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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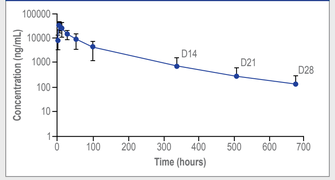
Introduction

- Fabry disease is a rare X-linked disorder caused by deficiency of lysosomal enzyme alpha-galactosidase-A (α-Gal-A), causing accumulation of sphingolipids, such as globotriaosylceramide (Gb3) and globotriaosylsphingosine (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 (E2W)[4,5]
- Pegunigalsidase alfa, a novel PEGylated recombinant α-Gal-A enzyme in development for Fabry disease, has an increased 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
  - Measurable levels of pegunigalsidase alfa were detected in plasma throughout a 4-week infusion interval (**Figure 1**)

Figure 1. Pegunigalsidase Alfa (2 mg/kg) Concentration Over Time



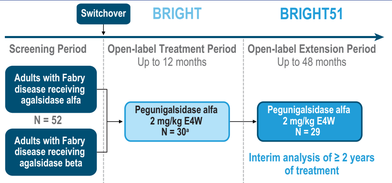
- Pegunigalsidase alfa 2 mg/kg every 4 weeks (E4W) was initially investigated in the 1-year BRIGHT study (F50; NCT03180840), and is currently being evaluated in the open-label extension study BRIGHT51 (F51; NCT03614234)
- Results from BRIGHT showed that patients with Fabry disease receiving ERT E2W can be successfully transitioned to pegunigalsidase alfa 2 mg/kg E4W:
  - Following the switch from existing ERTs administered E2W, Fabry disease was stable throughout pegunigalsidase alfa administration E4W for up to 12 months
  - Positive safety profile for up to 12 months – mild to moderate treatment-emergent adverse events (TEAEs) and infusion-related reactions (IRRs) with the majority resolved by end of study; no patients developed de novo antidrug antibodies (ADAs)

Objective

- Evaluate the long-term safety and efficacy of 2 mg/kg pegunigalsidase alfa administered once E4W for ≥ 2 years in adults with Fabry disease, who previously received agalsidase alfa or agalsidase beta E2W

Methods

Figure 2. Study Design



[a]The patient who did not complete the study withdrew due to a major traffic accident unrelated to Fabry disease.
E4W, every 4 weeks.

Figure 3. Study Inclusion and Exclusion Criteria[a]

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/1.73m²[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/1.73m²/year based on ≥ 4 serum creatinine values over approximately 2 years

[a]Criteria for baseline patient characteristics are only for BRIGHT.
[b]There was no upper eGFR limit considered for study exclusion.
eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy

Results

- 29 out of 30 adults completed BRIGHT and are currently undergoing treatment in BRIGHT51 (**Table 1**)
  - 27 patients are receiving pegunigalsidase alfa 2 mg/kg E4W
  - 2 patients on pegunigalsidase alfa 2 mg/kg E4W moved to pegunigalsidase alfa 1 mg/kg E2W due to either deterioration of kidney function (patient switched at Week 40 during BRIGHT and continued during BRIGHT51) or increased pain crisis (patient switched at Week 84 during BRIGHT51 and had increasing pain on average from Week 0 to Weeks 24 and 52, and overall increased pain interference); efficacy data after moving to 1 mg/kg pegunigalsidase alfa is not included in this interim analysis
- At interim analysis, mean pegunigalsidase alfa exposure was 38.3 (range: 25.3–44.8) months

Table 1. Patient Characteristics and Demographics at Baseline

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)
ADA+, n (%)	9 (39.1)	0 (0)	9 (39.1)
eGFR mL/min/1.73m²			
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/1.73m²/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)

ADA, antidrug antibody; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; lyso-Gb3, globotriaosylsphingosine; nM, nanomolar (nmol/L); SD, standard deviation; SE, standard error.

Safety

- All serious TEAEs were considered unrelated to study treatment, and no TEAEs led to death or study withdrawal (**Table 2**)
- All treatment-related TEAEs were mild/moderate in severity, non-serious, and were resolved or resolving at the interim analysis (08 August 2021)

Table 2. Incidence of Treatment-emergent Adverse Events

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

[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]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.
[c]Serious TEAEs included pain, pyrexia, musculoskeletal chest pain, overdose, ileus, peritonitis bacterial, and hypoesthesia oral.
[d]Related TEAEs include events which are possibly, probably, or definitely related to study treatment.
TEAE, treatment-emergent adverse event.

- 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 resolved before the cutoff date (**Table 3**)
  - The 1 unresolved event was due to increased systolic blood pressure during infusion; blood pressure was also high during several subsequent infusions, and blood pressure between infusions was not recorded

Table 3. Infusion-related Reactions

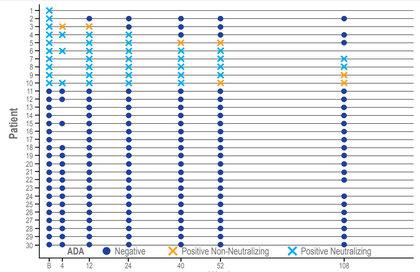
Parameter	Overall N = 29		
	Patients, n (%)	Events, n	Number of Infusions[a]
IRR[b]	6 (20.7)	38	31
Mild or moderate IRR	6 (20.7)	38	31

[a]The number of infusions associated with at least 1 IRR for each category.
[b]IRRs were defined as TEAEs occurring during the infusion or within 2 hours of 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), all of whom had previously received agalsidase beta (**Figure 4**)
  - 1 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

Figure 4. Antibody Status by Visit



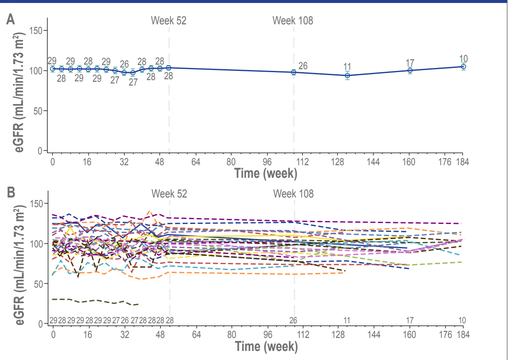
Each line represents an individual patient.
ADA, antidrug antibody; B, baseline; IgG, immunoglobulin G.

- 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

Change in eGFR during treatment

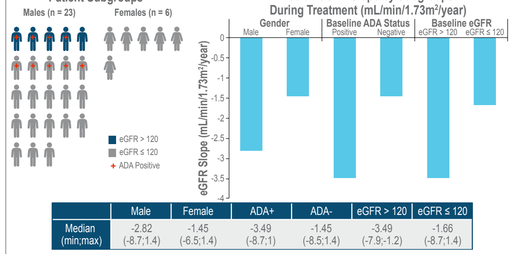
- Week 108 (~2 years of pegunigalsidase alfa treatment; n = 26): eGFR had a mean (SE; median) change from baseline of -5.10 (1.96; -4.23) mL/min/1.73m² (**Figure 5**)
  - Mean annualized eGFR slope: -2.77 mL/min/1.73m²/year
- Median (min; max) annualized eGFR slope during treatment was -2.47 (-8.7; 1.4) mL/min/1.73m²/year (**Figure 6**)
  - Males: -2.82 (-8.7; 1.4) mL/min/1.73m²/year
  - Females: -1.45 (-6.5; 1.4) mL/min/1.73m²/year
- Following the switch to pegunigalsidase alfa, median annualized eGFR slope was more negative in ADA positive patients, indicating that pre-exisiting ADAs can have an impact on the rate of eGFR decline

Figure 5. Mean (A) and Individual (B) eGFR Values Over Time



eGFR was calculated using the CKD-EPI equation; units are mL/min/1.73m². Numbers on each graph indicate the patient n value at each timepoint, which decreases after Week 108. Each line on Panel B represents an individual patient.
CKD-EPI, Chronic Kidney Disease - Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; SE, standard error.

Figure 6. Annualized eGFR Slope During Treatment



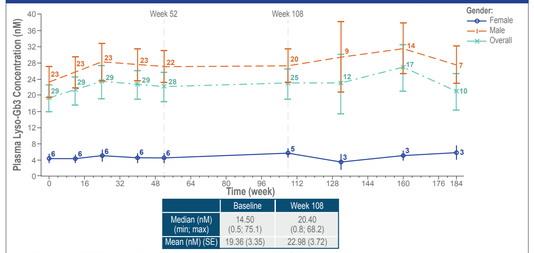
	Male	Female	ADA+	ADA-	eGFR > 120	eGFR ≤ 120
Median (min;max)	-2.82 (-8.7;1.4)	-1.45 (-6.5;1.4)	-3.49 (-8.7;1)	-1.45 (-8.5;1.4)	-3.49 (-7.9;-1.2)	-1.66 (-8.7;1.4)

ADA, antidrug antibody; eGFR, estimated glomerular filtration rate.

Plasma lyso-Gb3 concentration

- Plasma lyso-Gb3 concentrations were relatively stable throughout the study (**Figure 7**):
  - 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)
  - Baseline (n = 29) median (min; max) values were 14.50 nM (0.5 nM; 75.1 nM) compared with 20.40 nM (0.8 nM; 68.2 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)

Figure 7. 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)
Mean (nM) (SE)	19.36 (3.35)	22.98 (3.72)

Numbers on the graph indicate the patient n value at each timepoint, which decreases after Week 108.
Lyso-Gb3, globotriaosylsphingosine; nM, nanomolar (nmol/L); SE, standard error.

Conclusions

- The switch from previous ERTs to 2 mg/kg pegunigalsidase alfa E4W 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
- This interim analysis of the ongoing BRIGHT51 study shows that long-term pegunigalsidase alfa 2 mg/kg administration E4W 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 E4W in patients with Fabry disease will be further confirmed and evaluated when the ongoing BRIGHT51 extension study is completed

References

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.

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