# Safety and Efficacy of Pegunigalsidase Alfa vs Agalsidase Beta on Renal Function in Fabry Disease: 24-Month Results from the Phase III Randomized, Double-blind, BALANCE Study

E Wallace[1], O Goker-Alpan[2], S Alon[3], R Chertkoff[3], E Almon[3], R Rocco[4], DG Warnock[1], N Longo[5]

*[1]University of Alabama at Birmingham, Birmingham, AL, USA; [2]LDRTCenter, Fairfax, VA, USA; [3]Protalix Biotherapeutics, Carmiel, Israel; [4]Chiesi USA, Inc., Boston, MA, USA; [5]University of Utah, Salt Lake City, UT, USA*

## Introduction

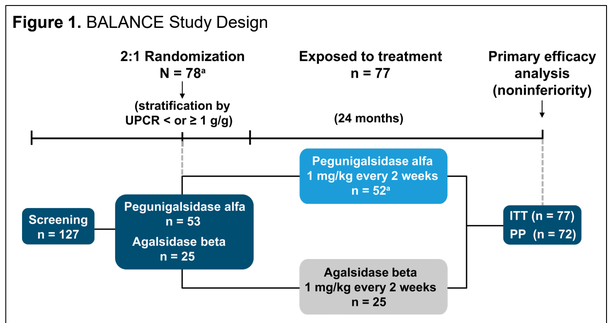
- Fabry disease (FD) renal pathology is associated with progressive chronic kidney disease with reduced glomerular filtration rate (GFR), proteinuria, and, eventually, end-stage kidney disease[1]
- Current therapeutic approaches for FD include the reduction of accumulated glycosphingolipids to stabilize renal function using enzyme replacement therapy (ERT)[2,3]
  - 2 ERTs using recombinant human α-galactosidase A are commercially available in various countries: agalsidase alfa (Replagal®)[4] and agalsidase beta (Fabrazyme®)[5]
- Pegunigalsidase alfa is a novel PEGylated α-galactosidase A ERT in development to treat FD[6,7] and is designed to offer:
  - Enhanced bioavailability and prolonged half-life
  - Reduced immunogenicity (incidence of antidrug antibodies [ADAs])
  - Potentially improved tolerability benefits
- Previous single-arm or switchover studies show pegunigalsidase alfa treatment has a favorable safety and efficacy profile for up to 60 months[8]
  - A head-to-head trial of pegunigalsidase alfa against another ERT can provide information on the comparative efficacy, safety, and tolerability of the therapies

## Objective

- This Phase III BALANCE study, aimed to evaluate the efficacy and safety of pegunigalsidase alfa compared to agalsidase beta in patients with FD and deteriorating renal function

## Methods

**Figure 1.** BALANCE Study Design




[a]1 Patient withdrew consent prior to the first dose.
ITT, intent-to-treat; PP, per protocol; UPCR, urinary protein-to-creatinine ratio.

- BALANCE (NCT02795676) is a randomized, double-blind, active-controlled study of pegunigalsidase alfa in adults with FD (**Figure 1**)
  - Key inclusion criteria:
    - Symptomatic adult patients with FD (aged 18–60 years)
    - Screening $eGFR_{CKD\text{-}EPI}$ of 40–120 mL/min/1.73 $m^2$
    - Screening linear eGFR slope < −2 mL/min/1.73 $m^2$/year
    - Treatment with agalsidase beta (1.0 mg/kg) every other week for ≥ 1 year with at least 80% compliance over the last 6 months
  - Key exclusion criteria:
    - Screening eGFR value of 91–120 mL/min/1.73 $m^2$ and a historical eGFR value > 120 mL/min/1.73 $m^2$ (9–18 months before screening)
    - Urinary protein-to-creatinine ratio (UPCR) > 0.5 g/g and not treated with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers
- Patients were randomly assigned 2:1 either to switch to pegunigalsidase alfa or to continue with agalsidase beta, both administered at 1.0 mg/kg every 2 weeks for 24 months
  - Randomization was stratified by a UPCR of < or ≥ 1 g/g

### Study Populations

- Intent-to-treat (ITT) population: all randomly assigned patients who received at least 1 dose of treatment (n = 77)
- Per-protocol (PP) population: all patients who completed at least 24 months of treatment (n = 72)
- Safety population: all patients who received at least 1 dose (partial or complete) of treatment (n = 77)

### Efficacy

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

### Safety, Tolerability, and Immunogenicity

- To assess safety, treatment-emergent adverse events (TEAEs) were evaluated using the Medical Dictionary for Regulatory Activities preferred terms
- To assess tolerability, infusion-related reactions (IRRs)
- To assess immunogenicity, the prevalence and incidence of ADAs and neutralizing antibodies (nAbs)

## Results

### Patients

- Study arms were generally well-balanced, with comparable patient demographic and baseline clinical characteristics (**Table 1**)
- On average, patients were treated with agalsidase beta for approximately 6 years before enrollment into BALANCE
- The group that switched to pegunigalsidase alfa had 5 discontinuations (4 due to withdrawal of consent; 1 due to a related TEAE of hypersensitivity)
- The group that remained on agalsidase beta had 1 discontinuation due to withdrawal of consent

**Table 1.** Patient Demographics and Baseline Characteristics

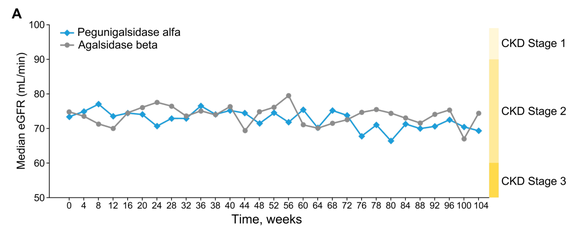
| Parameter | Pegunigalsidase alfa (n = 52) | Agalsidase beta (n = 25) | Overall (N = 77) |
|---|---|---|---|
| **Age, years** | | | |
| Mean ± SE | 43.9 ± 1.4 | 45.2 ± 1.9 | 44.3 ± 1.1 |
| Range: min, max | 20, 60 | 18, 58 | 18, 60 |
| **Sex, n (%)** | | | |
| Male | 29 (56) | 18 (72) | 47 (61) |
| Female | 23 (44) | 7 (28) | 30 (39) |
| **Race, n (%)** | | | |
| White | 49 (94) | 23 (92) | 72 (94) |
| Black | 1 (2) | 2 (8) | 3 (4) |
| **Fabry disease type, n (%)[a]** | | | |
| Classic | 27 (52) | 14 (56) | 41 (53) |
| Nonclassic | 25 (48) | 11 (44) | 36 (47) |
| **Baseline eGFR values, mL/min/1.73 $m^2$** | | | |
| Mean ± SE, years | 73.3 ± 2.8 | 73.5 ± 4.0 | 73.3 ± 2.3 |
| Range: min, max | 30.2, 125.9 | 34.1, 107.6 | 30.2, 125.9 |
| **Baseline eGFR, n (%)** | | | |
| ≤ 60 mL/min/1.73 $m^2$ | 13 (25) | 8 (32) | 21 (27) |
| 60 < and ≤ 90 mL/min/1.73 $m^2$ | 28 (54) | 12 (48) | 40 (52) |
| > 90 mL/min/1.73 $m^2$ | 11 (21) | 5 (20) | 16 (21) |
| **Baseline eGFR slope, mL/min/1.73 $m^2$/year** | | | |
| Mean ± SE | −8.07 ± 0.91 | −8.48 ± 0.83 | −8.21 ± 0.67 |
| Range: min, max | −30.5, 6.3 | −20.3, −2.8 | −30.5, 6.3 |
| **Baseline UPCR, n (%)** | | | |
| UPCR ≤ 0.5 g/g | 36 (69) | 20 (80) | 56 (73) |
| 0.5 < UPCR < 1 g/g | 9 (17) | 2 (8) | 11 (14) |
| UPCR ≥ 1 g/g | 7 (14) | 3 (12) | 10 (13) |

[a]Classification based on phenotype.
eGFR, estimated glomerular filtration rate; UPCR, urinary protein-to-creatinine ratio.

### Primary Efficacy Analysis

- At 24 months, difference in median eGFR slope between groups of the ITT population was −0.36 mL/min/1.73 $m^2$/year (95% CI: −2.444, 1.726; **Figure 2**)
  - Lower CI met prespecified noninferiority margin
  - 95% CI included 0, indicating no significant difference between groups
- Similar eGFR slope analyses with the PP population and UPCR adjusted sensitivity supported pegunigalsidase alfa noninferiority with results showing a more favorable trend toward pegunigalsidase alfa than the primary efficacy analysis

**Figure 2.** Evaluation of Renal Function (A) median eGFR values over time (B) primary efficacy analysis of the median difference in eGFR slope between baseline and 24 months




B

eGFR median slope analysis ($eGFR_{CKD\text{-}EPI}$), mL/min/1.73 $m^2$/year

| | Pegunigalsidase alfa n = 52 | Agalsidase beta n = 25 | Difference[a] |
|---|---|---|---|
| Median | −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.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; $eGFR_{CKD\text{-}EPI}$, eGFR chronic kidney disease-epidemiology collaboration equation.

### Safety

- The rate of related TEAEs (events per 100 patient years) was approximately 4-fold higher for agalsidase beta than for pegunigalsidase alfa; however, the proportions of patients experiencing related TEAEs were similar (**Table 2**)
- 1 Patient withdrew due to a hypersensitivity IRR (serious related TEAE) on the first infusion and was found to be IgE positive at baseline
- Most patients successfully reduced use of infusion premedication during the study:
  - At baseline, a higher proportion of patients in the agalsidase beta arm (n = 16; 64%) received infusion premedication than patients in the pegunigalsidase alfa arm (n = 21; 40%)
  - At 24 months, a higher proportion of patients in the agalsidase beta arm (n = 3; 12%) continued to receive infusion premedication than in the pegunigalsidase alfa arm (n = 3; 6%)
- While similar proportions of patients in both groups experienced IRRs, the number of IRR events and normalized rate of IRR events were higher for agalsidase beta than pegunigalsidase alfa by ~4-fold and ~8-fold, respectively (**Table 2**)
- No deaths were reported

**Table 2.** Treatment-emergent Adverse Events

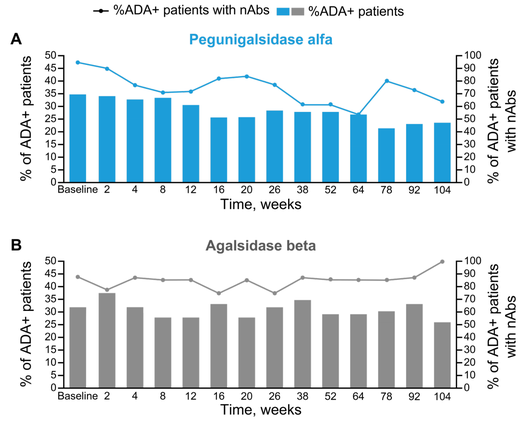
| Parameter | Pegunigalsidase alfa (n = 52) | Agalsidase beta (n = 25) | Overall (N = 77) |
|---|---|---|---|
| **Any TEAE** | | | |
| Events, n (rate[a]) | 561 (572) | 406 (817) | 967 (655) |
| Patients, n (%) | 47 (90) | 24 (96) | 71 (92) |
| **Related TEAEs** | | | |
| Events, n (rate[a]) | 42 (43) | 76 (153) | 118 (80) |
| Patients, n (%) | 21 (40) | 11 (44) | 32 (42) |
| **Related Serious TEAEs** | | | |
| Events, n (rate[a]) | 1 (1) | 0 | 1 (0.7) |
| Patients, n (%) | 1 (2) | 0 | 1 (1) |
| **Related TEAEs leading to withdrawal** | | | |
| Events, n (rate[a]) | 1 (1) | 0 | 1 (0.7) |
| Patients, n (%) | 1 (2) | 0 | 1 (1) |
| **IRRs** | | | |
| Events, n (rate[b]) | 13 (0.5) | 51 (3.9) | 64 |
| Patients, n (%) | 11 (21) | 6 (24) | 17 (22) |

[a]Per 100 exposure-years.
[b]Per 100 infusions.
IRR, infusion-related reaction; TEAE, treatment-emergent adverse events.

### Tolerability

- For pegunigalsidase alfa, 18/52 (35%) patients were ADA+ at baseline compared with 11/47 (23%) patients at month 24 (**Figure 3A**)
  - nAbs were present in 17/18 (94%) patients at baseline and 7/11 (64%) patients at month 24
- For agalsidase beta, 8/25 (32%) patients were ADA+ at baseline compared with 6/23 (26%) patients at month 24 (**Figure 3B**)
  - nAbs were present in 7/8 patients (88%) at baseline and 6/6 (100%) patients at month 24

**Figure 3.** Rates of ADA+ patients and ADA+ Patients with nAbs Over Time for (A) Pegunigalsidase alfa and (B) Agalsidase beta




ADA+, positive for antidrug antibodies; nAbs, neutralizing antidrug antibodies.

- The treatment-emergent ADA+ rate was lower for patients who switched to pegunigalsidase alfa than for patients who remained on agalsidase beta (**Table 3**)

**Table 3.** Total ADAs and Treatment-emergent ADAs

| Parameter | Pegunigalsidase alfa | Agalsidase beta |
|---|---|---|
| **Baseline, n (%)** | n = 52 | n = 25 |
| ADA+ | 18 (35) | 8 (32) |
| nAb+ | 17 (94) | 7 (88) |
| ADA− | 34 (65) | 17 (68) |
| **Postbaseline ADAs, n (%)** | | |
| Month 24 | n = 47 | n = 23 |
| ADA+ | 11 (23) | 6 (26) |
| nAb+ | 7 (64) | 6 (100) |
| ADA− | 36 (77) | 17 (74) |
| **Treatment-emergent ADAs, n (%)** | | |
| Yes | 6 (12) | 4 (16) |
| Titer boosted[a,b] | 3 (50) | 1 (25) |
| De novo[a,c] | 3 (50) | 3 (75) |
| No | 46 (88) | 21 (84) |

[a]% calculated out of patients with treatment-emergent ADAs.
[b]Titer at least 4-fold baseline values.
[c]If the patient was ADA− at baseline and became ADA+ positive at any subsequent time.
ADA, antidrug antibody; ADA+, positive for antidrug antibodies; ADA−, negative for antidrug antibodies; nAb+, positive for neutralizing antibodies.

## Conclusions

- Pegunigalsidase alfa showed noninferiority to agalsidase beta based on the median eGFR annualized slope, a key measure of FD progression
- No new safety concerns were identified
  - Overall, the tolerability and immunogenicity profiles were favorable for patients who switched to pegunigalsidase alfa
    - The rate of related TEAEs was approximately 4-fold lower for pegunigalsidase alfa than for agalsidase beta
    - The proportion of ADA+ patients with nAbs was lower for pegunigalsidase alfa than for agalsidase beta at 24 months
    - The event rate of IRRs was approximately 8-fold lower for pegunigalsidase alfa than agalsidase beta
- After study completion, most patients opted to continue treatment with pegunigalsidase alfa in an open-label extension study for 60 months (NCT03566017)

**References**
1. Germain, DP. *Orphanet J Rare Dis.* 2010;5:30. 2. Lenders M and Brand E. *Gut Microbes.* 2022;14:2027852. 3. Ortiz A et al. *Clin Kidney J.* 2021;14:1136-1146. 4. REPLAGAL® (agalsidase alfa for injection). Takeda Canada Inc. 5. Fabrazyme® (agalsidase beta injection powder). Genzyme Corporation. 6. Schiffmann R et al. *J Inherit Metab Dis.* 2019;42:534-544. 7. Kizhner T et al. *Mol Genet Metab.* 2015;114:259-267. 8. Bernat J et al. Poster presented at: ACMG. Salt Lake City, UT; March 22-26, 2022. eP149.

**Acknowledgments:** The authors thank the patients and their families for participation, all investigators participating in the study, and Dr Anat Sakov for her support. The study was sponsored by Protalix Biotherapeutics. Medical writing support was provided by Keith M. Olson, PhD, of Oxford PharmaGenesis Inc., Newtown, PA, USA, and funded by Chiesi USA, Inc.

**Disclosures: EW** has consulting and/or grants with Sanofi, Protalix, Chiesi, Idorsia, 4DMT, Amicus, and Natera. **OGA** has conducted contract research, received consulting fees, and/or served on advisory boards with Amicus, Freeline, Genentech, Protalix, Sangamo, Sanofi, Takeda, Sangamo, 4DMT, and Avrobio. **SA**, **RC**, and **EA** are full-time employees of Protalix Biotherapeutics. **RR** is a full-time employee of Chiesi Farmaceutici S.p.A., Parma, Italy. **DGW** has active consulting arrangements with Amicus, Chiesi, Idorsia, Protalix, and Reata. **NL** has received research support from and has participated in advisory boards for Amicus, Astellas, Avrobio, BioMarin Pharmaceutical, Homology, Horizon, Moderna, Pfizer, Protalix Biotherapeutics, PTC Biotherapeutics, Reneo, Sanofi, Takeda, and Ultragenyx (no direct funding is received as funds were institution directed).