PROTALIX Biotherapeutics

PROTALIX BIOTHERAPEUTICS

CORPORATE PRESENTATION

December 2022

Note Regarding Forward-Looking Statements

This presentation (the "Presentation") contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements are subject to many risks and uncertainties that could cause our actual results to differ materially from any future results expressed or implied by the forward-looking statements as a result of several factors. Examples of the risks and uncertainties include, but are not limited to, the following: that the U.S. Food and Drug Administration (FDA) might not grant marketing approval for PRX-102 by the PDUFA date or at all and, if approved, whether PRX-102 will have significant limitations on its use; risks related to the timing, progress and likelihood of final approval by the FDA and European Medicines Agency (EMA) of the resubmitted Biologics License Application and of a Marketing Authorization Application, respectively; risks related to the commercial success of PRX-102, and of our other product and product candidates, if approved; likelihood that the FDA, EMA or other applicable health regulatory authorities will approve an alternative dosing regimen; failure or delay in the commencement or completion of our preclinical studies and clinical trials which may be caused by several factors, including: slower than expected rates of patient recruitment; unforeseen safety issues; determination of dosing issues; lack of effectiveness during clinical trials; inability to satisfactorily demonstrate non-inferiority to approved therapies; inability or unwillingness of medical investigators and institutional review boards to follow our clinical protocols; and inability to monitor patients adequately during or after treatment; delays in our preparation and filing of, or in the approval or potential rejection of, any applications we file with the FDA, EMA or other health regulatory authorities for our other product candidates, and other risks relating to the review process; risks associated with the novel coronavirus disease, or COVID-19, outbreak, which may adversely impact our business, preclinical studies and clinical trials; risks related to any transactions we may effect in the public or private equity markets to raise capital to finance future research and development activities, general and administrative expenses and working capital; the risk that the results of the clinical trials of our product candidates will not support the applicable claims of safety or efficacy, or that our product candidates will not have the desired effects or will be associated with undesirable side effects or other unexpected characteristics; risks related to reforms in the healthcare industry and the risk that uncertainty associated with pharmaceutical pricing, reimbursement and related matters could adversely affect the marketing, pricing and demand for our products, if approved; risks related to our ability to maintain and manage our relationship with our collaborators, distributors or partners; risks related to the amount and sufficiency of our cash and cash equivalents and short-term bank deposits; risks relating to our ability to make scheduled payments of the principal of, to pay interest on or to refinance our outstanding notes or any other indebtedness; our dependence on performance by third party providers of services and supplies, including without limitation, clinical trial services; the inherent risks and uncertainties in developing drug platforms and products of the type we are developing; the impact of development of competing therapies and/or technologies by other companies and institutions; potential product liability risks, and risks of securing adequate levels of product liability and other necessary insurance coverage; and other factors described in the Company's filings with the U.S. Securities and Exchange Commission. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of today's date. The Company undertakes no obligation to update or revise the information contained in this Presentation whether as a result of new information, future events or circumstances or otherwise.

Investment Highlights

Plant cell expressed recombinant proteins with improved therapeutic profiles

Revenue Generating, FDA-Approved Drug

FDA approved, commercially marketed drug for Gaucher disease. Elelyso® (alfataliglicerase in Latin America).

Clinically-Validated Platform

Proprietary ProCellEx® platform for recombinant protein expression cGMP manufacturing facility successfully inspected and audited by multiple regulatory agencies, including the FDA & EMA.

Fabry Disease Product Candidate

Completed three phase III studies of PRX-102 for the treatment of Fabry Disease. Submitted a Marketing Authorization Application to the European Medicines Agency (EMA) in February 2022. Resubmitted a BLA to the U.S. FDA in November 2022. PDUFA date is May 9, 2022.

Pipeline

Uricase (PRX-115) for the treatment of severe gout,
LA DNase I (PRX-119) for the treatment of NETs-related diseases, as well as other product candidates, in discovery and preclinical phases.

Partnerships

Chiesi Farmaceutici S.p.A.
Pfizer Inc.
Fundação Oswaldo Cruz (Fiocruz)

Solid Balance Sheet

Successfully completed a Note Exchange in late 2021, which effectively extended the maturity of the 2021 Sr. Sec. Convertible Notes until 2024 and lowered the aggregate principal amount by approximately half.

PROTALIX Biotherapeutics

Note: cGMP = Current Good Manufacturing Practice.

KOL Event
December 2022

Pegunigalsidase alfa (PRX-102) for Fabry Disease

Myrl D. Holida, PA-C
University of Iowa Health Care, Iowa City, Iowa

Disclaimer

Myrl Holida has been or is currently involved in clinical trials with Sanofi-Genzyme, Sangamo, AVROBIO, Amicus Therapeutics, Takeda, Protalix Biotherapeutics, Chiesi and Idorsia. No direct funding is received for these trials as they are institution directed. He has also been a consultant for Sanofi and Chiesi.

MYRL D. HOLIDA, PA-C

University of Iowa Health Care

Iowa City, Iowa

Myrl D. Holida is a Physician Assistant with 35 years of experience in patient care, initially treating Pediatric Bone Marrow Transplant (BMT) patients with end stage malignancies and Lysosomal Storage Disorder patients in a clinical trial setting. Myrl's experience includes many levels of research from the cardiovascular animal lab to Clinical Trial Investigator for Lysosomal Storage Disorders.

He was involved in the original enzyme replacement trials for Fabry disease in the late 90s and early 2000s and was a principal investigator for coadministration of agalsidase beta and migalastat oral chaperone therapy, and for agalsidase alfa and velaglucerase "rescue therapy" during the enzyme shortages starting in 2009.

Myrl brought Protalix's initial phase I PRX-102 trials to his institution, and recruited almost half of the United States agalsidase beta patients to Protalix's phase III BRIGHT switch-over clinical trial, which assessed every 4 week dosing. His institution is a major Fabry treatment center, recently recognized as a National Organization for Rare Disorders (NORD) Center of Excellence, in part due to his efforts over the years.

He has treated patients with Adrenoleukodystrophy, Metachromatic Leukodystrophy, MPS I, MPS II, MPS III, MPS IV, MPS VI, Gaucher disease, Lysosomal Acid Lipase Deficiency (LALD), Pompe disease, and multiple hematological disorders. Myrl is also actively involved in a Fabry gene therapy trial and manages three generations of Fabry patients.

Fabry Disease, a Multisystemic Disease

Fabry Disease

Fabry disease (FD) is a progressive, X-linked inherited disorder of glycosphingolipid metabolism due to deficient or absent lysosomal a-galactosidase-A activity and intracellular accumulation of glycosphingolipids (especially globotriaosylceramide (Gb_3) and globotriaosylsphingosine (lyso-Gb_3)). Leading to a multisystemic disease with progressive renal failure, cardiomyopathy with potentially malignant cardiac arrhythmias and strokes, which considerably limits the life expectancy of affected patients[1,2].

Current commercially available enzyme replacement therapies (ERT) [3,4] for FD are agalsidase alfa (Replagal®)[5[*]]and agalsidase beta (Fabrazyme®)[6] available in various countries. The dosing is 0.2 mg/kg and 1.0 mg/kg, respectively.

ERTs are associated with complications related to anti-drug antibodies (ADAs) and infusion-related reactions (IRRs) which can lead to safety concerns and reduced efficacy[7].

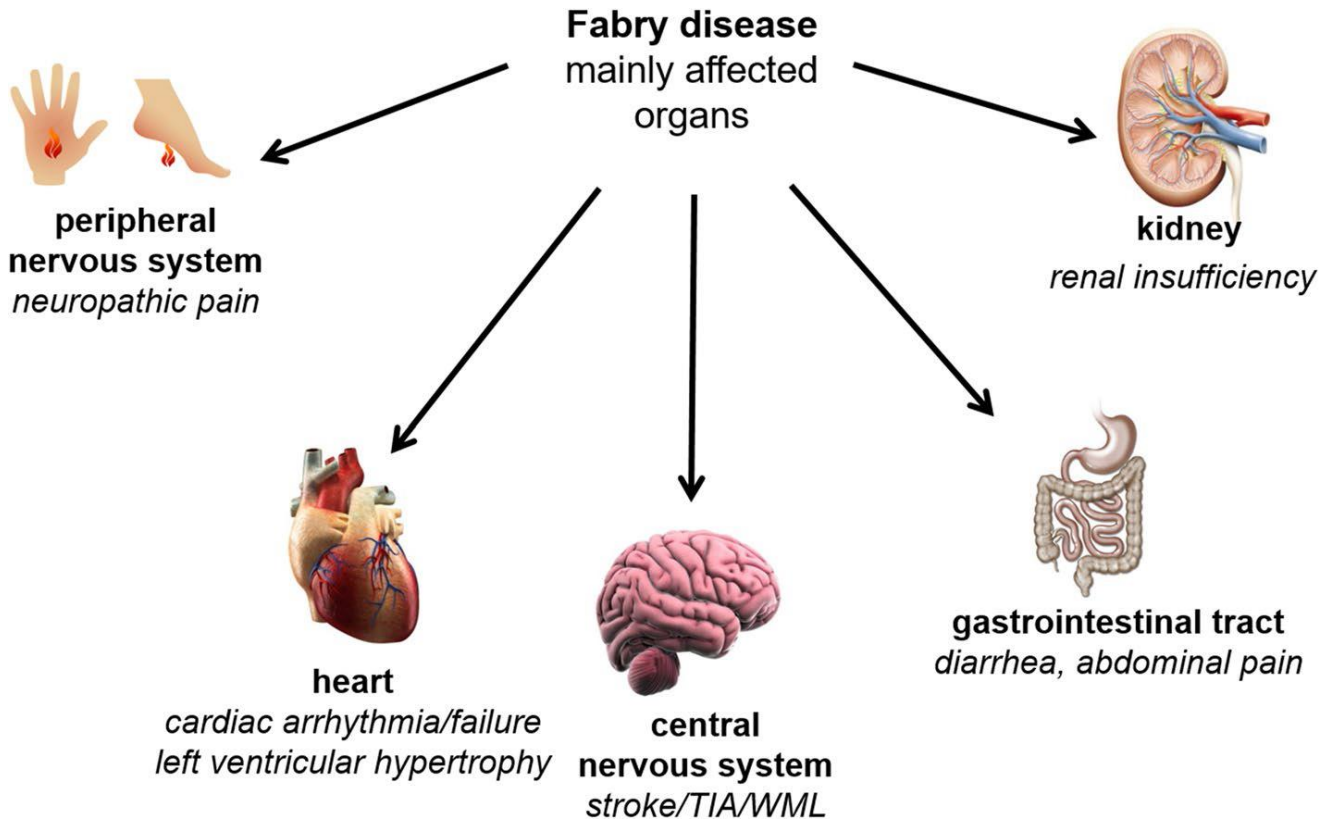


Figure from "Fabry Disease: The Current Treatment Landscape," Lenders M., Brand E. *Drugs*. 2021. 81:635–645 [http://creativecommons.org/licenses/by-nc/4.0]

TIA = transient ischemic attack; *WML* = white matter lesion

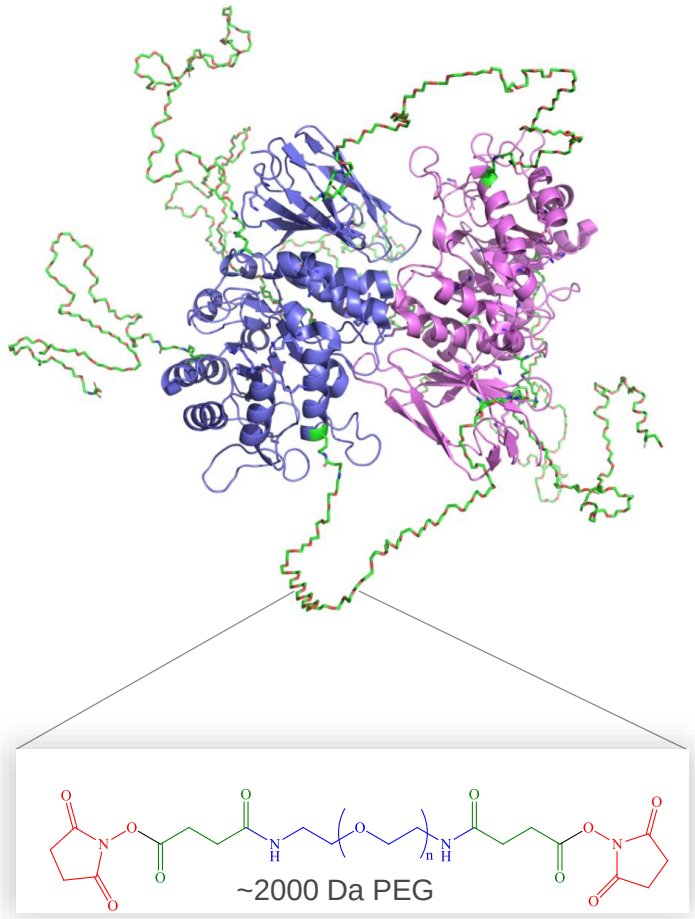
[*] Replagal is not approved in the United States.

References:

1. Lenders M., Brand E. *Drugs*. 2021. 81:635–645
2. Schiffmann R et al. *Nephrol Dial Transplant.* 2009;24: 2102–2111.
3. Muntean C et al. *Front Pediatr.* 2022; 10: 908657
4. Lenders M and Brand E. *Gut Microbes.* 2022;14:2027852.
5. REPLAGAL® (agalsidase alfa for injection). Takeda Canada Inc.
6. Fabrazyme® (agalsidase beta injection powder). Genzyme Corporation.
7. Lenders M., Brand E. *J Am Soc Nephrol . 2018.* 29: 2265–2278

Pegunigalsidase Alfa

Chemically modified, plant cell derived, PEGylated, covalently linked homodimer



Pegunigalsidase Alfa

- ✓ Pegunigalsidase alfa is a PEGylated enzyme designed to potentially have lower immunogenicity and an improved safety profile
- ✓ Covalent linked via short 2000 Da PEG having two reactive ends results in a more stabilized enzyme and extended circulatory and tissue half-life
- ✓ Continuous coverage/presence of enzyme over infusion intervals without compromising the enzyme activity and internalization to target organ and cells
- ✓ Providing potentially increased enzyme exposure and enhanced activity to target organs and sustain hydrolysis to prevent accumulation and re-accumulation of substrate
- ✓ PEGylation potentially reduces immunogenicity by masking immunogenic epitopes, which, together with the continued presence, has the potential to induce immune tolerance
- ✓ PEGylation potentially reduces the cross reactivity and reduces serum mediated enzyme inhibition of already existing ADAs (in patients previously treated with other ERT)
- ✓ Development of two alternative dose and regimens with potential for once every 4 weeks dosing

ADAs, Anti Drug Antibodies; Da, Dalton; ERT, Enzyme Replacement Therapy; PEG, Polyethylene glycol.

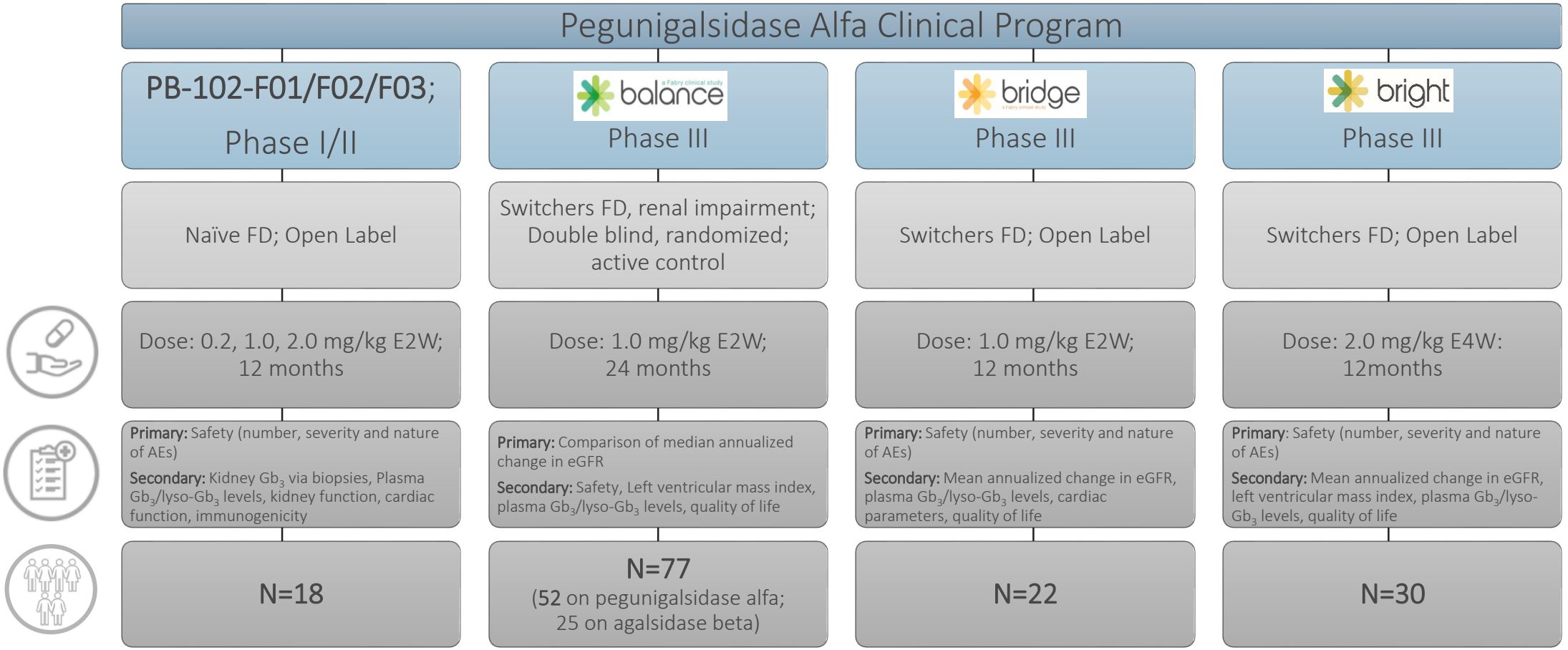
References:

1. Kizhner T. et al. (*Molecular Genetics and Metabolism.* 2005 114, 259–267
2. Ruderfer I., et al. *Bioconjugate Chem.* 2018. 29, 5, 1630–1639
3. Schiffmann R., et al. *J Inherit Metab Dis.* 2019. 42:534–544

Pegunigalsidase Alfa: Robust Clinical Development Program

Overall, >140 patients received at least 1 infusion of pegunigalsidase alfa in the clinical program

Hundreds of patient-years exposure to the treatment (~300 patient-years at 1 mg/kg E2W; ~100 patient-years at 2 mg/kg E4W)



All patients enrolled in studies have the opportunity to enter open label, extension studies investigating the long-term safety and efficacy of **pegunigalsidase alfa** (including additional **24** patients from the agalsidase beta arm of the BALANCE study)

FD, Fabry Disease; E2W, every 2 weeks; E4W, every 4 weeks.

Robust Clinical Development Program Supports Regulatory Submissions in Various Regions

Worldwide, multicenter, program

Collaboration with TOP Fabry disease KOLs and patient groups

Year of Completion:

2018	2020	2021	2022	2022
Phase I/II	**Phase III**	**Phase III**	**Phase III**	**Regulatory Submissions**
n=18	n=22	n=30	n=77	

Anticipated Approvals 1H 2023

EU EMA MAA Submission ✓ **currently under review**

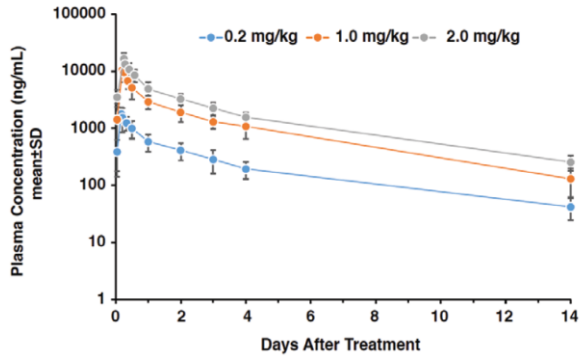
U.S. FDA BLA Resubmission ✓ **PDUFA - May 9, 2023**

Phase I/II study with ERT Naïve Fabry disease patients

Up to 6 years of pegunigalsidase alfa treatment; include treatment under long-term extension study

Pharmacokinetics

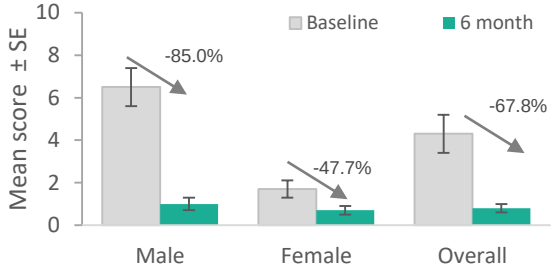
Pharmacokinetics Profiles



- Active enzyme throughout the 2-week infusion interval
- Enhanced pharmacokinetics parameters
- Half-life of ~80 hours

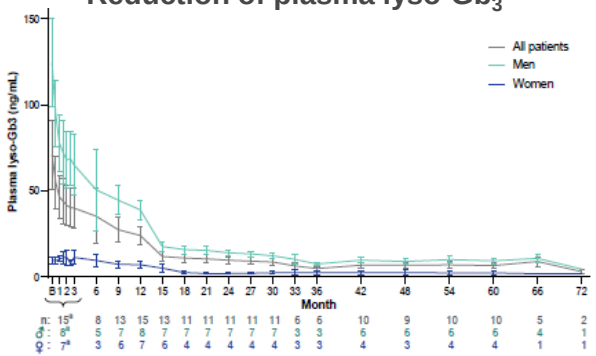
Pharmacodynamics

Reduction of Gb_3 in the kidney



Treatment with pegunigalsidase alfa led to reduction of Gb_3 inclusions in the kidney (based on kidney biopsy) in both male and female patients.

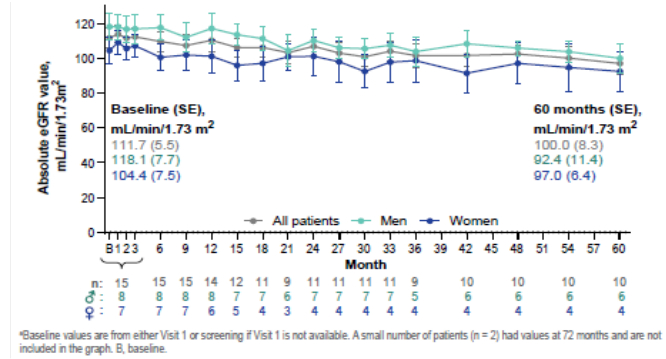
Reduction of plasma lyso-Gb_3



Lyso-Gb_3 concentrations in the plasma, in both male and female patients, were reduced and remained low following >60 months of treatment with pegunigalsidase alfa

Clinical Activity Data

Mean (±SE) Absolute eGFR Values Over Time



*Baseline values are from either Visit 1 or screening if Visit 1 is not available. A small number of patients (n = 2) had values at 72 months and are not included in the graph. B, baseline.

At 60 months, renal function remained relatively stable based on eGFR and annualized eGFR slopes during the treatment

Cardiac outcomes:
- no cardiac fibrosis developed over 60 months of treatment
- LVMI mean values were within normal ranges

Safety Data

- Most TEAEs were mild to moderate in severity and unrelated to pegunigalsidase alfa
- One patient experienced a hypersensitivity reaction (bronchospasm) during the first infusion and was withdrawn from the study per protocol
- ADAs were infrequent and transitory in most patients

Summary

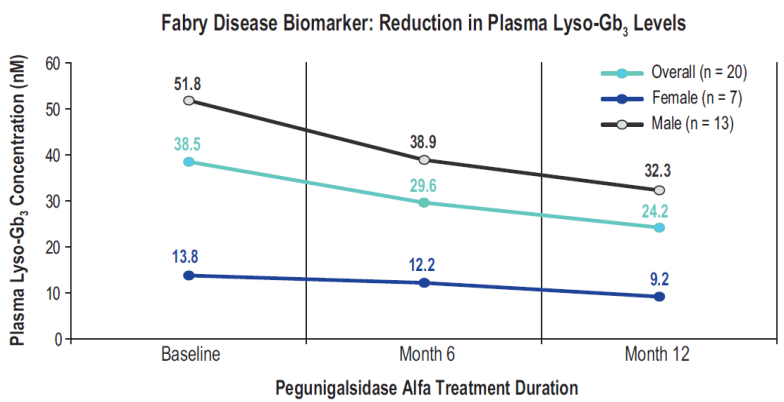
The results of this study suggest that long-term pegunigalsidase alfa treatment provided continued benefits in patients with Fabry disease, based on: stability in cardiac and renal function, initial reduction and plasma lyso-Gb_3 concentrations which remained low, and the safety data, which indicates that pegunigalsidase alfa has been well tolerated.

ADAs, Anti Drug Antibodies; eGFR, estimated glomerular filtration rate; TEAE, Treatment-emergent Adverse Events; LVMI, Left Ventral Mass Index; Gb_3, globotriaosylceramide; lyso-Gb_3, globotriaosylsphingosine

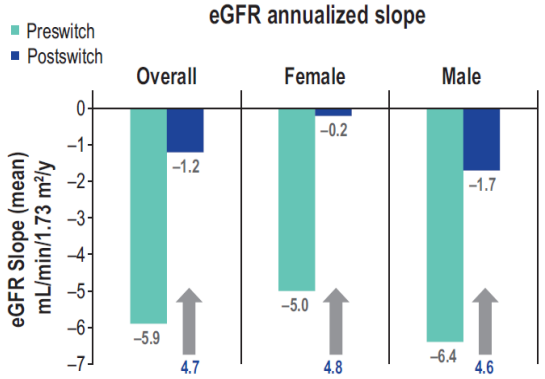
BRIDGE Phase III Trial Summary

Switch from agalsidase alfa to pegunigalsidase alfa

Clinical Activity Data



Lyso-Gb_3, plasma globotriaosylsphingosine.



eGFR, estimated glomerular filtration rate.

Reduction in Fabry disease biomarker lyso-Gb_3

Overall, the mean plasma lyso-Gb_3 concentration decreased by 31.5%; from mean of 38.5 nM at baseline to mean of 24.2 nM at month 12 following pegunigalsidase alfa treatment

Improvement in kidney disease progression as measured by eGFR slope after 12 months of pegunigalsidase alfa treatment:

Mean overall annualized eGFR slope improved from -5.9 to -1.2 mL/min/1.73 m^2/year

Safety Data

Favorable tolerability and immunogenicity profile

- Most TEAEs were mild or moderate in severity, with all AEs being transient
- 2 patients (9.1%) withdrew from treatment due to hypersensitivity reaction (resolved following withdrawal)
- Only patients (n=2) with pre-existing ADAs were positive for neutralizing antibodies

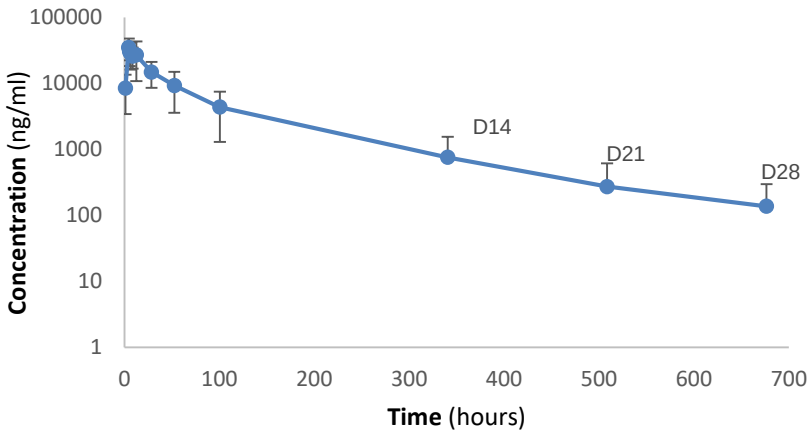
eGFR, estimated glomerular filtration rate; AEs, Adverse Events TEAEs; Treatment-emergent Adverse Events; ADAs, Anti Drug Antibodies; lyso-Gb_3, globotriaosylsphingosine.

BRIGHT Phase III Trial with Alternative Dosing Regimen - Summary

Pegunigalsidase Alfa Administered at 2 mg/kg Every 4 Weeks

Pharmacokinetics

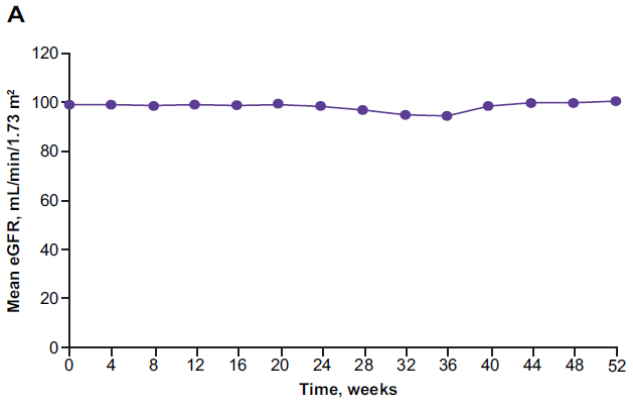
Pegunigalsidase alfa concentration over time



Measurable levels of pegunigalsidase alfa in the plasma throughout the 4-week infusion interval

Clinical Activity Data

Stable eGFR throughout 1 year of pegunigalsidase alfa therapy



Mean change in eGFR values from baseline to month 12 was -1.27 mL/min/1.73 m^2

Safety Data

Favorable tolerability profile:

- Most TEAEs were mild to moderate in severity and unrelated to pegunigalsidase alfa
- Reduction of infusion duration, indicating good drug tolerability
- No de-novo ADAs were reported following switch to pegunigalsidase alfa

Summary:

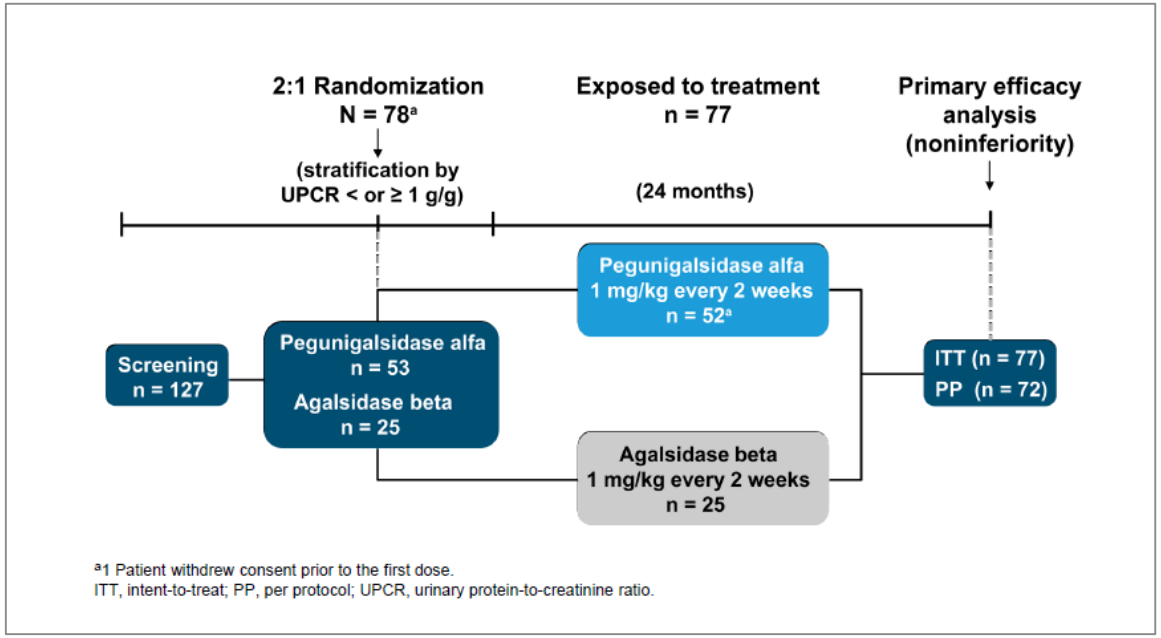
- 30 patients were enrolled in the BRIGHT study; 29 patients that completed the study enrolled in the long term extension study.
- Most patients have been treated with this 2 mg\kg every 4 weeks regimen for >4 years (including the extension study).
- Supports potentially transitioning patients with Fabry disease currently receiving ERT 1 mg/kg every 2 weeks to pegunigalsidase alfa 2 mg/kg every 4 weeks, if approved.

eGFR, estimated glomerular filtration rate; ERT, Enzyme Replacement Therapy; TEAEs; Treatment-emergent Adverse Events; ADAs, Anti Drug Antibodies.

BALANCE, a Phase III, Randomized, Double-blind, Active-Controlled Study

Assessed safety and efficacy of pegunigalsidase alfa vs. agalsidase beta in adult patients with Fabry disease with deteriorating renal function

Study Design



- Patients were randomly assigned 2:1 either to switch to pegunigalsidase alfa or to continue with agalsidase beta, both administered at 1 mg/kg every 2 weeks for 24 months
- Randomization was stratified by a urine protein to creatinine ratio (UPCR) of < or ≥ 1 g/g

Study Assessments

Efficacy Assessments:

- The primary efficacy endpoint was the change in annualized eGFR slope
- It was assessed at 24 months based on a prespecified non-inferiority margin of median annualized eGFR slope change difference ($eGFR_{CKD\text{-}EPI}$) and its confidence interval (CI) between groups

Safety, Tolerability, and Immunogenicity Assessments:

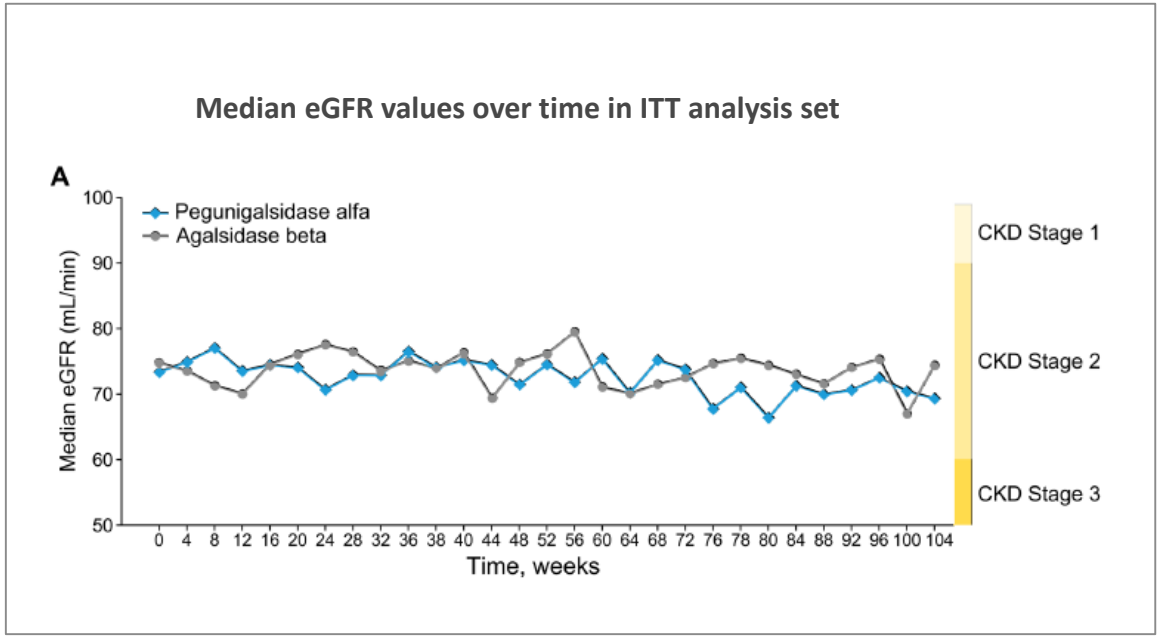
- Treatment-emergent adverse events (TEAEs), including:
  - Evaluation of treatment severity and relatedness
  - Infusion-related reactions (IRRs)
- Use of infusion pre-medication
- Immunogenicity, the prevalence and incidence of Anti-drug Antibodies (ADAs) and neutralizing antibodies (nAbs)

balance a Fabry clinical study

BALANCE, a Phase III Trial – Efficacy Data Summary

Assessed safety and efficacy of pegunigalsidase alfa vs. agalsidase beta in adult patients with Fabry disease with deteriorating renal function

Efficacy Assessment: Evaluation of Renal Function



- eGFR values over time show high overlap between treatment arms

Primary efficacy analysis of the difference in median of eGFR slope between the treatment arms

Primary Analysis (ITT set)	Pegunigalsidase alfa (N=52)	Agalsidase beta (N=25)	Difference[a]
Median (mL/min/1.73 m^2/year)	-2.514	-2.155	-0.359
95% Confidence Interval	-3.788; -1.240	-3.805; -0.505	(**-2.444**[b]; 1.726)

[a](pegunigalsidase alfa) - (agalsidase beta).
[b]Value above the predefined noninferiority margin.

Primary Efficacy Analysis

At 24 months, the difference in median eGFR slope between groups of the ITT population was –0.359 mL/min/1.73 m^2/year (95% CI: –2.444, 1.726)

- Lower CI met pre-specified non-inferiority margin
- 95% CI included 0, indicating no significant difference between groups

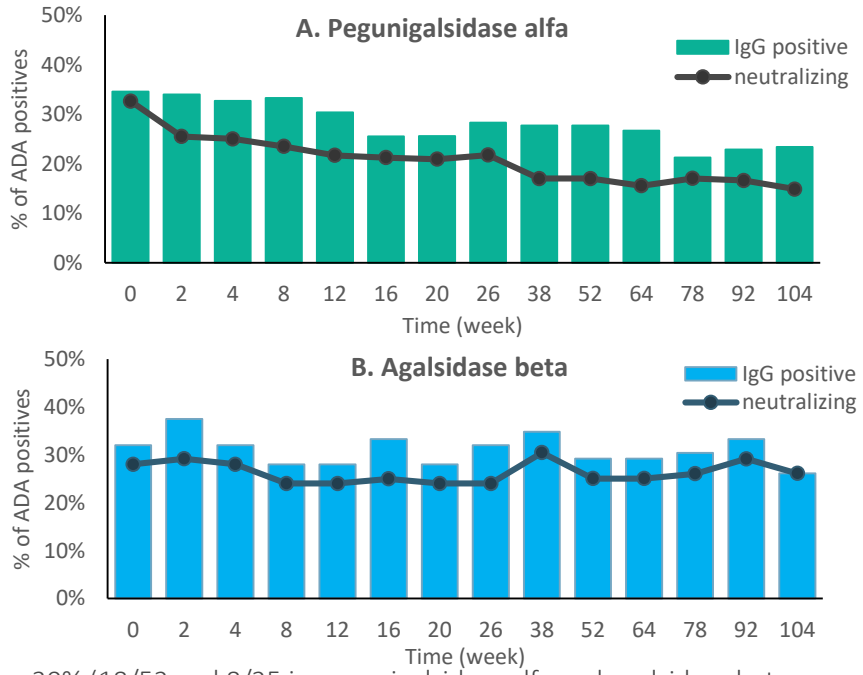
CKD, chronic kidney disease; CI, Confidence Interval; eGFR, estimated glomerular filtration rate; $eGFR_{CKD\text{-}EPI}$, eGFR chronic kidney disease-epidemiology collaboration equation; ITT, Intent to Treat.

BALANCE, a Phase III Trial – Safety Data Summary

Assessed safety and efficacy of pegunigalsidase alfa vs. agalsidase beta in adult patients with Fabry disease with deteriorating renal function

Immunogenicity Data

Rates of ADA+ patients and nAb+ patients over time (ITT analysis set)



- >30% (18/52 and 8/25 in pegunigalsidase alfa and agalsidase beta, respectively) of the patients had pre-existing ADAs at baseline, due to the previous ERT treatment.
- Pegunigalsidase alfa arm: reduction in the portion of ADA+ (35% to 23%) and nAb+ (33% to 15%) patients.
- Agalsidase beta arm: reduction in the portion of ADA+ (32% to 26%) patients, but no change in the portion of patients with nAb+ (28% to 26%).

Safety Data

- Similar proportions of patients experiencing related **TEAEs** in the two treatment arms. However, the rate of related TEAEs (events per 100 patient years) was approximately 4-fold lower for pegunigalsidase alfa than for agalsidase beta, 42.85 and 152.91 events per 100 patient years, respectively
- 1 patient, receiving pegunigalsidase alfa, had a **serious related TEAE,** hypersensitivity reaction (withdrew from the study)
- Most patients successfully reduced the previously used **infusion premedication** during the study in both treatment arms
- While similar proportions of patients in both groups experienced **IRRs**, the number of IRR events were lower for pegunigalsidase alfa than agalsidase beta by ~4-fold, 13 and 51 events, respectively (and ~8-fold 0.5 and 3.9, respectively when normalized to per 100 infusions)
- **No deaths** were reported
- **Immunogenicity:**
  - >30% of the patients had pre-existing ADAs at baseline, due to the previous ERT treatment
  - Overall trend of reduction in the portion of nAb+ patients is shown in the pegunigalsidase alfa arm, while no-change in the agalsidase beta arm
  - Low percentage of treatment-emergent ADA+ rate

TEAEs, Treatment-emergent Adverse Events; IRR, Infusion related reaction; ADA, Anti Drug Antibodies; nAb, neutralizing antibodies.

BALANCE, a Phase III Trial Summary

Assessed safety and efficacy of pegunigalsidase alfa vs. agalsidase beta in adult patients with Fabry disease with deteriorating renal function

Summary

- Pegunigalsidase alfa showed non-inferiority to agalsidase beta based on the median eGFR annualized slope, a key measure of Fabry disease progression
- No new safety concerns were identified
- Tolerability and immunogenicity profiles were favorable for patients in the pegunigalsidase alfa arm
- Discontinuations: The group that switched to pegunigalsidase alfa had 5 discontinuations (4 due to withdrawal of consent; 1 due to a serious related TEAE of hypersensitivity); the group that remained on agalsidase beta had 1 discontinuation due to withdrawal of consent
- After study completion, most patients that completed the study (97%) opted to continue treatment with pegunigalsidase alfa in an open-label extension study for 60 months (NCT03566017)

TEAEs, Treatment-emergent Adverse Events; IRR, Infusion related reaction; ADA, Anti Drug Antibodies; nAb, neutralizing antibodies; eGFR, estimated glomerular filtration rate

Summary & Current Status of Pegunigalsidase Alfa Clinical Development Program

Ongoing Clinical Studies and Expanded Access Programs:

- **PB-102-F60 -** Open label extension study with 1 mg/kg E2W: **90 active patients**, some for >6 years
  - BALANCE (from both arms), BRIDGE and phase I/II trial completers who opted to continue treatment with pegunigalsidase alfa
- **PB-102-F51 -** Open label extension study with 2 mg/kg E4W: **28 active patients,** some for >5 years
- **Expanded Access Program in the US -** 1 mg/kg E2W: **32 patients enrolled**

Summarizing Statement:

- Overall, **>140** patients received at least 1 infusion of pegunigalsidase alfa in the clinical program
- Some patients have been treated with pegunigalsidase alfa for >5 years
- The cumulative exposure to pegunigalsidase alfa: ~300 patient years at 1 mg/kg E2W and ~100 patient years at 2 mg/kg E4W