Long-term Safety and Efficacy of Pegunigalsidase Alfa Administered Every 4 Weeks in Patients With Fabry Disease: 2-year Interim Results from the Ongoing Phase 3 BRIGHT51 Open-label Extension Study

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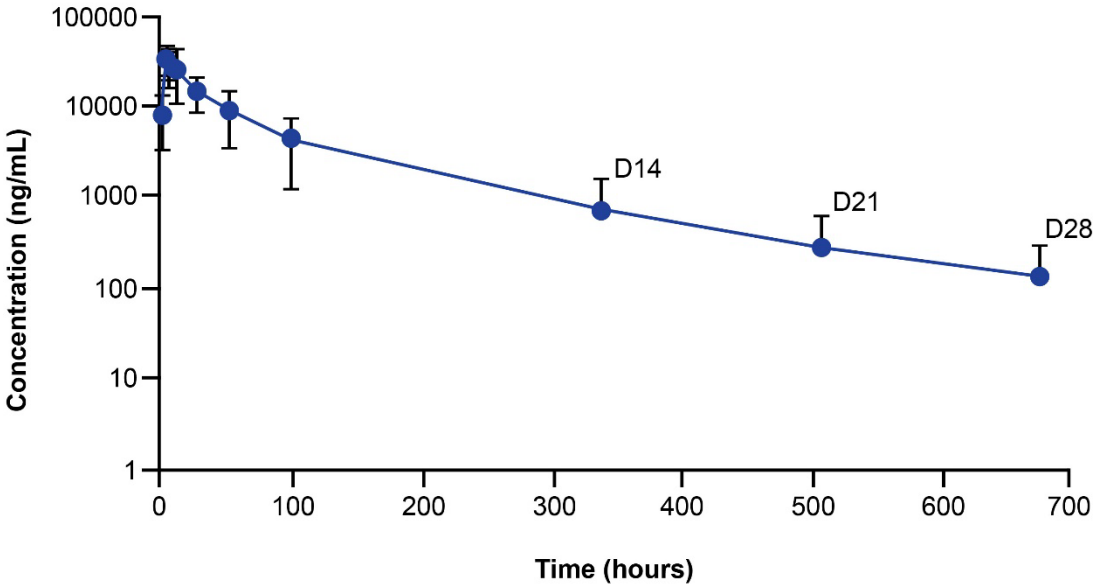
Introduction

- **Fabry disease** is a rare X-linked disorder caused by deficiency of lysosomal enzyme α-Gal-A, causing accumulation of sphingolipids, such as Gb3 and lyso-Gb3, leading to impaired organ function[1-3]
- **Current treatments for Fabry disease include the enzyme replacement therapies (ERTs)** agalsidase alfa and agalsidase beta, which require infusions every 2 weeks[4,5]
- **Pegunigalsidase alfa,** a novel PEGylated recombinant α-Gal-A enzyme in development for Fabry disease, has an increased plasma half-life (~80 hours) compared with current ERTs (~≤ 2 hours)[2]
- Increased stability and enhanced half-life of **pegunigalsidase alfa may allow for dosing flexibility and the interval between infusions to be extended**, thereby decreasing treatment burden for patients with Fabry disease

Pegunigalsidase alfa (2 mg/kg) concentration over time



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

α-Gal-A, alpha-galactosidase-A; ERT, enzyme replacement therapy; Gb3, globotriaosylceramide; lyso-Gb3, globotriaosylsphingosine.

1. Schiffmann R et al. *Nephrol Dial Transplant*. 2009;24:2102-2111; 2. Schiffmann R et al. *J Inherit Metab Dis*. 2019;42:534-544; 3. Germain DP. *Orphanet J Rare Dis*. 2010;5:30; 4. Replagal© (agalsidase alfa). Summary of Product Characteristics. 2022. Takeda Pharmaceuticals; 5. Fabrazyme (agalsidase beta) for injection, for intravenous use. Prescribing Information. March 2021. Genzyme Corporation.

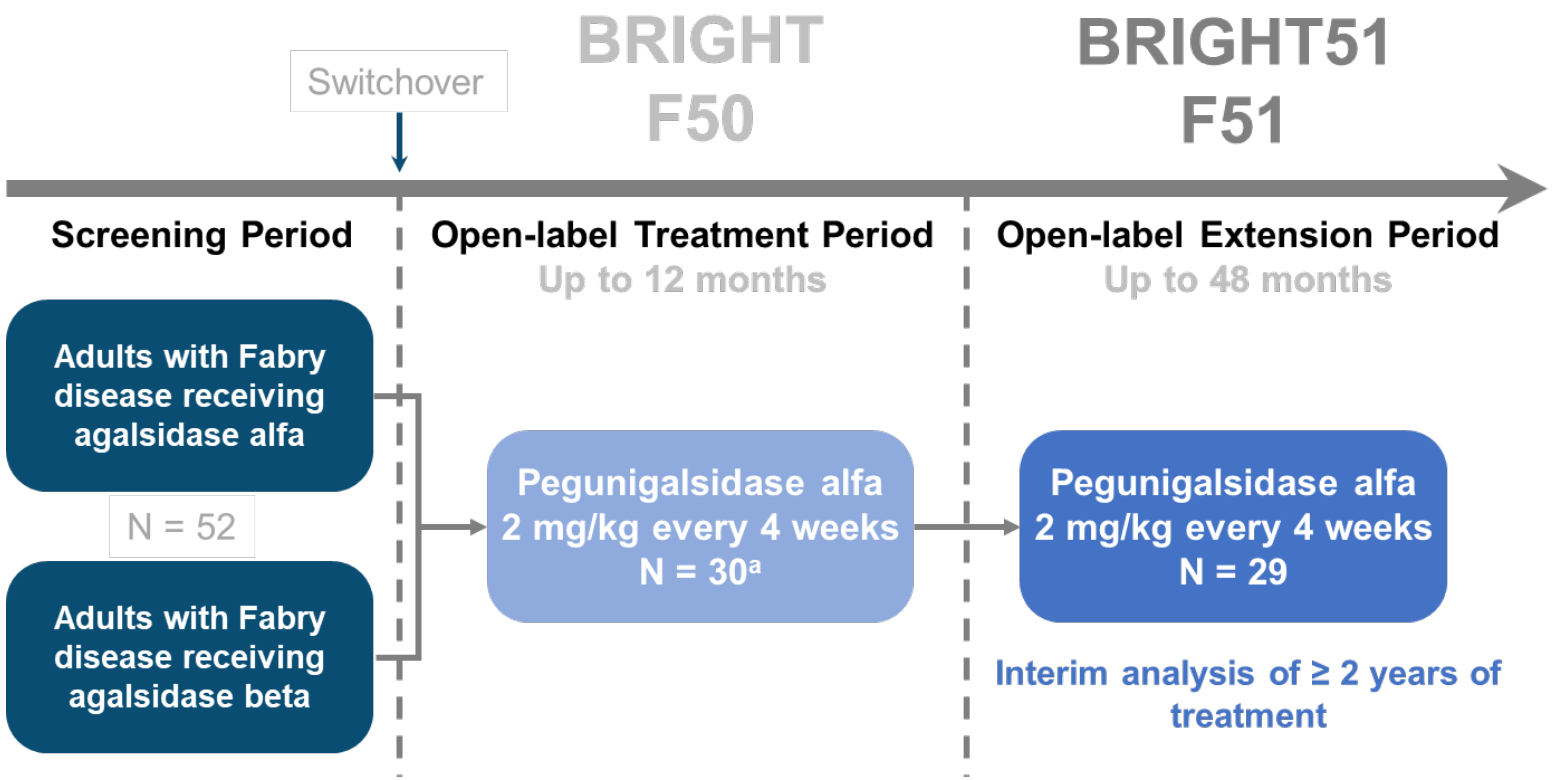
Background and objective

- **Pegunigalsidase alfa 2 mg/kg every 4 weeks** was initially investigated in the 1-year BRIGHT[a] study, and is currently being evaluated in the open-label extension study BRIGHT51[b]
- Results from **BRIGHT** showed that patients with Fabry disease receiving ERT every 2 weeks can be successfully transitioned to pegunigalsidase alfa 2 mg/kg every 4 weeks:
  - Following the switch from existing ERTs administered every 2 weeks, **Fabry disease was stable throughout pegunigalsidase alfa administration every 4 weeks** for up to 12 months
  - **Positive safety profile for up to 12 months** – mild to moderate TEAEs and IRRs with the majority resolved by end of study; no patients developed de novo ADAs

Objective of BRIGHT51: evaluate the long-term safety and efficacy of 2 mg/kg pegunigalsidase alfa administered once every 4 weeks for ≥ 2 years in adults with Fabry disease, who previously received agalsidase alfa or agalsidase beta every 2 weeks

[a]BRIGHT (F50; NCT03180840).
[b]BRIGHT51 (F51; NCT03614234).
ADA, antidrug antibody; ERT, enzyme replacement therapy; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.

Study design



Main inclusion criteria

- Completed the BRIGHT study
- Adults with Fabry disease previously treated with other ERTs for ≥ 3 years and on a stable dose (> 80% labeled dose/kg) for ≥ 6 months
- Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73m^2[b]
- Availability of at least 3 historical serum creatinine evaluations no more than 2 years old

Main exclusion criteria

- eGFR slope more negative than or equal to -2 mL/min/1.73m^2/year based on ≥ 4 serum creatinine values over approximately 2 years

[a]The patient who did not complete the study withdrew due to a major traffic accident unrelated to Fabry disease.
[b]There was no upper eGFR limit considered for study exclusion.
eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy.

Main study endpoints

Safety Endpoints

- Treatment-emergent adverse events (TEAEs)[a] including:
  - Treatment-related adverse events[b]
  - Infusion-related reactions (IRRs)[c]
- Development of antidrug antibodies (ADAs)

Efficacy Endpoints

- Change in eGFR[d]
- Annualized change in eGFR (eGFR slope)
- Change in plasma globotriaosylsphingosine (lyso-Gb3) concentration

[a]A TEAE was any AE occurring after start of study treatment and within the time of residual drug effect (30 days after last administration of study medication); or a pre-treatment adverse event or pre-existing medical condition that worsened in intensity after start of study treatment and within the time of residual drug effect.
[b]Related TEAEs include events which are possibly, probably, or definitely related to study treatment.
[c]IRRs were defined as TEAEs that occurred during the infusion or within 2 hours after its completion.
[d]eGFR was calculated using the CKD-EPI equation; units are mL/min/1.73m^2.
ADA, antidrug antibody; CKD-EPI, Chronic Kidney Disease – Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IRR, infusion-related reaction; lyso-Gb3, globotriaosylsphingosine; TEAE, treatment-emergent adverse event.

Baseline characteristics and demographics at the start of BRIGHT

- **29 out of 30 adults completed BRIGHT and are currently undergoing treatment in BRIGHT51**
  - 27 patients are receiving pegunigalsidase alfa 2 mg/kg every 4 weeks
  - 2 patients on pegunigalsidase alfa 2 mg/kg every 4 weeks moved to pegunigalsidase alfa 1 mg/kg every 2 weeks due to either deterioration of kidney function[a] or increased pain crisis[b]
- At interim analysis, mean pegunigalsidase alfa exposure was 38.3 (range: 25.3–44.8) months

Parameter	Male Patients n = 23	Female Patients n = 6	Overall N = 29
Age (years), mean (SD)	39.8 (12.2)	45.2 (5.3)	40.9 (11.3)
Previous ERT, n (%)			
Agalsidase alfa	5 (21.7)	2 (33.3)	7 (24.1)
Agalsidase beta	18 (78.3)	4 (66.7)	22 (75.9)
eGFR mL/min/1.73m^2			
Mean (SE)	100.7 (5.0)	94.7 (6.8)	99.4 (4.2)
Median (min;max)	102.3 (30.3;135.9)	100.4 (61.7;106.1)	102.1 (30.3;135.9)
eGFR slope mL/min/1.73m^2/year			
Mean (SE)	-1.2 (0.7)	-4.2 (1.9)	-1.8 (0.7)
Median (min;max)	-0.6 (-10.5;3.6)	-3.1 (-13.6;-0.5)	-1.1 (-13.6;3.6)
Plasma lyso-Gb3 (nM)			
Mean (SE)	23.3 (3.8)	4.4 (1.0)	19.4 (3.4)
Median (min;max)	17.2 (0.5;75.1)	4.4 (0.7;7.8)	14.5 (0.5;75.1)

[a]1 patient was switched at week 40 during BRIGHT due to deterioration of kidney function and continued the 1 mg/kg every 2 weeks regimen during BRIGHT51.
[b]1 patient was switched at week 84 during BRIGHT51 due to increased pain crisis, with increasing pain on average from week 0 to weeks 24 and 52, and overall increased pain interference.
eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; lyso-Gb3, globotriaosylsphingosine; nM, nanomolar (nmol/L); SD, standard deviation; SE, standard error.

Incidence of treatment-emergent adverse events

- All serious TEAEs were considered unrelated to study treatment, and no TEAEs led to death or study withdrawal
- **All treatment-related TEAEs were mild/moderate in severity,** non-serious, and were resolved or resolving at the interim analysis cutoff date (08 August 2021)
  - Of the 46 treatment-related TEAEs, 38 were IRRs

Parameter	Male Patients n = 23		Female Patients n = 6		Overall N = 29	
	Patient, n (%)	Event, n	Patients, n (%)	Event, n	Patients, n (%)	Event, n
≥ 1 TEAE	22 (95.7)	303	5 (83.3)	36	27 (93.1)	339
≥ 1 mild or moderate TEAE	22 (95.7)	296	5 (83.3)	36	27 (93.1)	332
≥ 1 severe TEAE[a]	3 (13.0)	7	0 (0.0)	0	3 (10.3)	7
≥ 1 serious TEAE[b]	5 (21.7)	7	0 (0.0)	0	5 (17.2)	7
≥ 1 related TEAE[c]	9 (39.1)	43	2 (33.3)	3	11 (37.9)	46
≥ 1 related mild or moderate TEAE[a]	9 (39.1)	43	2 (33.3)	3	11 (37.9)	46

[a]The "severe" category also includes events classified as "very severe" (grade 4) or fatal (grade 5) according to the Common Terminology Criteria for Adverse Events classification.
[b]Serious TEAEs included pain, pyrexia, musculoskeletal chest pain, overdose, ileus, peritonitis bacterial, and hypoesthesia oral.
[c]Related TEAEs include events which are possibly, probably, or definitely related to study treatment.
IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.

Infusion-related reactions

- Of the 46 treatment-related TEAEs, **38 were IRRs and were experienced only by male patients** (n = 6; 20.7%)
  - 5 of these 6 patients were previously treated with agalsidase beta; 4 of those 5 were positive for anti-pegunigalsidase alfa ADAs at baseline

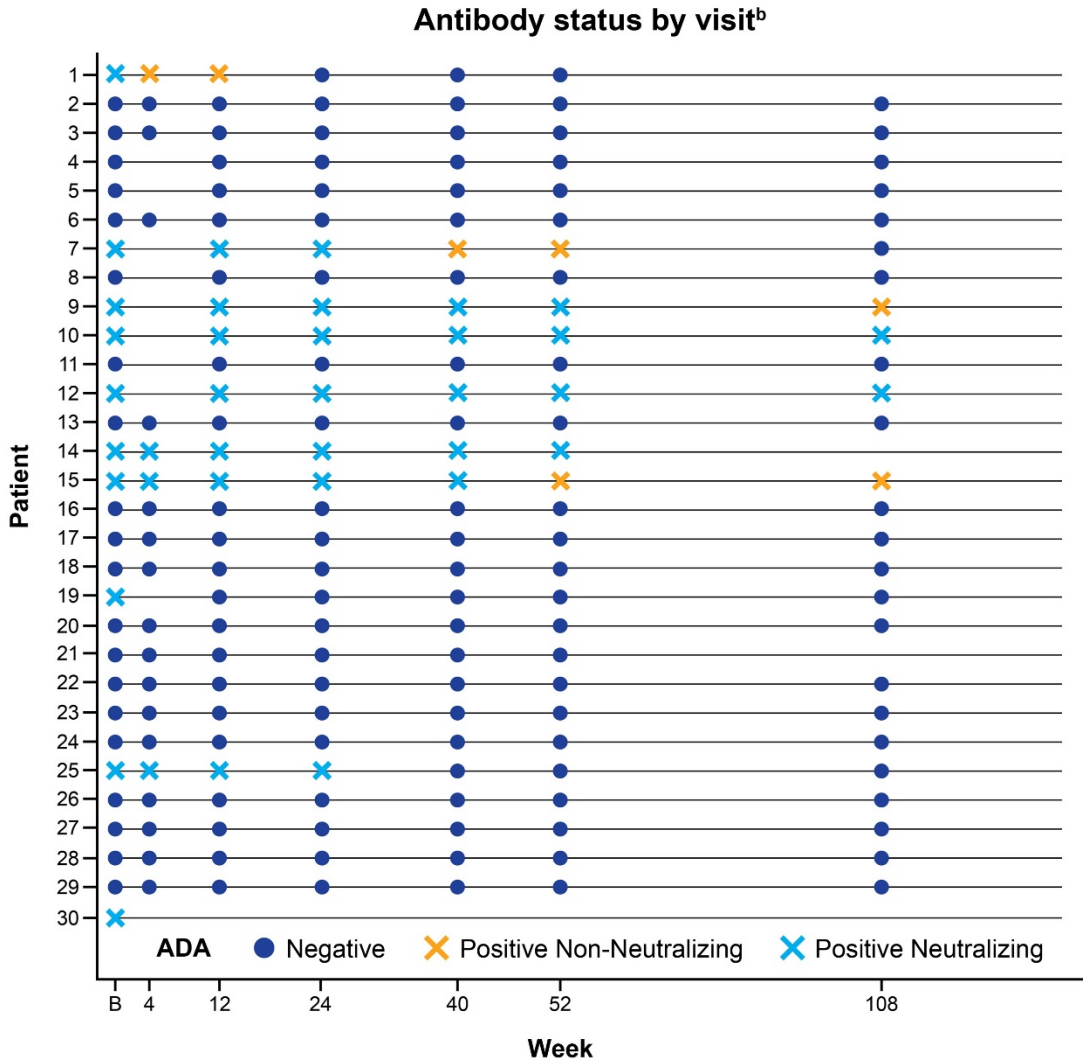
- **All IRRs were non-serious**, mild/moderate in severity, and all except 1 event[a] resolved before the cutoff date

	Overall N = 29		
	Patients n (%)	Events n	Number of Infusions[b]
≥ 1 IRR[c]	6 (20.7)	38	31
≥ 1 mild or moderate IRR	6 (20.7)	38	31

[a]Increased systolic blood pressure during infusion: blood pressure was also high during several subsequent infusions, and blood pressure between infusions was not recorded.
[b]The number of infusions associated with at least 1 IRR for each category.
[c]IRRs were defined as TEAEs occurring during the infusion or shortly after its completion with causality that was definitely, probably, or possibly related (excluding those TEAEs defined as injection site reactions).
ADA, antidrug antibody; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.

Development of antidrug antibodies

- Only patients with pre-existing IgG antibodies were positive for ADAs to pegunigalsidase alfa during the study (n = 10[a]), all of whom had previously received agalsidase beta
- **No patients developed de novo ADAs following the switch to pegunigalsidase alfa treatment**
- The proportion of patients positive for ADAs decreased over time
- At most timepoints where ADAs were observed, patients also had neutralizing activity
- All patients tested negative for antibodies to the plant glycans or PEG moieties of pegunigalsidase alfa throughout the duration of the study

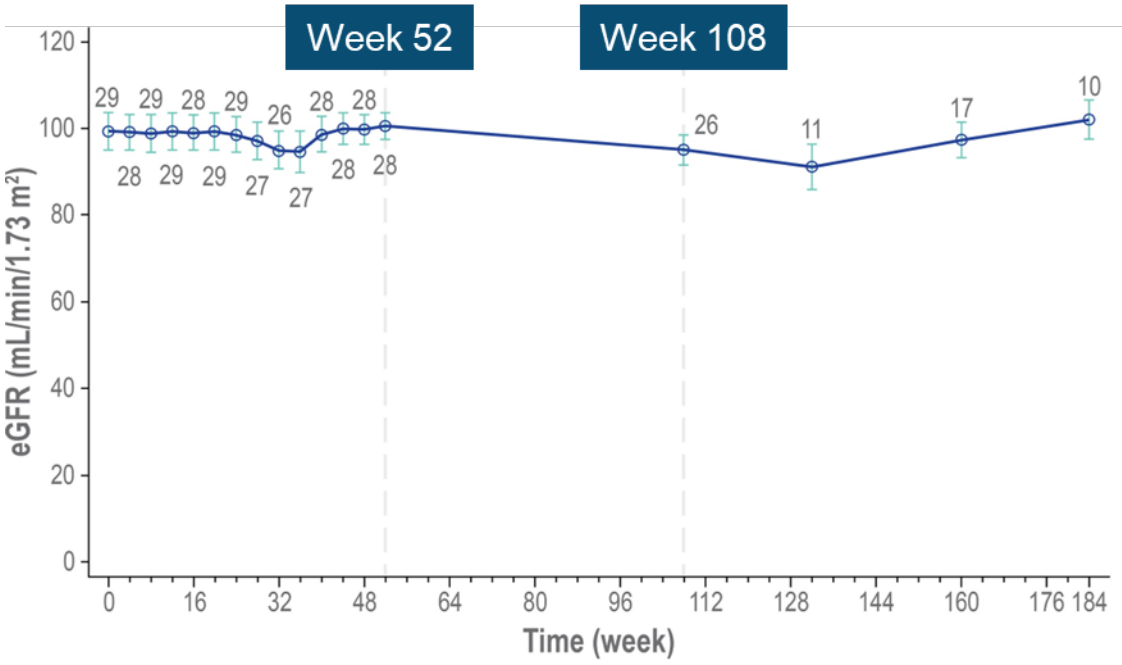


[a]One patient who was ADA positive at baseline withdrew consent after the first infusion and no ADA data is available for this patient post-pegunigalsidase alfa treatment.
[b]Each line represents an individual patient.
ADA, antidrug antibody; B, baseline; IgG, immunoglobulin G.

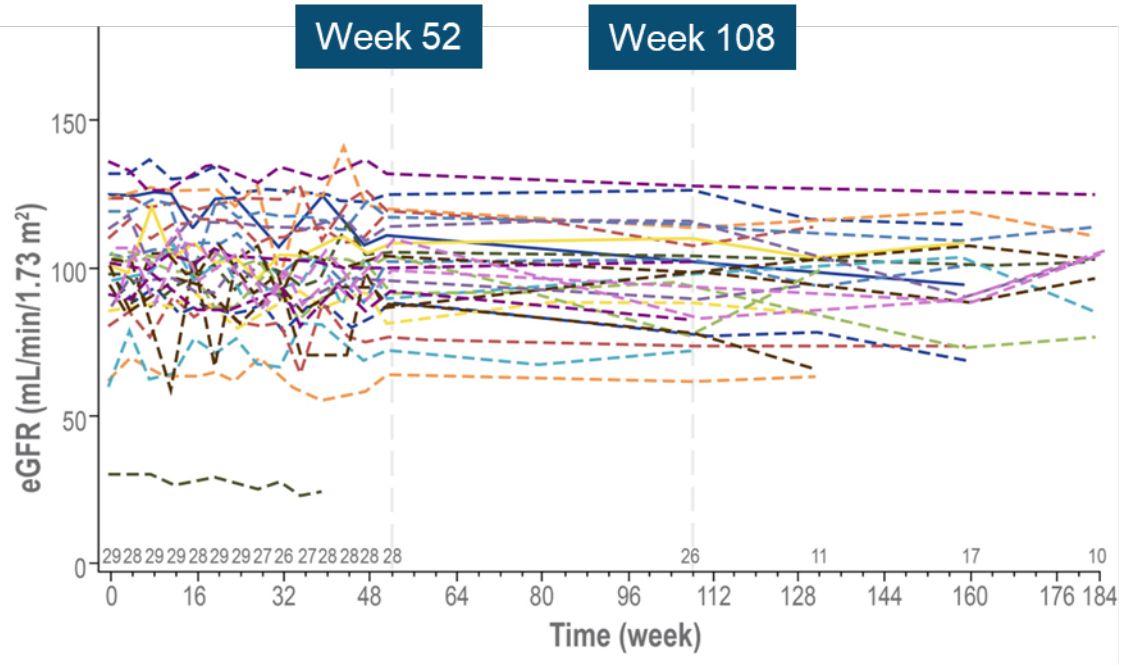
Mean eGFR during treatment

- Week 108 (~2 years of pegunigalsidase alfa treatment; n = 26): eGFR had a mean (SE; median) change from baseline of -5.10 (1.96; -4.23) mL/min/1.73m^2
  - **Annualized eGFR slope:** -2.77 mL/min/1.73m^2/year

Mean eGFR values over time



Individual eGFR values[a]

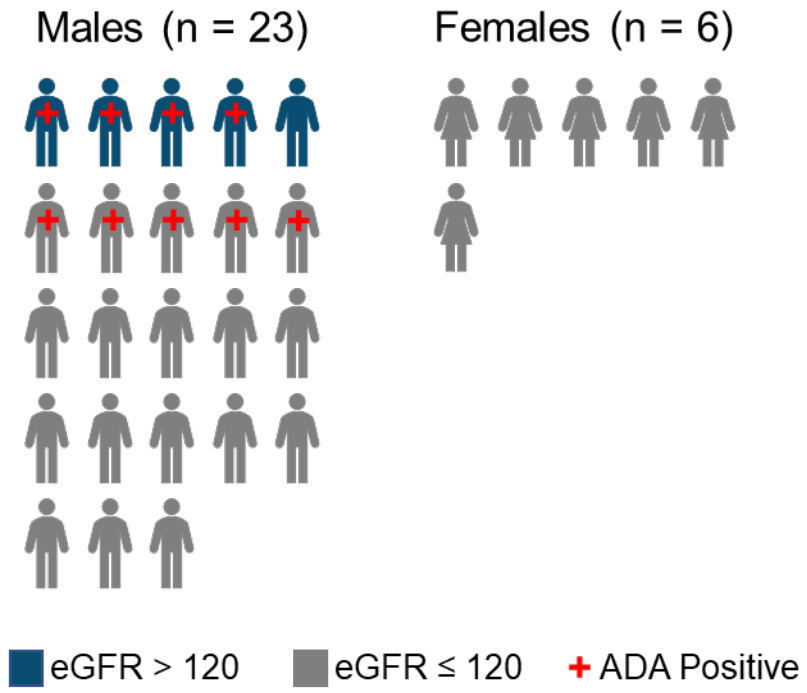


[a]Each line represents an individual patient.
eGFR, estimated glomerular filtration rate; SE, standard error.

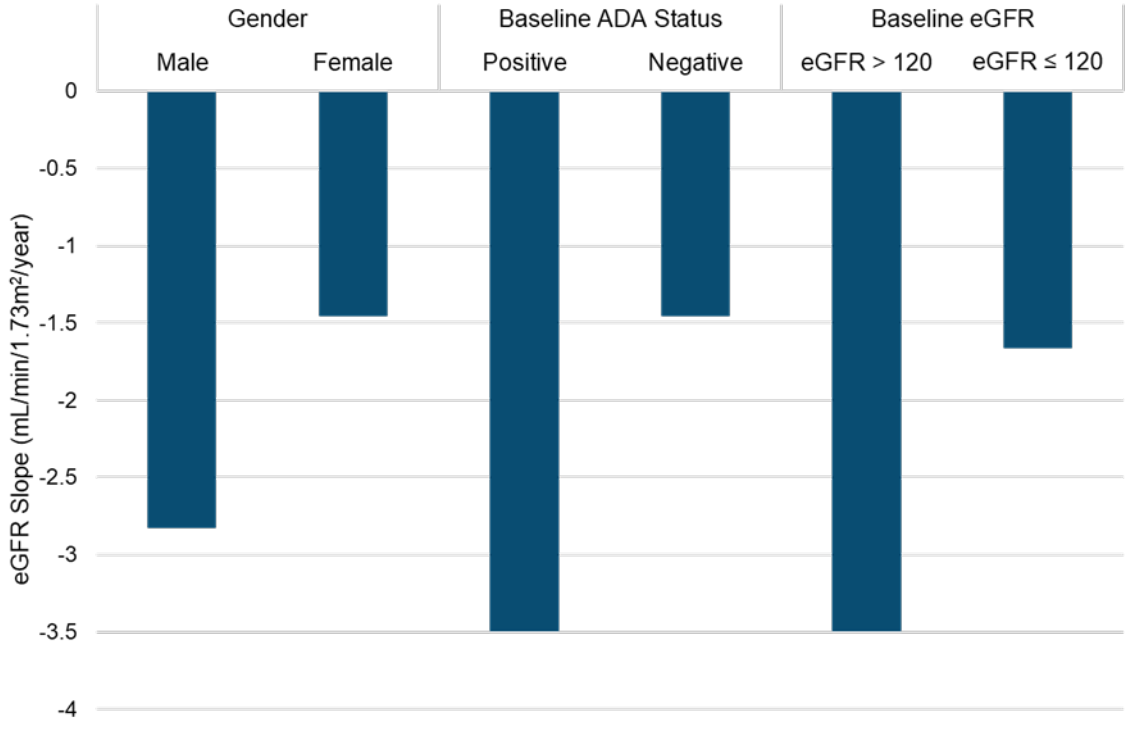
Annualized eGFR slope during treatment

- Median (min; max) eGFR annualized slope during treatment was -2.47 (-8.7; 1.4) mL/min/1.73m^2/year
  - **Males:** -2.82 (-8.7; 1.4) mL/min/1.73m^2/year
  - **Females:** -1.45 (-6.5; 1.4) mL/min/1.73m^2/year

Patient Subgroups



Median eGFR slope during treatment (mL/min/1.73m^2/year)



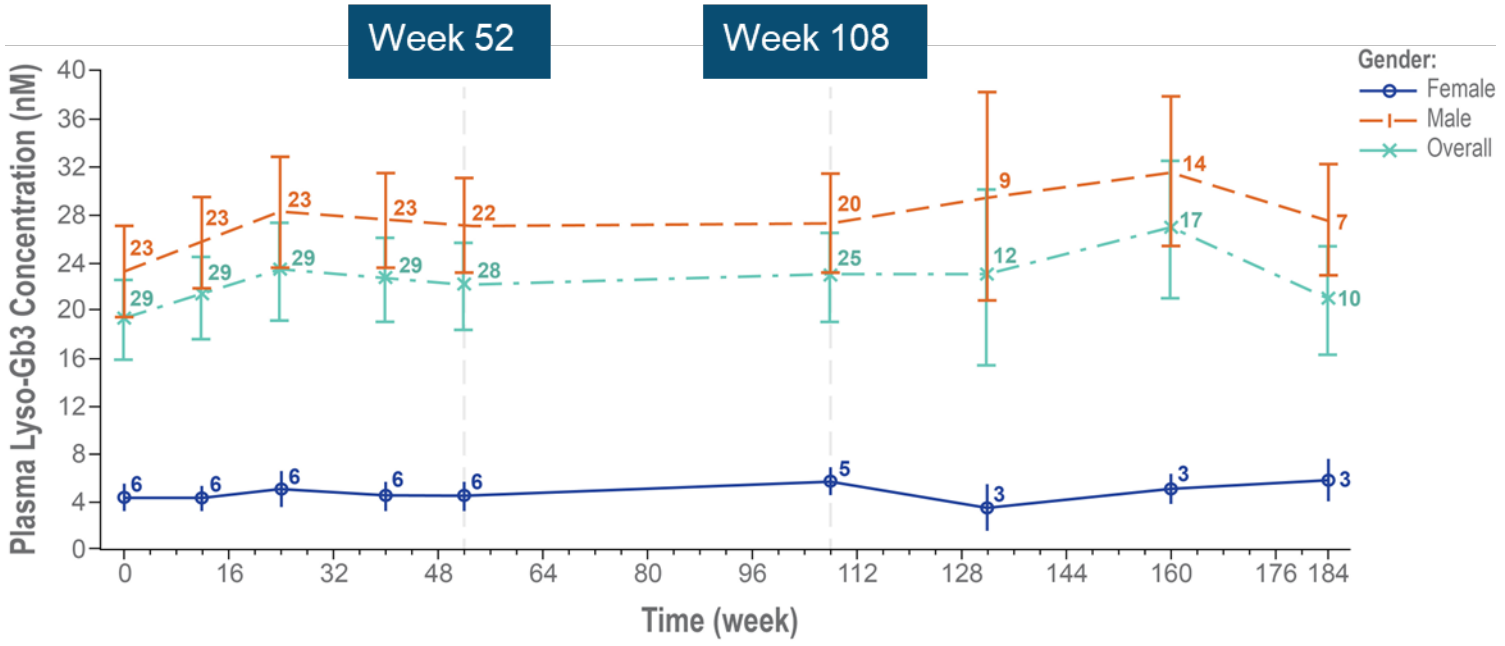
	Male	Female	ADA+	ADA-	eGFR > 120	eGFR ≤ 120
Median (min;max)	-2.82 (-8.7;1.4)	-1.45 (-6.5;1.4)	-3.49 (-8.7;1)	-1.45 (-8.5;1.4)	-3.49 (-7.9;-1.2)	-1.66 (-8.7;1.4)

ADA, antidrug antibody; eGFR, estimated glomerular filtration rate; SE, standard error.

Plasma lyso-Gb3 concentration

- **Plasma lyso-Gb3 concentrations were relatively stable throughout the study**:
  - Baseline (n = 29) mean (SE) values were 19.36 nM (3.35 nM) compared with 22.98 nM (3.72 nM) at Week 108 (n = 26)
- Most patients (84.0%) had a change of < 10 nM in plasma lyso-Gb3 concentration at Week 108
  - Increases > 10 nM from baseline were observed in 4 male patients (3 of whom were ADA positive) who had been previously treated with agalsidase beta
- Mean (SE) plasma lyso-Gb3 concentrations at Week 108 were higher in males (27.30 [4.11] nM) vs females (5.74 [1.07] nM)

Mean plasma lyso-Gb3 concentration over time overall and by gender



	Baseline	Week 108
Median (nM) (min; max)	14.50 (0.5; 75.1)	20.40 (0.8; 68.2)

ADA, antidrug antibody; lyso-Gb3, globotriaosylsphingosine; nM, nanomolar (nmol/L); SE, standard error.

Conclusions

- The **switch from previous ERTs to 2 mg/kg pegunigalsidase alfa every 4 weeks had a favorable safety and tolerability profile over ≥ 2 years**, with no patients developing de novo ADAs, and some patients becoming ADA negative over time
- Pre-existing ADAs could have a potential impact on the overall eGFR and eGFR slope results
  - All patients with ADAs were previously treated with agalsidase beta and had ADAs at baseline
- The ongoing BRIGHT51 study shows that pegunigalsidase alfa 2 mg/kg administration every 4 weeks is effective and safe in adults with Fabry disease
  - With the reduction of infusion administration frequency, there is a possibility of improving patient quality of life and reducing treatment burden, subsequently increasing patient compliance

Long-term safety and efficacy of pegunigalsidase alfa 2 mg/kg every 4 weeks in patients with Fabry disease will be further confirmed and evaluated in the ongoing BRIGHT51 extension study

ADA, antidrug antibody; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy.

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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