Tolerability and Infusion Duration of Pegunigalsidase Alfa in Patients with Fabry Disease: Data from 5 Completed Clinical Trials

John Bernat[1], Myrl Holida[1], Ozlem Goker-Alpan[2], Ankit Mehta[3], Nicola Longo[4], Eric Wallace[5], Khan Nedd[6], Mirjam Langeveld[7], William Wilcox[8], Derralynn Hughes[9], Rossana Rocco[10], Irene Koulinska[11], Einat Almon[12], Sari Alon[12], Raul Chertkoff[12], Pilar Giraldo[13], Antonio Pisani[14], Ales Linhart[15]

[1]University of Iowa Hospital and Clinics, Iowa City, IA, USA; [2]LRDRT Center, Fairfax, VA, USA; [3]Baylor University Medical Center, Dallas, TX, USA; [4]University of Utah, Salt Lake City, UT, USA; [5]University of Alabama at Birmingham, Birmingham, AL, USA; [6]Infusion Associates, Grand Rapids, MI, USA; [7]Academisch Medisch Centrum Universiteit van Amsterdam, Netherlands; [8]Emory University School of Medicine, Atlanta, GA, USA; [9]LSDU, Royal Free London NHS Foundation Trust, and University College London, England, UK; [10]Chiesi Farmaceutici S.p.A., Parma, Italy; [11]Chiesi USA, Inc., Boston, MA, USA; [12]Protalix Biotherapeutics, Carmiel, Israel; [13]Hospital de Dia Quiron, Zaragoza, Spain; [14]University of Naples Federico II, Naples, Italy; [15]Charles University, Prague, Czech Republic

Introduction

- Fabry disease is a rare X-linked genetic disorder caused by deficiency in lysosomal enzyme alpha-galactosidase A (α-Gal A) activity[1]
  - This deficiency results in accumulation of glycosphingolipids, mainly globotriaosylceramide (Gb3), which can lead to multisystemic disease and early death[1]
- Pegunigalsidase alfa is a novel PEGylated α-Gal A enzyme replacement therapy (ERT) in development for the treatment of patients with Fabry disease that was designed to offer prolonged half-life and lower immunogenicity with potential tolerability benefits[1]
  - These features of pegunigalsidase alfa may reduce immunogenicity that would result in a lower incidence of infusion-related reactions (IRR) and demonstrate improved overall tolerability, compared with other ERTs on the market,[2] when infused at the same dose (1.0 mg/kg)
- Theoretically, patients previously treated with other ERTs can potentially experience IRRs when switched to pegunigalsidase alfa because of differences in dose or differences in immunogenicity between therapies

Objective

- To characterize the tolerability profile of pegunigalsidase alfa using data from 5 clinical trials that had been completed by 2021, with a focus on the incidence of IRRs and change in infusion duration over time

Methods

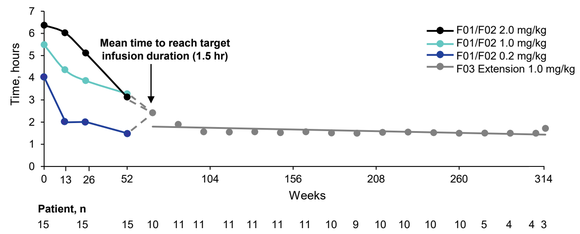
- Patients were included from 5 pegunigalsidase alfa clinical trials
- IRRs were defined as possibly, probably, or definitely related treatment-emergent adverse events (TEAEs) occurring during the infusion or within 2 hours postinfusion (excluding those TEAEs defined as injection-site reactions)
- Study designs and baseline patient characteristics for all 5 studies are shown in **Table 1**
- The following outcomes are described:
  - Incidence of IRRs
  - Mean duration of infusions at beginning and end of study
  - Number of patients achieving the minimum duration of infusion allowed per protocol
  - Time to achieve the minimum per-protocol infusion duration

Results

Infusion Duration

- In the F01 and F02 studies, 18 treatment-naïve patients received pegunigalsidase alfa every other week (EOW)
  - Initial mean infusion durations were 4.0, 5.5, and 6.4 hours for pegunigalsidase alfa 0.2 mg/kg, 1.0 mg/kg, and 2.0 mg/kg, respectively (**Figure 1**)
  - Mean infusion durations were decreased at 12 months to 1.5, 3.3, and 3.1 hours for pegunigalsidase alfa 0.2 mg/kg, 1.0 mg/kg, and 2.0 mg/kg, respectively
- In the F03 extension, all patients (n = 15) received pegunigalsidase alfa 1.0 mg/kg infusions EOW, and 13 achieved protocol-specified minimum 1.5-hour infusion durations between months 12 and 22

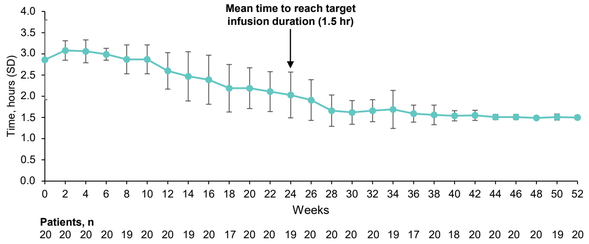
Figure 1. F01/F02/F03 Studies: Mean Infusion Duration Over Time of Pegunigalsidase Alfa EOW (n = 15)



F03 extension data represent the mean infusion values for 15 patients receiving pegunigalsidase alfa 1.0 mg/kg over 12 to 72 months. The grey line represents the best fit of infusion duration values from F03

- In the BRIDGE study, patients (n = 22) receiving pegunigalsidase alfa 1.0 mg/kg EOW had an initial mean infusion duration of 2.9 hours (standard deviation [SD] 0.9 h) (**Figure 2**)
  - 2 Patients discontinued treatment owing to type 1 IgE mediated- hypersensitivity reactions that occurred within 2 hours of the first infusion
  - All 20 patients who completed the study reached the minimum protocol-allowed infusion duration of 1.5 hours ± 10 minutes by 12 months ($p < 0.001$ vs baseline)

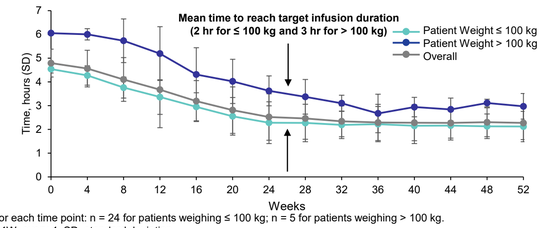
Figure 2. BRIDGE Study: Mean Infusion Duration Over Time of Pegunigalsidase Alfa 1.0 mg/kg EOW (n = 20)



n = 20 at 12 months; $p < 0.001$ from baseline to 12 months.
EOW, every other week; SD, standard deviation.

- In the BRIGHT study, 30 patients initially received pegunigalsidase alfa 2.0 mg/kg every 4 weeks
  - Mean infusion duration decreased from 4.8 hours (n = 30; SD 0.59 h) at baseline to 2.3 hours (n = 29; SD 0.7 h; $p < 0.001$) by month 12 (**Figure 3**)
  - At study completion, most patients had reached targeted infusion durations of:
    - 3 Hours for patients weighing > 100 kg (n = 5): mean of 2.97 hours (SD 0.24 h); 100% of patients reached target
    - 2 Hours for patients weighing ≤ 100 kg (n = 24): mean 2.1 hours (SD 0.13); 96% of patients reached target
    - 1 Patient discontinued because of a motor vehicle accident and 1 patient did not reach target infusion time

Figure 3. BRIGHT Study: Mean Infusion Duration Over Time of Pegunigalsidase Alfa 2.0 mg/kg Q4W (n = 29)



For each time point: n = 24 for patients weighing ≤ 100 kg; n = 5 for patients weighing > 100 kg.
Q4W, every 4; SD, standard deviation.

Safety

- F01/F02 Study:
  - 5 Patients (28% [n = 3] women) experienced 24 IRRs (**Table 2**)
    - With 1 exception, all were of mild or moderate severity
    - There was 1 serious adverse event (SAE) of an IgE mediated-hypersensitivity reaction (bronchospasm) during the first infusion that resulted in a discontinuation per study protocol

Table 2. F01/F02 Studies: Infusion-Related Reactions

PA dose, mg/kg	Sex	IRR Severity classification	Visit number	IRR Description	IRRs, n
0.2	Female	Mild or moderate	1, 3	Chest tightening / discomfort	5
			1	Sneezing	
			3	Nausea	
			27	Sinus drainage / paranasal sinus hypersecretion	
1.0	Female	Mild or moderate	2, 15	Hypotension	5
			3	Lightheadedness / dizziness	
			9	Short of breath / dyspnea	
			13	Maculo-papular erythematous rash	
	Male	Mild or moderate	6, 8	Infusion reaction / IRR	6
			15	Pain at left chest / chest pain	
			17	Itching / pruritus	
			20	Nausea	
			20	Dizziness	
	Male[a]	Serious adverse event (Severe)	1	Bronchospasm	1
2.0	Female	Mild or moderate	1–7	Abdominal cramping / abdominal pain	7
Total, n					**24**
Total IRR incidence, %					**28**

[a]Patient discontinued.
IRR, infusion-related reaction; PA, Pengunigalsidase alfa.

- F03 Extension Study:
  - 1 IRR of mild peripheral swelling was reported in 1 male patient (12.5%)
  - Of patients who had IRRs (n = 6), 3 (50%) were IgG ADA positive[a]
  - Of patients without IRRs (n = 9), 3 (33.3%) were IgG ADA positive[a]
- BRIDGE Study:
  - 9 IRRs were reported in 5 patients (22.7%; all men) (**Table 3**)
    - Of patients who had IRRs (n = 5), 2 (40%) were IgG ADA positive[a]
    - Of patients without IRRs (n = 17), 5 (29.4%) were IgG ADA positive[a]
    - Most IRRs (7) were nonserious and mild severity
    - 2 IRRs experienced by 2 male patients were severe and serious
      - Both were type 1 IgE mediated-hypersensitivity reactions and lead to discontinuation
      - 1 Patient was positive for immunoglobulin E antidrug antibodies at baseline
- BRIGHT Study:
  - 27 IRRs were reported in 5 patients (17%; all men) (**Table 4**)
    - Of patients who had IRRs (n = 5), 4 (80%) were IgG ADA positive[a]
    - Of patients without IRRs (n = 25), 6 (24%) were IgG ADA positive[a]
    - 17 IRRs were mild and 10 were moderate severity
    - All patients completed the study

[a]IgG ADA positive at any time including baseline or any follow up visits.

Table 3. BRIDGE Study: Infusion-Related Reactions

PA dose, mg/kg	Sex	IRR Severity classification	Visit number	IRR Description	IRRs, n
1.0	Male	Mild	4	Itching/Rash pruritus	5
			5	Erythema	
			9	Pruritus	
			10, 11	IRR	
	Male[a]	Serious adverse event (severe)	1	Type 1 IgE mediated-hypersensitivity reaction	1
	Male[a]	Serious adverse event (severe)	1	Type 1 IgE mediated-hypersensitivity reaction	1
	Male	Mild	20	Nasal congestion	1
	Male	Mild	19	Dizziness	1
Total, n					**9**
Total IRR incidence, %					**23**

[a]Patient discontinued.
IRR, infusion-related reaction; PA, Pengunigalsidase alfa.

Table 4. BRIGHT Study: Infusion-Related Reactions

PA dose, mg/kg	IRR Severity classification	IRR Description	Patients (n = 5; all men)	IRRs, n
2.0	Moderate	Infusion-related reaction	1	11
		Nausea	1	1
		Asthenia	1	1
		Pain	1	1
		Chest discomfort	1	1
		Paresthesia	1	1
		Tremor	1	1
		Total	17	
	Moderate	Infusion-related reaction	3	4
		Pain	1	1
		Hypersensitivity	1	1
		Vomiting	1	1
		Myalgia	1	1
		Pain in extremity	1	1
		Headache	1	1
		Total	10	
Overall total, n				**27**
Total IRR incidence, %				**17**

IRR, infusion-related reaction; PA, Pengunigalsidase alfa.

Table 1. Study Design Summaries and Patient Baseline Characteristics

Study	Clinical trials NCT #	Study design	Previous ERT-treatment status	Study duration, months	Pegunigalsidase alfa dose regimen, mg/kg, and frequency	Men, n	Women, n	Overall, N	Mean age, years (SD)
F01/F02	NCT01678898 NCT01769001	Open-label, dose-ranging studies in treatment-naïve patients	None	F01: 3 F02: 9	0.2 EOW 1.0 EOW 2.0 EOW	4 6 1	2 2 3	6 8 4	30.0 (10.8) 33.5 (11.7) 40.0 (16.5)
Extension F03	NCT01981720	Open-label extension of F01/F02	Yes: pegunigalsidase alfa for up to 60 months	≤ 60	1.0 EOW	8	7	15	33.4 (12.5)
BRIDGE	NCT03018730	Open-label, single-arm, switchover from agalsidase alfa	Yes: agalsidase alfa for 2+ years	12	1.0 EOW	15	7	22	34.8 (11.9)
BRIGHT	NCT03180840	Open-label, single-arm, switchover from other approved ERTs	Yes: agalsidase beta or agalsidase alfa for 3+ years	12	2.0 Q4W	24	6	30	40.5 (11.3)

EOW, every other week; ERT, enzyme replacement therapy; NA, not available; Q4W, every 4 weeks; SD, standard deviation.

Conclusions

- This analysis of data from studies completed by 2021 supports the favorable tolerability profile of pegunigalsidase alfa in patients with Fabry disease
- Mean infusion durations by study ends were reduced and/or met target rates
- IRR incidence in pegunigalsidase alfa trials completed by 2021 ranged from 17% in BRIGHT to 28% in F01/02, which compares favorably to available ERTs administered at the same dose (55%–67%)[2,3]
- The percentage of patients who were IgG ADA positive among those with IRRs were higher than among those without IRRs, especially in BRIGHT
- Most (57/60) IRRs reported during pegunigalsidase alfa treatment were of mild or moderate severity
- Overall, SAEs were reported in 3 of the 60 IRRs: one bronchospasm and two Type I hypersensitivity reactions, all were IgE mediated
- Additional data from the pegunigalsidase alfa clinical program may further characterize its potential to offer both tolerability and improved quality-of-life benefits for patients with Fabry disease

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