 hours
    - 3rd sample taken 24-48 hours to verify the return to baseline.

In the case of progressive or severe hypersensitivity, treat appropriately.

Treat as follows:

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

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

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

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

Bronchospasm

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

Laryngeal edema

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

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATROULA I SMPOKOU
04/27/2021 07:41:58 PM

HYLTON V JOFFE
04/27/2021 07:46:14 PM
I concur with the Complete Response action.