Long-term Safety and Efficacy of Pegunigalsidase Alfa: A Multicenter Extension Study in Adult Patients with Fabry Disease

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Introduction

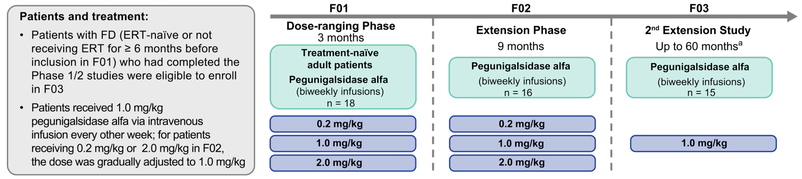
- Fabry disease (FD) is a rare, X-linked, lysosomal storage disorder caused by mutations in the gene encoding α-galactosidase (α-Gal)-A[1,2]
- Mutations associated with lower residual α-Gal-A enzyme activity lead to accumulation of increasingly toxic levels of glycosphingolipids, such as globotriaosylceramide (Gb3), and, ultimately, progressive end organ failure[1–3]
- Pegunigalsidase alfa is a novel PEGylated α-Gal-A enzyme replacement therapy (ERT) being developed for the treatment of FD[1,4]
- Pegunigalsidase alfa has enhanced bioavailability compared with available treatments, and published reports note favorable safety and efficacy for up to 12 months of treatment[1]
- Study F03 (NCT01981720) is the extension of two Phase 1/2 trials of pegunigalsidase alfa, with a combined treatment duration of up to 6 years

Objective

- To investigate the long-term (up to 6 years) safety, tolerability, and efficacy of pegunigalsidase alfa ERT in adults with FD

Study Design

Figure 1. Study Design



[a]The maximum overall duration of treatment with pegunigalsidase alfa was 72 months: 3 months in F01, 9 months in F02, and up to 60 months in F03. Planned evaluation visits occurred ± 6 days at Months 2 and 3, every 3 months to Month 24, then every 6 months to Month 60. A final visit occurred at 3 months after the last infusion (± 6 days).

Endpoints

- Safety endpoints:
  - Treatment-emergent adverse events (TEAEs): frequency, type, severity, and number of events, and infusion-related reactions (IRR)
  - Development of antidrug antibodies (ADAs) against pegunigalsidase alfa
- Main exploratory efficacy endpoints:
  - Plasma globotriaosylsphingosine (lyso-Gb3) concentrations
  - Plasma Gb3 concentrations
  - Kidney function, as measured by estimated glomerular filtration rate (eGFR) and annualized slope by CKD-EPI
  - Left ventricular mass (LVM) and LVM index (LVMI), as measured by cardiac magnetic resonance imaging (MRI)
  - Ejection fraction (EF), as measured by cardiac MRI
  - Myocardial fibrosis assessment, as measured by cardiac MRI

Baseline Characteristics

- As of the final database lock (August 5, 2021), the cumulative duration of treatment over the 3 studies was > 1 year for 15 patients (100.0%), ≥ 3 years for 11 patients (73.3%), and ≥ 5 years for 10 patients (66.7%)
- 10 Patients (6 men, 4 women; 66.7%) completed the F03 study and enrolled to a further extension study (F60)
  - 5 Patients (33.3%) discontinued the F03 study: 4 owing to withdrawal of consent and 1 death unrelated to study treatment (non-cardiac-related death following exacerbation of chronic obstructive pulmonary disorder)

Table 1. Baseline Characteristics at F01 Entry

Category	Duration of Treatment[a]		
	> 1 year	≥ 3 years	≥ 5 years
	n = 15	n = 11	n = 10
Median age, years (range)	32.0 (17–54)	33.0 (20–54)	30.5 (20–54)
Sex, n (%)			
Men	8 (53.3)	7 (63.6)	6 (60.0)
Women	7 (46.7)	4 (36.4)	4 (40.0)
Race, n (%)			
White	11 (73.3)	9 (81.8)	8 (80.0)
Black	3 (20.0)	1 (9.1)	1 (10.0)
Other[b]	1 (6.7)	1 (9.1)	1 (10.0)

[a]Treatment duration refers to the total duration in studies F01/F02/F03.
[b]Middle Eastern.

Results

Safety

Table 2. TEAEs

Category, n (%)	Duration of Treatment[a]					
	> 1 year		≥ 3 years		≥ 5 years	
	n = 15		n = 11		n = 10	
	Patients	Events	Patients	Events	Patients	Events
At least 1 TEAE	15 (100.0)	440	11 (100.0)	387	10 (100.0)	352
At least 1 mild or moderate TEAE[b]	15 (100.0)	429 (97.5)	11 (100.0)	376 (97.2)	10 (100.0)	342 (97.2)
At least 1 severe TEAE[b]	5 (33.3)	11 (2.5)	5 (45.5)	11 (2.8)	4 (40.0)	10 (2.8)
At least 1 SAE	3 (20.0)	4 (0.9)	3 (27.3)	4 (1.0)	2 (20.0)	2 (0.6)
At least 1 related TEAE[b]	9 (60.0)	59 (13.4)	6 (54.5)	43 (11.1)	5 (50.0)	41 (11.6)
At least 1 TEAE leading to discontinuation	1 (6.7)	1 (0.2)	1 (9.1)	1 (0.3)	0	0
At least 1 TEAE leading to death	1 (6.7)	1 (0.2)	1 (9.1)	1 (0.3)	0	0

[a]Treatment duration refers to the total duration in studies F01/F02/F03; at the start of F03 all patients were dose-adjusted to receive pegunigalsidase alfa 1.0 mg/kg.
[b]Possibly, probably, or definitely related to study treatment. SAE, serious adverse event; TEAE, treatment-emergent adverse event.

- In the overall treatment period, most (97.5%) TEAEs were mild or moderate in severity (**Table 2**)
  - The most common TEAEs were fatigue (8/15 patients [53.3%]), back pain (6/15 patients [40.0%]), abdominal pain, nausea, upper respiratory tract infection, nasopharyngitis, headache, paresthesia, vomiting, rash, or cough (5/15 patients each [33.3%])
- In the overall treatment period, TEAEs defined as severe (5/15 patients [33.3%]) or serious (3/15 patients [20.0%]) occurred only in men
  - No severe or serious TEAEs or deaths were considered related to study treatment
- In the overall treatment period, 2/8 men (25.0%) and 4/7 women (57.1%) experienced ≥ 1 IRR; all were categorized as mild to moderate severity (**Table 3**), and only 1 IRR occurred during F03
  - IRRs noted were dizziness and nausea (both reported by 2 patients), and abdominal pain, chest discomfort, chest pain, dyspnea, fatigue, hypotension, infusion reaction, maculopapular rash, paranasal sinus hypersecretion, peripheral swelling, pruritus, and sneezing (each reported by 1 patient)
- No IRRs were serious, severe, or led to withdrawal or death
- 5 Patients were positive for anti-pegunigalsidase alfa immunoglobulin G ADAs
  - 4 Patients were transiently positive for ADAs and, of these, 2 patients were transiently positive for neutralizing antibodies
  - 1 Patient was positive for non-neutralizing antibodies at visit 1 but remained negative thereafter
  - 1 Patient was positive for ADAs starting at month 48, and was positive for neutralizing antibodies from month 54 until study completion

Table 3. IRRs[a]

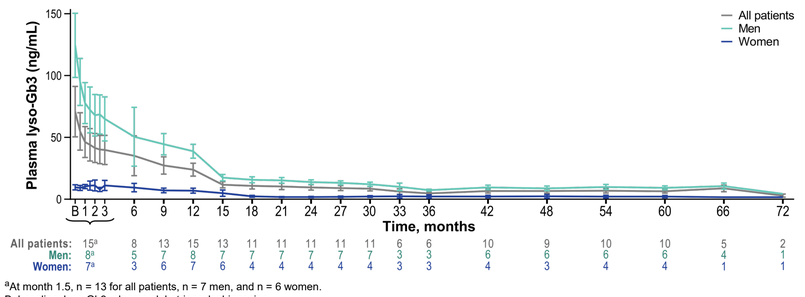
Category, n (%)	Duration of Treatment[b]		
	> 1 year	≥ 3 years	≥ 5 years
	n = 15	n = 11	n = 10
Any IRR	6 (40.0)	4 (36.4)	4 (40.0)
Mild or moderate IRR	6 (40.0)	4 (36.4)	4 (40.0)

[a]IRRs were defined as TEAEs occurring during the infusion or within 2 hours after its completion. [b]Treatment duration refers to the total duration in studies F01/F02/F03.
IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.

Efficacy

- The reduction from baseline in plasma lyso-Gb3 concentration was maintained to 60 months (last time point with 10 patients; **Figure 2**)

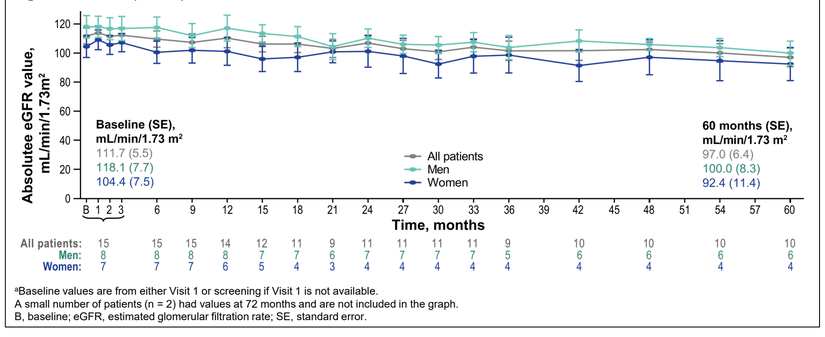
Figure 2. Mean (± SE) Plasma Lyso-Gb3 Over Time



[a]At month 1.5, n = 13 for all patients, n = 7 men, and n = 6 women.
B, baseline; lyso-Gb3, plasma globotriaosylsphingosine.

- Mean (SE) reduction from baseline at 60 months:
  - All patients: 68.4 (25.0) ng/mL
  - Men: 111 (31.0) ng/mL
  - Women: 4.6 (0.9) ng/mL
- There was a high correlation (R = 0.963) between the absolute change from baseline to 6 months in mean Gb3 deposition in kidney peritubular capillaries and the absolute change from baseline to 24 months in plasma lyso-Gb3 concentrations
- At 60 months, renal function remained relatively stable; according to KDIGO classification,[5] mean slope was considered stable overall and for men, and was within the normal range for women (**Figure 3**)
- Mean (SE) annualized eGFR slope was relatively stable up to 60 months:
  - All patients: −1.6 (0.8) mL/min/1.73 m²/y
  - Men: −2.4 (0.9) mL/min/1.73 m²/y
  - Women: −0.7 (1.3) mL/min/1.73 m²/y

Figure 3. Mean (± SE) Absolute eGFR Values Over Time[a]



[a]Baseline values are from either Visit 1 or screening if Visit 1 is not available.
A small number of patients (n = 2) had values at 72 months and are not included in the graph.
B, baseline; eGFR, estimated glomerular filtration rate; SE, standard error.

Cardiac Outcomes

- Based on cardiac MRI, no cardiac fibrosis developed over 60 months of treatment
- At month 60, mean LVMI (SE) had increased in women by 13.6 g/m² (5.3) compared with 5.7 g/m² (2.2) in men; the mean values for both groups were within normal ranges
- LVM showed a slight increase at month 60 but all values remained normal
- EF was stable over 60 months of treatment, with a mean (SE) decrease at month 60 of 0.5% (1.4)
- Of the cardiac parameters that were assessed by echocardiography (PR, QRS, and QT durations) and stress test (chest pain, dizziness, palpitations, shortness of breath, other), most remained stable and within normal ranges
- Taken together, these results suggest stability of the cardiac disease involvement

Conclusions

- The results of this study suggest that long-term pegunigalsidase alfa treatment provides continued benefits in patients with FD
  - Most TEAEs were mild to moderate in severity and unrelated to pegunigalsidase alfa
  - ADAs were infrequent and transitory in most patients
  - Cardiac and renal function were stable throughout the follow up, up to 60 months of treatment
  - Plasma lyso-Gb3 concentrations decreased steadily from baseline and remained low throughout the follow up, up to 60 months of treatment
- These results are consistent with safety and efficacy findings from other studies with pegunigalsidase alfa[1,6,7]

References

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