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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Background

- **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]

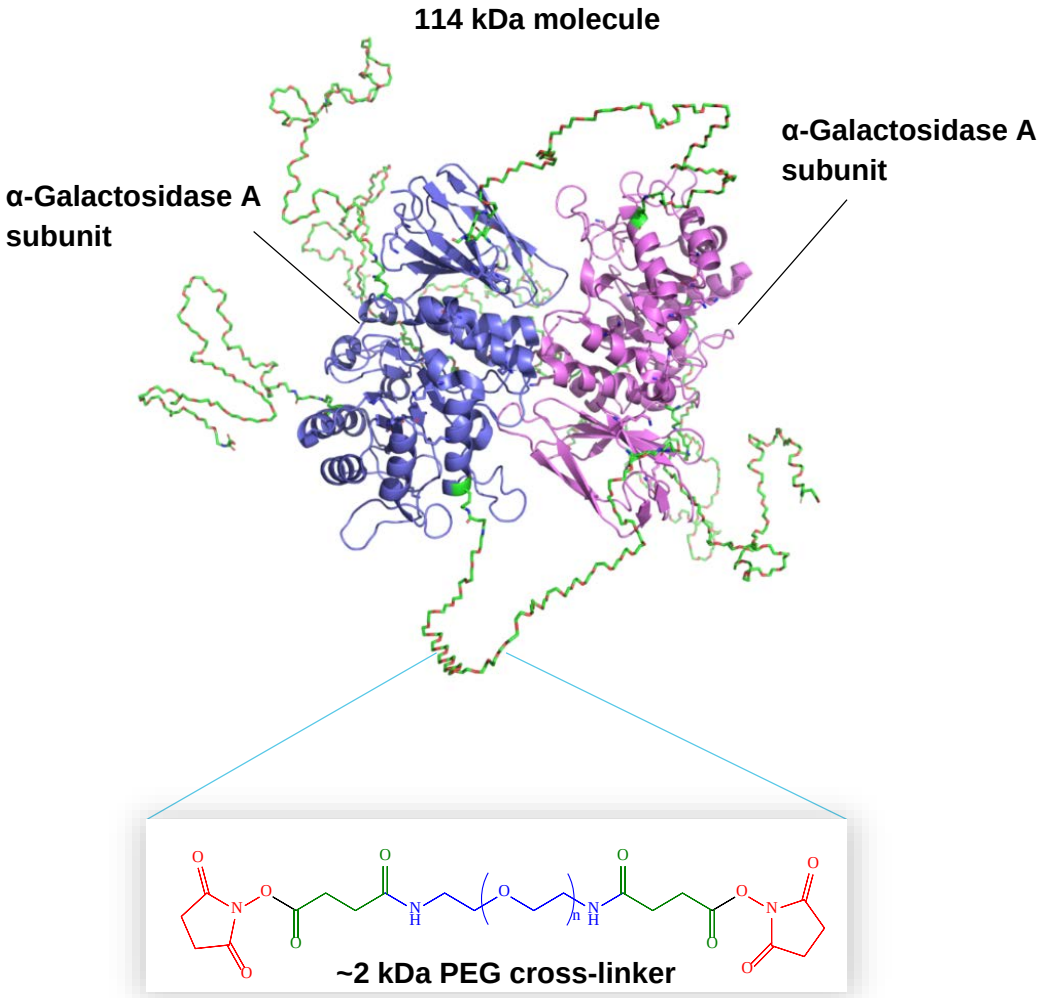
- **Unmet needs include progressive clinical decline** with decreasing renal function and immunogenicity with ERT[2,3]

[1]Schiffmann R et al. *Nephrol Dial Transplant.* 2009;24: 2102–2111; [2]Muntean C et al. *Front Pediatr.* 2022; 10: 908657; [3]Lenders M and Brand E. *J Am Soc Nephrol.* 2018;29:2265–2278.

Pegunigalsidase alfa is a novel PEGylated recombinant α-galactosidase A ERT in development to treat FD

- Pegunigalsidase alfa is designed to offer **enhanced bioavailability, prolonged half-life, reduced incidence of ADAs, and potentially improved tolerability compared with available ERTs[1]**

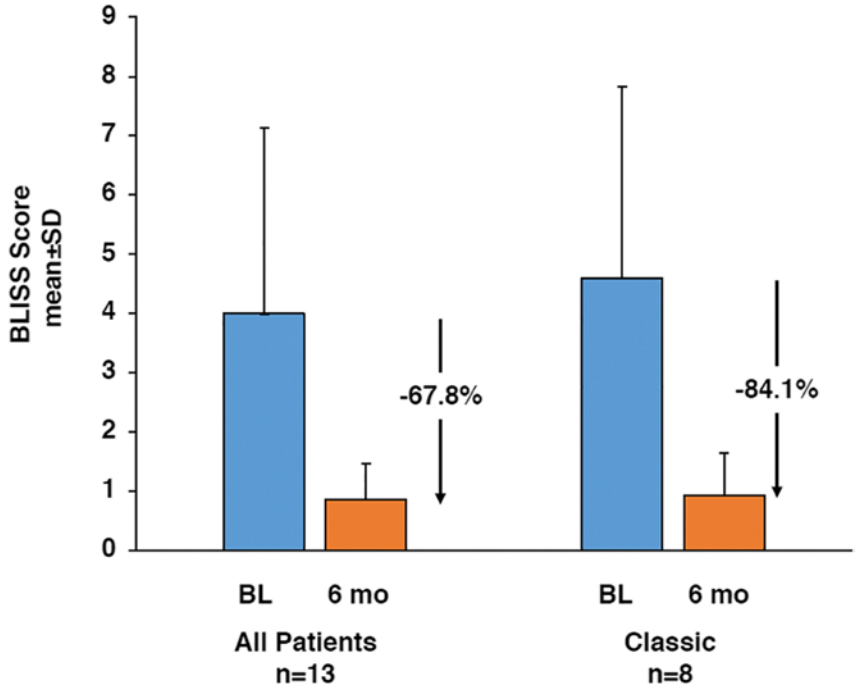
- The molecule is a covalently linked homodimer composed of:
  - 2 plant cell-derived subunits of α-galactosidase A linked through the ~2 kDa PEG cross-linker, resulting in a 114 kDa enzyme



[1]Ruderfer I et al. *Bioconjug Chem*. 2018;29(5):1630–1639.
ADA, antidrug antibody; ERT, enzyme replacement therapy; FD, Fabry disease; PEG, polyethylene glycol.

BALANCE study rationale

Pegunigalsidase alfa cleared Gb3 depositions in kidney peritubular capillaries after 6 months in ERT-naïve adults[1,2]



- BRIDGE[3] (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

Image is used with permission from Schiffman et al. *JIMD*. 2019;42:534–544 under the Creative Commons Attribution License.
[1]Schiffmann R et al. *J Inherit Metab Dis.* 2019;42(3):534–544; [2]Patients were naïve to ERT or had not received ERT in the previous 6 months; dosing groups were combined (0.2, 1, and 2 mg/kg E2W); [3]NCT03018730.
BL, baseline; BLISS, Barisoni Lipid Inclusion Scoring System; E2W, every 2 weeks; FD, Fabry disease; Gb3, globotriaosylceramide; mo, months; SD, standard deviation.

BALANCE study 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

E2W, every 2 weeks; FD, Fabry disease.

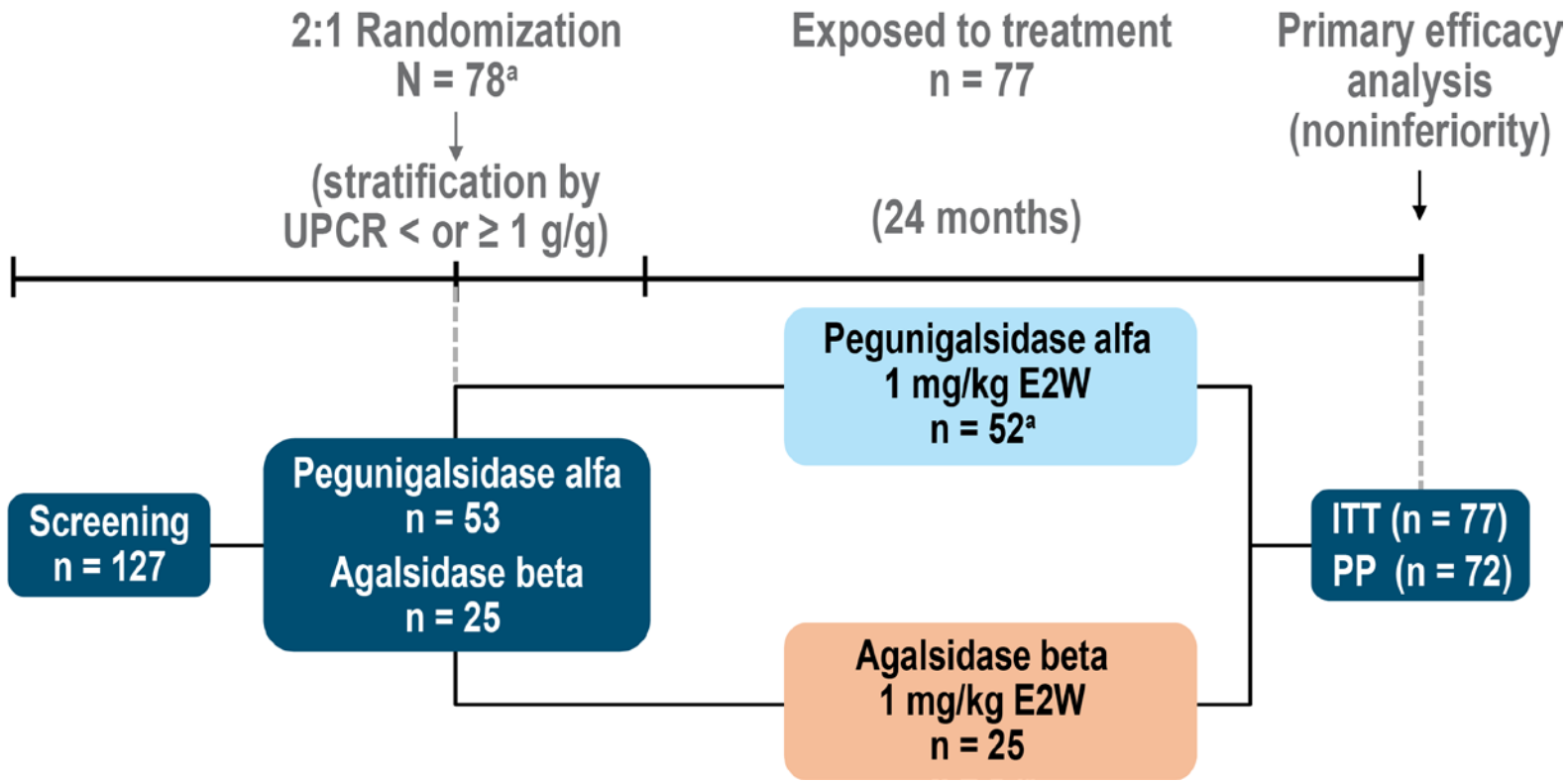
BALANCE study design

Main inclusion criteria

- Symptomatic **adults with FD** (18–60 years)
- **Linear eGFR[b] 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[b] 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]1 Patient withdrew consent prior to the first dose. [b]The chronic kidney disease epidemiology collaboration (CKD-EPI) 2009 equation (Levey AS et al. *Ann Intern Med*. 2009;150:604–612) 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; ITT, intent-to-treat; PP, per protocol; UPCR, urinary protein-to-creatinine ratio.

BALANCE study endpoints

Main efficacy endpoints

- **Primary efficacy endpoint:** noninferiority of pegunigalsidase alfa to agalsidase beta with respect to annualized change (slope) in $eGFR_{CKD\text{-}EPI}$ (biomarker for progressive kidney decline) at 24 months
- **Secondary endpoints** included change from baseline at all time points in plasma lyso-Gb3 levels

Main safety, tolerability, and immunogenicity endpoints

- **Treatment-emergent adverse events** (TEAEs) including:
  - Infusion-related reactions (IRRs)
  - Treatment-related TEAEs
- Use of **pre-infusion medication**
- **Immunogenicity** (antidrug antibodies)

CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate.

Baseline patient characteristics and demographics

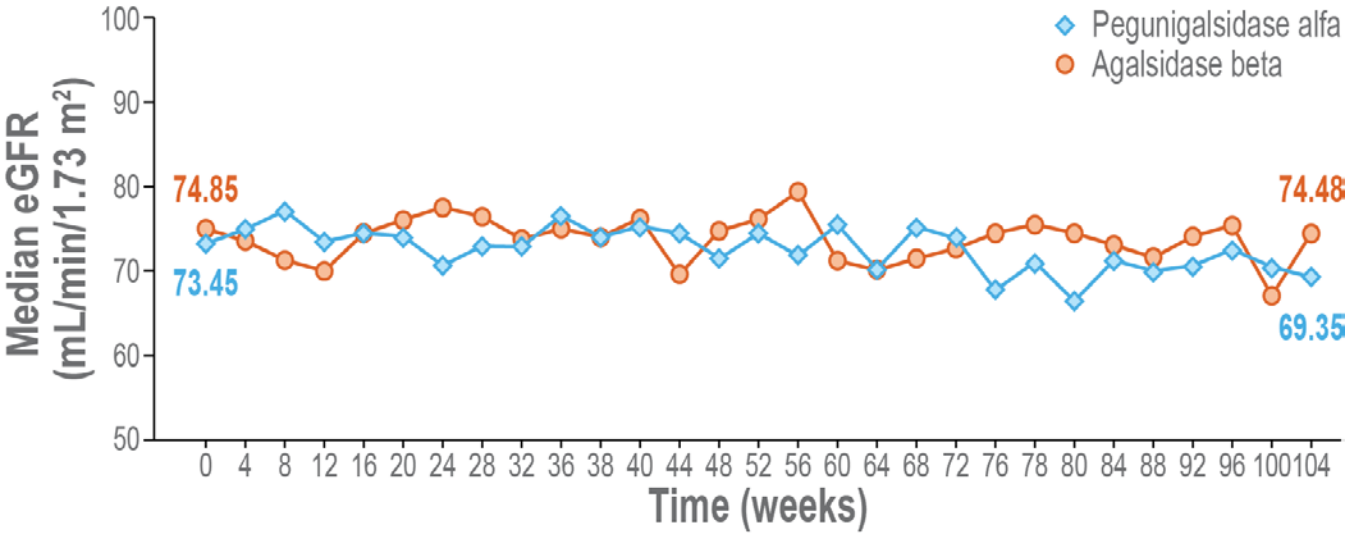
	Pegunigalsidase alfa (n = 52)	Agalsidase beta (n = 25)	*p*-value
Age, years			
Mean ± SE	43.9 ± 1.4	45.2 ± 1.9	0.60[a]
Sex, n (%)			
Male	29 (56)	18 (72)	
Female	23 (44)	7 (28)	0.19[b]
UPCR, n (%)			
UPCR ≤ 0.5 g/g	36 (69)	20 (80)	
0.5 < UPCR < 1 g/g	9 (17)	2 (8)	
UPCR ≥ 1 g/g	7 (14)	3 (12)	0.52[b]
eGFR, mL/min/1.73 m^2			
Mean ± SE	73.5 ± 2.8	74.2 ± 4.2	
Median (min, max)	73.5 (30.2, 125.9)	74.9 (34.1, 107.6)	0.82[c]
eGFR slope, mL/min/1.73 m^2/y[d]			
Mean ± SE	−8.0 ± 0.9	−8.3 ± 0.9	
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 ± SE	26.2 ± 3.8	32.1 ± 7.1	
Median (min, max)	15.2 (0.8, 143.9)	17.6 (2.1, 142.0)	0.58[c]
Previous agalsidase beta exposure, mo			
Mean ± SE	65.0 ± 6.7	77.3 ± 8.3	
Min, max	12.6, 236.9	27.6, 168.3	0.25[a]

- **Mean duration of previous agalsidase beta exposure: ~6 years (range: 1–20 years)**

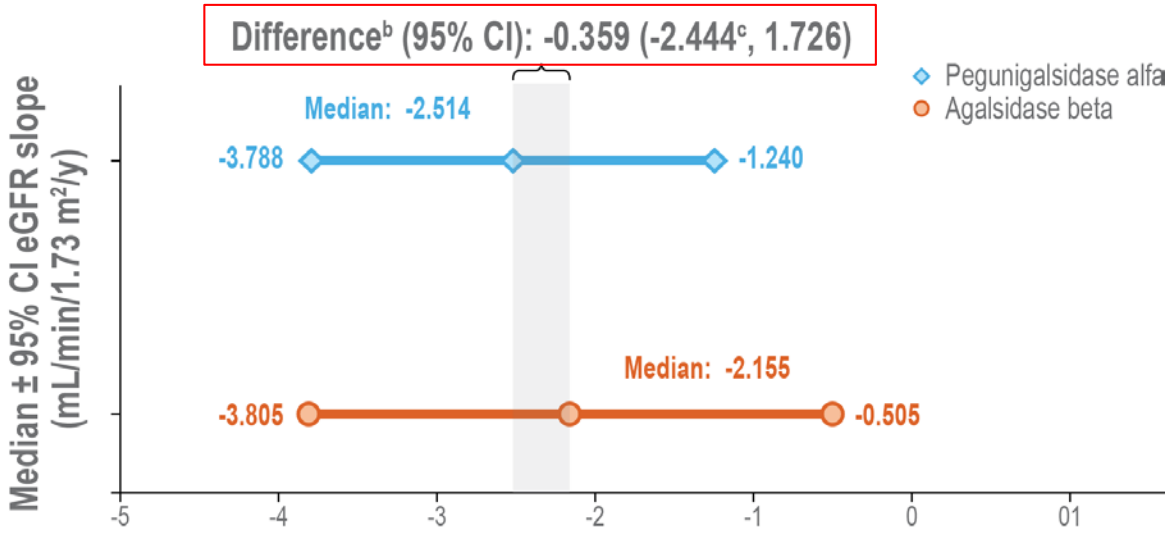
[a]T-test; [b]Pearson chi-squared; [c]Wilcoxon; [d]eGFR slope at baseline was based on historical, screening, and baseline serum creatinine and was more positive than -2 mL/min/1.73 m^2/y for some patients. [e]At screening, each sample was tested for reactivity to both drugs, but due to the high cross-reactivity, only data for the assigned drug are presented.
ADA, antidrug antibody; eGFR, estimated glomerular filtration rate; max, maximum; min, minimum; mo, months; nM, nanomolar (nmol/L); SE, standard error; UPCR, urine protein creatinine ratio.

Overlap between arms: eGFR over time, median slopes and its CI limits – noninferiority was met

eGFR values over time show comparability between the treatment arms



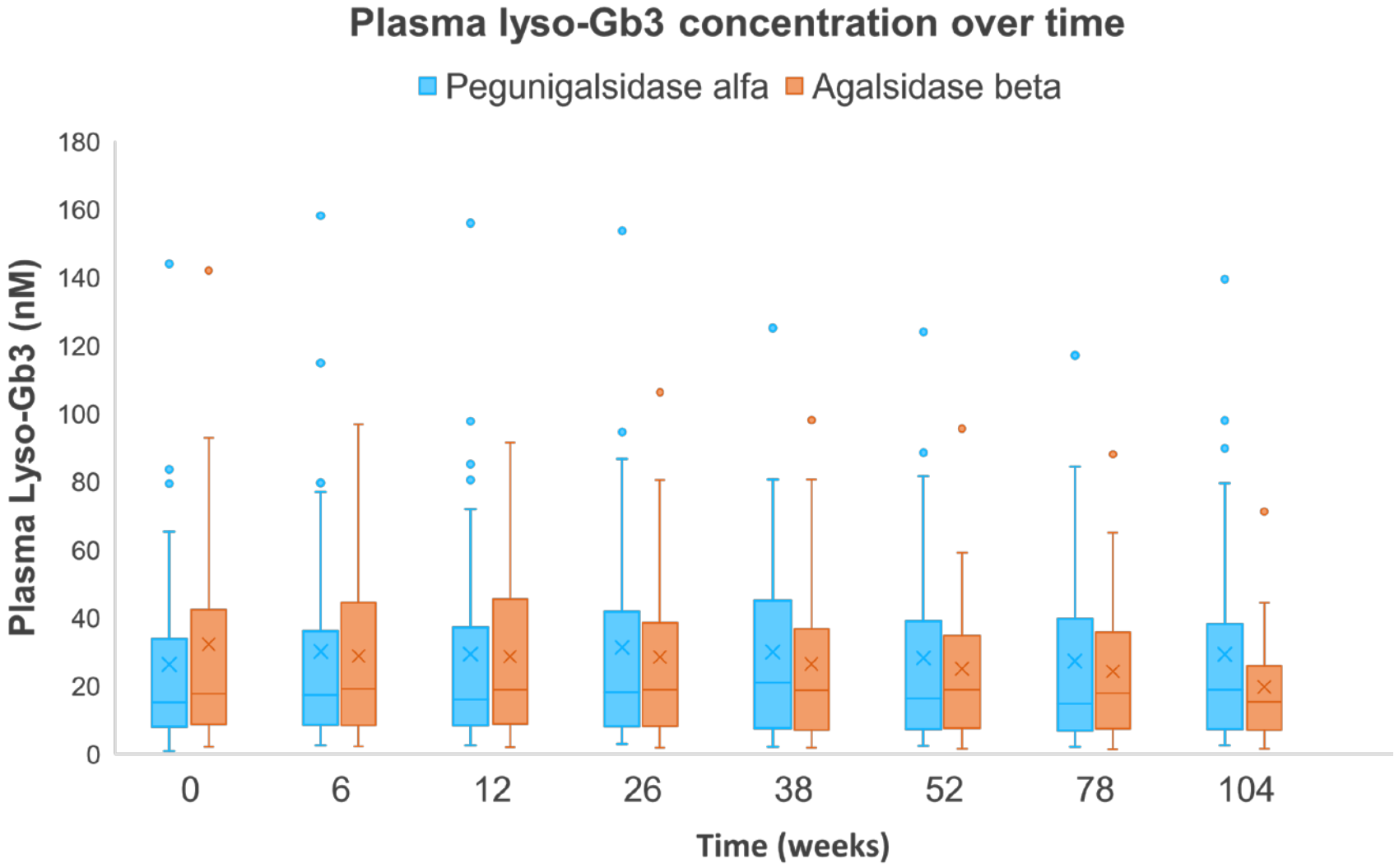
High overlap between median slopes and the 95% CI limits, analysis using quantile regression[a]



- The analysis was repeated, adjusting the model for gender, and the conclusions remained unchanged

[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 m^2/year; [b](Pegunigalsidase alfa) − (agalsidase beta); [c]Value above the predefined noninferiority margin.
CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; $eGFR_{CKD-EPI}$, eGFR chronic kidney disease epidemiology collaboration equation.

Plasma lyso-Gb3 was stable and overlapped between arms



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

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 measures: rate of treatment-emergent AEs

- The exposure-adjusted rate of related TEAEs was ~4-fold higher for **agalsidase beta** than **pegunigalsidase alfa**
- 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
- 1 patient on agalsidase beta discontinued
- No deaths were registered during the study

	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.

Rate of infusion-related reactions (IRRs)

- The number and rate of IRR events was higher for **agalsidase beta** than **pegunigalsidase alfa** by ~4-fold and ~8-fold, respectively
- Most IRRs were mild or moderate in severity
- As planned, there was a notable drop in the use of premedications at 24 months in both treatment arms

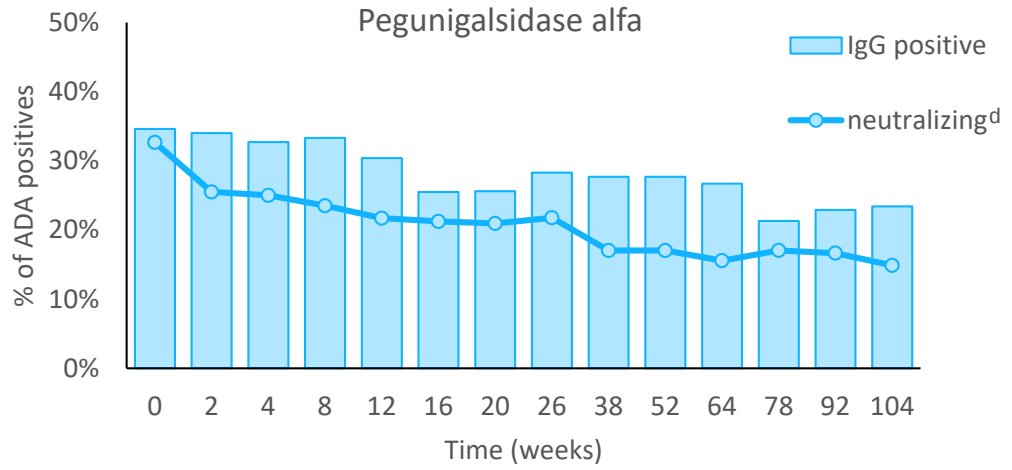
	Pegunigalsidase alfa (n = 52)	**Agalsidase beta (n = 25)**
Overall IRR		
Events, n (rate)	**13 (0.5)**	**51 (3.9)**
Patients, n (%)	11 (21.2)	6 (24.0)
Mild or moderate IRR		
Events, n (rate)	12 (0.5)	51 (3.9)
Patients, n (%)	11 (21.2)	6 (24.0)
Severe IRR		
Events, n (rate)	1 (0)	0 (0)
Patients, n (%)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

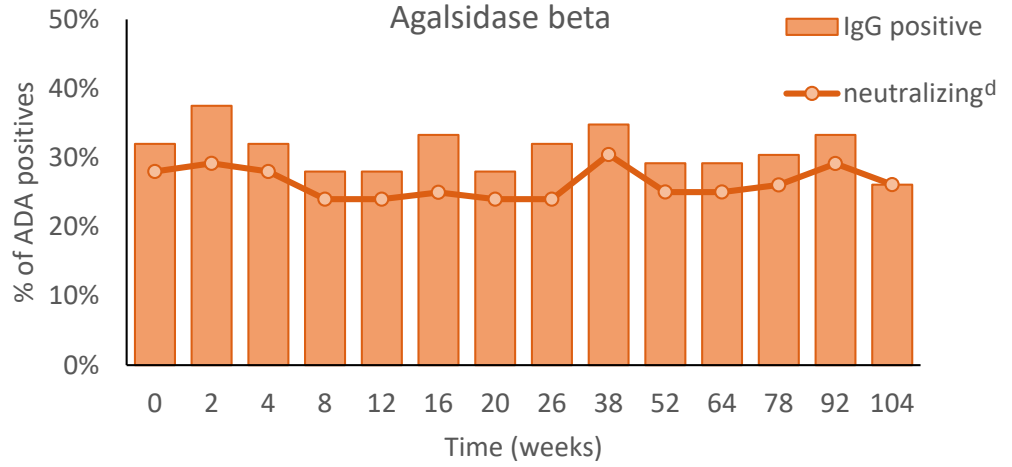
The rate of IRRs was calculated as events per 100 infusions.
IRR, infusion-related reaction.

Antidrug antibodies by treatment arm

- **Pegunigalsidase alfa:**
  - Reduction in ADA+ patients from 35% (18/52) to 23% (11/47)
  - Reduction in nAb+ patients from 33% (17/52) to 15% (7/48)
- **Agalsidase beta:**
  - Reduction in ADA+ patients from 32% (8/25) to 26% (6/23)
  - No change in nAb+ patients from 28% (7/25) to 25% (6/24)
- Treatment-emergent ADA+ rate was lower with pegunigalsidase alfa (6/52, 12%) than agalsidase beta (5/25, 20%)
  - Note that patients in the agalsidase beta arm had approximately 6 years of previous treatment

	Pegunigalsidase alfa	Agalsidase beta
Treatment-emergent ADAs, n (%)	**n = 52**	**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; [d]% of nAb+ calculated out of total patients in respective treatment arm.
ADA, antidrug antibody; ADA-, negative for antidrug antibodies; ADA+, positive for antidrug antibodies; nAb+, positive for neutralizing antibodies.

Conclusions

- **Pegunigalsidase alfa showed noninferior efficacy to agalsidase beta** based on median eGFR annualized slope, a key measure of FD progression
- Overall, patients who switched to pegunigalsidase alfa showed **favorable 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)

E2W, every 2 weeks; eGFR, estimated glomerular filtration rate; FD, Fabry disease.

Acknowledgements

- The author would like to acknowledge and thank the investigators involved in this study and Dr. Anat Sakov for her assistance in the statistical analysis.
- The trial was sponsored by Protalix Biotherapeutics and funding provided from Chiesi USA, Inc.

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