First Results of a Head-to-Head Trial of Pegunigalsidase Alfa vs Agalsidase Beta in Fabry Disease: 2-year Results of the Phase 3 Randomized, Double-blind, BALANCE Study

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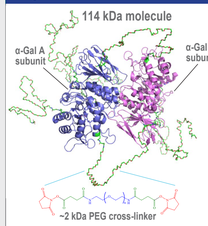
Introduction

- Chronic kidney disease is a main consequence of Fabry disease (FD) and is one of the leading causes of death in male patients with FD[1]
- Current therapeutic approaches for FD include reduction of accumulated glycosphingolipids to stabilize renal function using enzyme replacement therapy (ERT) or chaperone therapy (ie, migalastat)[2,3]
- Unmet needs include complications related to progressive clinical decline with deteriorating renal function and immunogenicity with ERT[2,3]
- Pegunigalsidase alfa is a novel PEGylated recombinant α-galactosidase A ERT in development to treat FD (**Figure 1**)
- Pegunigalsidase alfa is designed to offer prolonged half-life, reduced incidence of ADAs, and potentially improved tolerability compared with available ERTs[1,4]
- The molecule is a covalently linked homodimer composed of:
  - 2 plant cell-derived subunits of α-galactosidase A linked through the ~2 kDa PEG cross-linker, resulting in a 114 kDa enzyme
- Pegunigalsidase alfa cleared Gb3 depositions in kidney peritubular capillaries after 6 months in ERT-naïve adults (dosing groups: 0.2, 1, and 2 mg/kg every 2 weeks [E2W])[5]
- BRIDGE (NCT03018730; phase 3, open-label, single arm, switch-over from 0.2 mg/kg agalsidase alfa E2W) demonstrated safety and efficacy over 12 months of pegunigalsidase alfa (1.0 mg/kg E2W) treatment

Figure 1. PEGylated recombinant α-galactosidase A



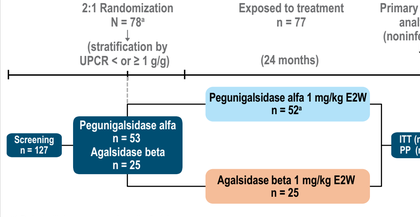
α-Gal A, α-Galactosidase A; PEG, polyethylene glycol.

Objective

- BALANCE (NCT02795676) was a phase 3 noninferiority study that evaluated the efficacy and safety of pegunigalsidase alfa (1.0 mg/kg E2W) compared with agalsidase beta (1.0 mg/kg E2W) in patients with FD previously treated with agalsidase beta who also had deteriorating renal function

Methods

Figure 2. BALANCE Study Design



[a]1 Patient withdrew consent prior to the first dose.

E2W, every 2 weeks; ITT, intent-to-treat; PP, per protocol; UPCR, urinary protein-to-creatinine ratio.

Figure 3. Study Inclusion and Exclusion Criteria

Main inclusion criteria
- Symptomatic adults with FD (18–60 years)
- Linear eGFR[a] slope more negative than or equal to −2 mL/min/1.73 m²/y
- Treatment with agalsidase beta (1.0 mg/kg E2W) for ≥1 year and ≥80% compliance over the last 6 months

Main exclusion criteria
- Screening eGFR[a] 91–120 mL/min/1.73 m² and historical eGFR >120 mL/min/1.73 m² during 9–18 months before screening
- UPCR >0.5 g/g and not treated with an ACEi or ARB

[a]The chronic kidney disease epidemiology collaboration (CKD-EPI) 2009 equation[2] was used to calculate eGFR based on serum creatinine measured at each visit.

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor block; E2W, every 2 weeks; eGFR, estimated glomerular filtration rate; FD, Fabry disease; UPCR, urinary protein-to-creatinine ratio.

Results

Baseline characteristics

- Mean duration of previous agalsidase beta exposure: ~6 years (range: 1–20 years) (**Table 1**)
- There were no statistically significant differences in baseline characteristics between the groups, although there was a numerically higher proportion of females and of patients with UPCR > 0.5 g/g in the pegunigalsidase alfa arm

Table 1. Patient Demographics and Baseline Characteristics

	Pegunigalsidase alfa (n = 52)	Agalsidase beta (n = 25)	*p*-value
Age, years			
Mean ± SD	43.9 ± 10.2	45.2 ± 9.6	0.60[a]
Sex, n (%)			
Male	29 (56)	18 (72)	
Female	23 (44)	7 (28)	0.19[b]
UPCR, n (%)			
UPCR ≤ 0.5 g/g	36 (69)	20 (80)	
0.5 < UPCR < 1 g/g	9 (17)	2 (8)	
UPCR ≥ 1 g/g	7 (14)	3 (12)	0.52[b]
eGFR, mL/min/1.73 m²			
Mean ± SD	73.5 ± 20.2	74.2 ± 21.0	
Median (min, max)	73.5 (30.2, 125.9)	74.9 (34.1, 107.6)	0.82[c]
eGFR slope, mL/min/1.73 m²/y[d]			
Mean ± SD	−8.0 ± 6.6	−8.3 ± 4.3	
Median (min, max)	−6.7 (−30.5, 6.3)	−7.8 (−20.3, −2.8)	0.37[c]
ADA status[e]			
Positive	18 (34.6)	8 (32.0)	
Negative	34 (65.4)	17 (68.0)	0.82[b]
Plasma lyso-Gb3, nM			
Mean ± SD	26.2 ± 27.3	32.1 ± 35.4	
Median (min, max)	15.2 (0.8, 143.9)	17.6 (2.1, 142.0)	0.58[c]
Previous agalsidase beta exposure, mo			
Mean ± SD	65.0 ± 48.0	77.3 ± 41.3	
Min, max	12.6, 236.9	27.6, 168.3	0.25[a]

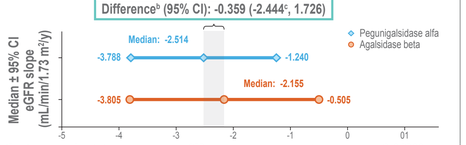
[a]*T*-test; [b]Pearson chi-squared; [c]Wilcoxon; [d]eGFR slope at baseline was based on historical, screening, and baseline serum creatinine and was more positive than -2 mL/min/1.73 m²/y for some patients; [e]At screening, each sample was tested for reactivity to both drugs, but due to the high cross-reactivity, only data for the assigned drug are presented.

ADA, antidrug antibody; eGFR, estimated glomerular filtration rate; lyso-Gb3, globotriaosylsphingosine; max, maximum; min, minimum; mo, months; nM, nanomolar (nmol/L); SD, standard deviation; UPCR, urine protein creatinine ratio.

Noninferiority met: eGFR slope analysis

- The median eGFR slopes during treatment and their 95% CI limits were −2.514 (95% CI: −3.788, −1.240) mL/min/1.73 m²/year with pegunigalsidase alfa and −2.155 (95% CI: −3.805, −0.505) mL/min/1.73 m²/year with agalsidase beta (**Figure 4**)
- The difference in median eGFR slope for the ITT population between treatment arms, the primary endpoint, was −0.36 mL/min/1.73 m²/year (95% CI: −2.444, 1.726)
  - Noninferiority was achieved: the lower bound of the difference in median eGFR slopes of the treatment arms was larger than the prespecified noninferiority margin of −3.0 mL/min/1.73 m²/year
  - The 95% CI included 0, and a high overlap between individual CIs, indicating no significant difference between the treatment arms
  - The analysis was repeated, adjusting the model for gender, and the conclusions remained unchanged

Figure 4. Median eGFR Slopes and the 95% CI Limits, Analysis Using Quantile Regression[a]

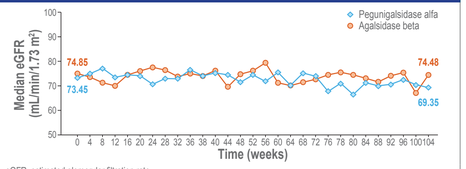


[a]To determine noninferiority, the annualized median eGFR slopes were analyzed by quantile regression using SAS PROC QUANTREG to obtain the corresponding 95% CI; noninferiority was declared if the lower bound of the CI for the treatment difference (pegunigalsidase alfa – agalsidase beta) was ≥ −3.0 mL/min/1.73 m²/year; [b](Pegunigalsidase alfa) − (agalsidase beta); [c]Value above the predefined noninferiority margin.

CI, confidence interval; eGFR, estimated glomerular filtration rate.

- At baseline, median eGFR values were nearly identical: 73.45 mL/min/1.73 m² in the pegunigalsidase alfa arm compared to 74.85 mL/min/1.73 m² in the agalsidase beta arm (**Figure 5**)
- The eGFR change from baseline showed a similar decline between baseline and 24 months in the two arms with a median change of -2.39 (mean [SD]: -3.60 [10.81]) mL/min/1.73 m² in the pegunigalsidase alfa arm and −3.20 (mean [SD]: -1.97 [7.42]) mL/min/1.73 m² in the agalsidase beta arm

Figure 5. eGFR Values Over Time

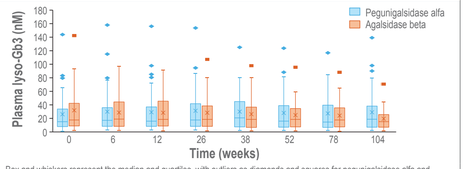


eGFR, estimated glomerular filtration rate.

Plasma lyso-Gb3 was stable and overlapped between arms

- High overlap of plasma lyso-Gb3 levels over time between both arms (**Figure 6**)
- Plasma lyso-Gb3 median change from baseline was stable with pegunigalsidase alfa (1.15 nM) and agalsidase beta (−1.50 nM)

Figure 6. Plasma Lyso-Gb3 Concentration Over Time



Box and whiskers represent the median and quartiles, with outliers as diamonds and squares for pegunigalsidase alfa and agalsidase beta, respectively; 'X' represents the mean.
Lyso-Gb3, globotriaosylsphingosine; nM, nanomolar (nmol/L).

Safety

- The exposure-adjusted rate of **related** TEAEs was ~4-fold higher for agalsidase beta than pegunigalsidase alfa (*p*<0.0001; **Table 2**)
- 1 patient receiving pegunigalsidase alfa withdrew due to a serious, related TEAE of hypersensitivity (this patient was IgE positive at baseline)
- 5 patients on pegunigalsidase alfa discontinued: 1 withdrew before first infusion, 4 withdrew throughout the study (n = 2 due to AE, n = 3 voluntary withdrawal of consent)
- 1 patient on agalsidase beta discontinued (voluntary withdrawal of consent)
- No deaths were registered during the study

Table 2. Rate of Treatment-emergent Adverse Events

	Pegunigalsidase alfa (n = 52)	Agalsidase beta (n = 25)
Any TEAE		
Events, n (rate)	561 (572)	406 (817)
Patients, n (%)	47 (90)	24 (96)
TEAE related to drug		
Events, n (rate)	42 (43)	76 (153)
Patients, n (%)	21 (40)	11 (44)
Serious TEAE related to drug		
Events, n (rate)	1 (1)	0 (0)
Patients, n (%)	1 (2)	0 (0)
Related TEAE leading to withdrawal		
Events, n (rate)	1 (1)	0 (0)
Patients, n (%)	1 (2)	0 (0)

The exposure-adjusted rate of TEAEs was calculated as events per 100 exposure-years.
TEAE, treatment-emergent adverse event.

- The number and rate of IRR events were higher for agalsidase beta than pegunigalsidase alfa by ~4-fold and ~8-fold, respectively (*p*<0.0001; **Table 3**)
- Most IRRs were mild or moderate in severity
- There was a notable drop in the use of premedications at 24 months in both treatment arms
  - In the pegunigalsidase alfa arm, the mean (min; max) infusion duration was reduced from 3.08 (0.6; 4.9) h at baseline to 1.56 (1.4; 2.1) h at 24 months; the reduction was less in the agalsidase beta arm, where the means were 2.96 (2.6; 3.3) h at baseline and 1.71 (1.4; 3.2) h at 24 months

Table 3. Rate of Infusion-related Reactions

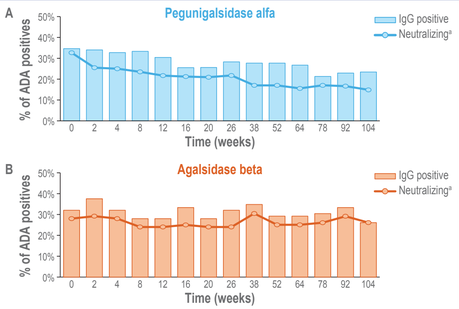
	Pegunigalsidase alfa (n = 52)	Agalsidase beta (n = 25)
Overall IRR		
Events, n (rate)	13 (0.5)	51 (3.9)
Patients, n (%)	11 (21.2)	6 (24.0)
Mild or moderate IRR		
Events, n (rate)	12 (0.5)	51 (3.9)
Patients, n (%)	11 (21.2)	6 (24.0)
Severe IRR		
Events, n (rate)	1 (0)	0 (0)
Patients, n (%)	1 (1.9)	0 (0)

The rate of IRRs was calculated as events per 100 infusions.
IRR, infusion-related reaction.

Prevalence of antidrug antibodies

- Reduction in ADA+ patients in pegunigalsidase alfa arm from 35% (18/52) to 23% (11/47) (**Figure 7A**) and in agalsidase beta arm from 32% (8/25) to 26% (6/23) (**Figure 7B**)
- Reduction in patients positive for neutralizing antibodies (nAb+) in pegunigalsidase alfa arm from 33% (17/52) to 15% (7/48) (**Figure 7A**) and slight decrease in agalsidase beta arm from 28% (7/25) to 25% (6/24) (**Figure 7B**)

Figure 7. Antidrug Antibodies



[a]% of nAb+ calculated out of total patients in respective treatment arm.
ADA, antidrug antibody; nAb+, positive for neutralizing antibodies.

- Treatment-emergent ADA+ rate was lower with pegunigalsidase alfa (6/52, 12%) than agalsidase beta (5/25, 20%), despite previous exposure of ~6y to agalsidase beta (**Table 4**)

Table 4. Treatment-emergent Antidrug Antibodies

Treatment-emergent ADAs, n (%)	Pegunigalsidase alfa (n = 52)	Agalsidase beta (n = 25)
Yes	6 (12)	5 (20)
Titer boosted[a,b]	3 (50)	2 (40)
De novo[a,c]	3 (50)	3 (60)
No	46 (89)	20 (80)

[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+ at any subsequent time.
ADA, antidrug antibody.

Conclusions

- **Pegunigalsidase alfa showed comparable efficacy to agalsidase beta** based on eGFR annualized slope (a key measure of FD progression), eGFR change, and plasma lyso-Gb3 level
- Overall, patients who switched to pegunigalsidase alfa showed **improved tolerability and immunogenicity profiles**
- **Most patients** who completed the study from both arms (97%: 45/47 on pegunigalsidase alfa and 24/24 on agalsidase beta) **opted to continue or initiate treatment with 1 mg/kg E2W pegunigalsidase alfa** in an open-label extension study for 60 months (NCT03566017)

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Disclosures

EW has consulting agreements and/or grants with Sanofi, Protalix, Chiesi, Idorsia, 4DMT, Amicus, and Natera. **OG-A** has conducted contracted research, received consulting fees, and/or served on advisory boards with Amicus, Freeline, Genentech, Protalix, Sangamo, Sanofi, Takeda, Sangamo, 4DMT, and Avrobio. **WRW** has been or is currently involved in clinical trials and/or registries with Alexion, Amicus, BioMarin, Chiesi, Freeline, Idorsia, Orphazyme, Pfizer, Protalix, Sanofi, Sangamo, Takeda, and 4DMT. He has received honoraria from Alexion, Amicus, Sanofi, Spark, and Takeda; and research funding from Amicus and Takeda. **MH** received speaker-related fees from Protalix and has been, or is currently, involved in clinical trials with Sanofi, Sangamo, Avrobio, Protalix, and Idorsia (no direct funding is received for these trials as they are institution directed). **JB** receives research support from Avrobio, BioMarin Pharmaceutical, Chiesi Farmaceutici, Idorsia Pharmaceuticals, Pfizer, Protalix Biotherapeutics, Sangamo Therapeutics, Sanofi, Takeda, Travere Therapeutics; and has received a speaker honorarium from the Fabry Support and Information Group; and has participated in advisory boards for Chiesi USA, Sanofi, and Takeda. **NL** receives 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 they are institution directed). **DH** has received honoraria for speaking and consulting fees for advisory boards from Protalix, Takeda, Sanofi, Freeline, and Sangamo, administered through University College London consultants, and used in part to support research in lysosomal storage diseases. **PG** has been involved in premarketing studies with Genzyme, Protalix, and Idorsia, and has received grants from Sanofi-Genzyme and Takeda; monies received for these activities have been deposited into the Spanish Foundation for the Study and Treatment of Gaucher Disease (FEETEG) to contribute to the development of research in lysosomal storage disorders. **MJM**, **DO**, **MM**, **BAB**, **VK**, **JK**, and **TG** have no disclosures. **RJH** has received consulting fees from Alexion, Amicus Therapeutics, Inc., Avrobio, Chiesi, Sangamo, Sanofi Genzyme and Takeda; advisory fees from Alexion, Amicus Therapeutics, Inc. and Sanofi/Genzyme; speakers' bureau fees from Alexion and Sanofi/Genzyme and grants/research funding from Alexion, Amicus Therapeutics, Inc., Idorsia, Protalix, Sangamo, Sanofi/Genzyme and Takeda. **CT** has received honoraria, travel support, and/or participated as an investigator in clinical studies supported by Protalix, Sanofi, Idorsia, Takeda, Amicus, Freeline and Acelink. **AL** has received consultancy and speaker's honoraria from Amicus Therapeutics, Sanofi, and Takeda. **PD** has been a paid consultant with Sanofi; received speaker honoraria from Sanofi and Takeda; and participated in an advisory board with Protalix. **AJ** has received a grant from Amicus and consultancy and speaker's honoraria from Takeda, Sanofi, Amicus. **BJ** has received honoraria, travel and accommodation funding from Greenovation Biotech GmbH, Sanofi, Takeda; member of the EU Advisory Board of Fabry Registry, sponsored by Sanofi. **AN** received lecturing honoraria and research support from Takeda, Amicus, Sanofi Genzyme. **AP** received travel expenses and grants from Takeda, Sanofi, Amicus and Chiesi. **DPG** has received consulting honoraria from Idorsia Pharmaceuticals, Sanofi, and Takeda, and speaker honoraria and travel support from Amicus Therapeutics, Sanofi, and Takeda. **IK** has received lecture, travel, and consulting fees from Amicus, Chiesi, Bayer, Boehringer-Ingelheim, Sanofi-Genzyme and Takeda-Shire. **AM** has received non-financial support from Chiesi Pharmaceuticals, during the conduct of the study; personal fees from AstraZeneca, personal fees from Bayer Pharmaceuticals, and personal fees from Janssen Pharmaceuticals, outside the submitted work. **SW** has been a paid consultant to Protalix. **EBA**, **SA**, and **RC** are full-time employees of Protalix Biotherapeutics. **RR** is a full-time employee of Chiesi Farmaceutici S.p.A., Parma, Italy. **DGW** has been or is currently involved in clinical trials and/or registries with Alexion, Amicus, BioMarin, Chiesi, Freeline, Idorsia, Orphazyme, Pfizer, Protalix, Sanofi, Sangamo, Takeda, and 4DMT. He has received honoraria from Alexion, Amicus, Sanofi, Spark, and Takeda; and research funding from Amicus and Takeda.

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