Safety and Efficacy of Pegunigalsidase Alfa Administered Every 4 Weeks in Patients with Fabry Disease: Results from the Phase 3, Open-label, BRIGHT Study

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Introduction

- Fabry disease is a rare genetic disorder caused by an X-linked deficiency of the lysosomal enzyme α-galactosidase A (α-Gal A)[1–3]
- Deficiency of α-Gal A leads to accumulation of potentially harmful sphingolipids, including globotriaosylceramide (Gb3), and its metabolite, globotriaosylsphingosine (lyso-Gb3),[4–6] resulting in debilitating organ dysfunction that primarily affects the kidneys, heart, and nervous system[4]
- Pegunigalsidase alfa is a novel, PEGylated, α-Gal A enzyme in development for the treatment of patients with Fabry disease, that has an increased half-life (approximately 80 hours) compared with current enzyme replacement therapies (ERTs; half-lives of approximately ≤ 2 hours)[7–9]
- The increased stability of pegunigalsidase alfa and its prolonged half-life may allow the interval between infusions to be extended from the 2 weeks required by current ERTs, to 4 weeks—thereby decreasing treatment burden for patients with Fabry disease

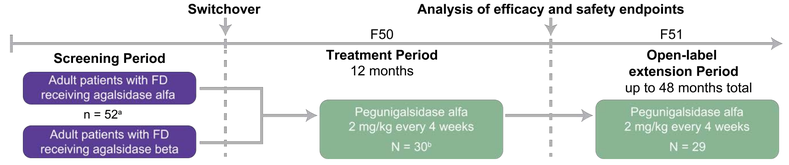
Objective

- To evaluate the safety and efficacy of pegunigalsidase alfa 2.0 mg/kg administered once every 4 weeks for 1 year to patients with Fabry disease who have previously received a licenced ERT

Methods

- Eligible patients with Fabry disease were enrolled at 14 sites in 7 countries to this phase 3 open-label, switch-over study (parent study [“F50”], NCT03180840; extension study [“F51”], NCT03614234) of pegunigalsidase alfa (**Figure 1**)
  - Patients had to have received treatment with agalsidase alfa or agalsidase beta for at least 3 years and to have been on a stable dose (> 80% labeled dose/kg) during the preceding 6 months prior to study entry

Figure 1. BRIGHT Study Design



[a]Patients with a linear negative eGFR slope of ≥ 2 mL/min/1.73 m²/year were excluded.
[b]The patient who did not complete the study withdrew due to a major traffic accident unrelated to Fabry disease.
FD, Fabry disease.

Study endpoints

- The safety endpoint included treatment-emergent adverse events (TEAEs), including treatment-related AEs
- Efficacy endpoints included changes in estimated glomerular filtration rate (eGFR) and plasma lyso-Gb3 concentration

Results

- Most patients had been treated with agalsidase beta prior to enrollment (**Table 1**)
- Classic Fabry disease was reported for 16 (72.7%) men; while nonclassic Fabry disease was reported for 6 (27.3%) men and 6 (100%) women

Table 1. Baseline Characteristics

Parameter	Men (n = 24)	Women (n = 6)	All (N = 30)
Age, years, mean (SD)	39.3 (12.2)	45.2 (5.3)	40.5 (11.3)
Previous ERT, n (%)			
Agalsidase alfa	5 (20.8)	2 (33.3)	7 (23.3)
Agalsidase beta	19 (79.2)	4 (66.7)	23 (76.7)

ERT, enzyme replacement therapy; SD, standard deviation.

Safety

- Overall, 33 of 183 total TEAEs (reported in 9 [30.0%] patients) were considered treatment related (**Table 2**)
  - All treatment-related TEAEs were mild or moderate in severity and the majority were resolved at the end of the study
    - Most patients (7/9) with treatment-related TEAEs were men
    - Of the treatment-related TEAEs, 27 were infusion-related reactions (IRRs) and the remainder included, but were not limited to, single events of diarrhea, erythema, fatigue, influenza-like illness, urine protein:creatinine ratio increased, and urine positive for white blood cells
  - No TEAEs led to death or study withdrawal, and no Fabry Clinical Events (Hopkin 2016)[3] were recognized or occurred
  - Two men experienced severe TEAEs, and 2 men experienced serious TEAEs; all events were considered unrelated to study treatment

Table 2. Summary of TEAEs by Sex and Overall

Parameter	Men (n = 24)		Women (n = 6)		All (N = 30)	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n
At least 1 TEAE	22 (91.7)	165	5 (83.3)	18	27 (90.0)	183
At least 1 mild or moderate TEAE	22 (91.7)	162	5 (83.3)	18	27 (90.0)	180
At least 1 severe TEAE[a,b]	2 (8.3)	3	0	0	2 (6.7)	3
At least 1 serious TEAE	2 (8.3)	2	0	0	2 (6.7)	2
At least 1 nonserious TEAE	22 (91.7)	163	5 (83.3)	18	27 (90.0)	181
At least 1 related TEAE[c]	7 (29.2)	30	2 (33.3)	3	9 (30.0)	33
At least 1 related mild or moderate TEAE[c]	7 (29.2)	30	2 (33.3)	3	9 (30.0)	33

TEAE, treatment-emergent adverse event.
[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 classifications.
[b]A total of 3 TEAEs in 2 men were severe; none were considered related to study treatment (pyrexia and infusion-related reactions in the same patient, and a road traffic accident in 1 patient who withdrew from the study).
[c]Related TEAEs include events which are possibly, probably, or definitely, related to study treatment.

- There were 27 IRRs reported in 5 (16.7%) patients, all men
  - Of these 5 patients, 4 were positive for antidrug antibodies (ADAs) against agalsidase beta at baseline and had previously received agalsidase beta; the 5th patient was previously on agalsidase alfa and negative for ADAs at all timepoints
  - All IRRs occurred during the infusion or within 2 hours postinfusion; no events were recorded that occurred between 2 and 24 hours postinfusion
- All IRRs were nonserious, mild (17 events in 3 [10.0%] patients) or moderate (10 events in 5 [16.7%] patients) in severity, and all resolved

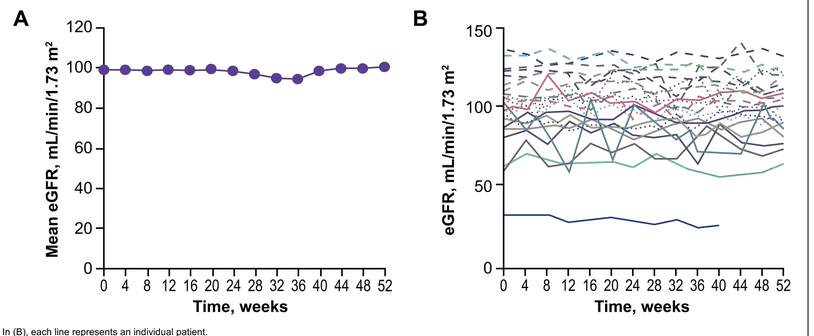
Antidrug antibodies (ADA)

- There were no cases of de novo ADAs reported
- All patients tested negative for antibodies to the plant glycans or PEG moieties of pegunigalsidase alfa at all timepoints during the study
- Only patients with pre-existing IgG antibodies were positive for anti-pegunigalsidase alfa antibodies
- Eleven male patients had pre-existing ADAs to agalsidase beta, 10 of whom had ADAs against pegunigalsidase alfa at baseline
  - Of these, 6 remained ADA positive until the end of study, 2 became ADA negative during the study, 1 was ADA negative at all subsequent timepoints after the baseline visit, and 1 withdrew consent after the baseline visit
- At most timepoints where ADAs were observed, patients generally also had neutralizing activity and antibodies targeting the non-PEGylated enzyme moiety

Efficacy

- During the 52-week treatment period, absolute eGFR values were stable, with a mean (standard error [SE]) change from baseline of −1.3 (1.4) mL/min/1.73 m² (**Figure 2A** and **2B**)
  - The mean (SE) eGFR annualized slope, calculated at the end of the study, was −2.9 (1.1) mL/min/1.73 m²/y for the overall population and −1.5 (1.1) mL/min/1.73 m²/year for the ADA-negative subgroup (n = 20), indicating stability

Figure 2. eGFR Values Over Time for (A) Average and (B) Individual



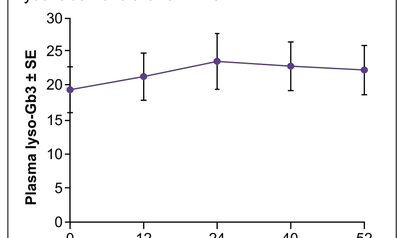
In (B), each line represents an individual patient.
eGFR, estimated glomerular filtration rate.

- Plasma lyso-Gb3 concentrations were stable throughout the study, with a mean (SE) concentration of 19.4 (3.4) nM at baseline and 22.2 (3.6) nM at week 52 (**Figure 3**)
  - Baseline plasma lyso-Gb3 concentrations were higher in men compared with women, with mean (SD) values of 23.3 (18.3) nM versus 4.4 (2.5) nM, respectively

Infusion duration

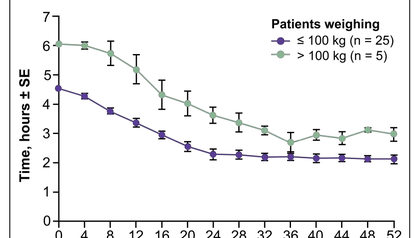
- Infusion duration generally decreased to the target time (ie, 2 hours for patients weighing ≤ 100 kg and 3 hours for patients weighing > 100 kg) from baseline to 52 weeks, based on the tolerability of the infusions (**Figure 4**)
  - Mean (SE) infusion duration times from baseline to week 52:
    - Patients ≤ 100 kg: 4.54 (0.03) to 2.12 (0.13) hours
    - Patients > 100 kg: 6.05 (0.01) to 2.97 (0.24) hours
  - Reduction of infusion duration indicated good drug tolerability

Figure 3. Mean Change From Baseline in Plasma Lyso-Gb3 Levels Over Time



Lyso-Gb3, globotriaosylsphingosine; SE, standard error.

Figure 4. Mean Infusion Duration by Weight



SE, standard error.

Conclusions

- Patients with Fabry disease who switched from their current ERT (agalsidase alfa or agalsidase beta) to pegunigalsidase alfa had an acceptable safety and tolerability profile and no de novo ADAs were reported
- Fabry disease was stable throughout pegunigalsidase alfa therapy
- Data suggests patients with Fabry disease who are currently receiving ERT every 2 weeks could be successfully transitioned to pegunigalsidase alfa 2.0 mg/kg every 4 weeks as an effective and safe alternative treatment option
- Additional evidence on dosing pegunigalsidase alfa every 4 weeks at reduced infusion durations in the first-line setting need to be confirmed from other long-term studies and larger sample sizes
- eGFR results and the impact of ADAs should be interpreted with caution until additional data becomes available from the ongoing open-label extension study and the characterization of risk factors in the subgroup of ADA-positive patients

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