Switching from agalsidase alfa to pegunigalsidase alfa to treat patients with Fabry disease: 1 year of treatment data from BRIDGE, a phase 3 open-label study

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Disclosure Information

Ales Linhart

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Background and Objectives

- Patients with Fabry disease lack lysosomal enzyme α-galactosidase A activity, leading to systemic buildup of globotriaosylceramide (Gb_3)
  - This results in a broad range of symptoms, including chronic kidney disease, peripheral neuropathy, early stroke or transient ischemic attack, early-onset cardiovascular disease, and gastrointestinal symptoms[a]
    - Therapeutic goals[b] , in terms of kidney disease in patients with Fabry disease, comprise improvements in estimated glomerular filtration rate and proteinuria levels
    - Although currently available enzyme-replacement therapies (ERT) provide some beneficial effects in Fabry disease, they are limited in their clinical efficacy and there is a need for more robust treatments[c]
- Pegunigalsidase alfa is a novel, polyethylene glycosylated, α-galactosidase A enzyme in development for the treatment of patients with Fabry disease offering enhanced pharmacokinetics compared with current treatments [d, e]
- **Here we report data from the analyses of the BRIDGE** (NCT03018730) **study, evaluating the treatment safety and efficacy profiles after switching patients from agalsidase alfa to pegunigalsidase alfa**

[a] Felis A et al. *Kidney Int Rep.* 2020;5:407-413. [b] Wanner C et al. *Mol Genet Metab.* 2018;124:189-203. [c] Schaefer RM et al. *Drugs*. 2009;69:2179-2205.[d] Kizhner T et al. *Mol Genet Metab*. 2015;114:259-267.[e] Ruderfer I et al. *Bioconjug Chem*. 2018;29:1630-1639.

Study Design

- BRIDGE is a phase 3, multicenter, open-label, single-group, switch-over study
- 22 Adults with Fabry disease (15 males and 7 females)
  - Previously treated with agalsidase alfa 0.2 mg/kg IV every other week for at least 2 years and on a stable dose (>80% labelled dose/kg) for at least 6 months
    - Patients were screened and evaluated over 3 months while receiving agalsidase alfa treatment
  - Eligible patients were enrolled and switched to pegunigalsidase alfa 1 mg/kg IV every 2 weeks for 12 months
  - After 12 months, patients could continue into an extension study (PB-102-F60)

Safety and Efficacy Endpoints

Key Safety Endpoints

- Treatment-emergent adverse events
- Treatment-emergent anti-pegunigalsidase alfa antibodies

Key Efficacy Endpoints

- Mean annualized change in $eGFR_{CKD\text{-}EPI}$
- Fabry Disease Biomarkers (plasma globotriaosylsphingosine [Lyso-Gb_3], plasma Gb_3, urine Lyso-Gb_3)

Additional endpoints evaluated:

- Safety: clinical laboratory tests, electrocardiogram, physical examination, ability to taper off infusion premedication and requirement for use of premedication, vital signs, concomitant medications, brain MRI
- Efficacy: brief pain inventory short form, Mainz severity score index, quality of life (EQ-5D-5L), left ventricular mass index by MRI, urine protein-to-creatinine ratio (UPCR), frequency of pain medication use, exercise tolerance (stress test), Fabry disease clinical events (renal, cardiac, cerebrovascular, and noncardiac death)

$eGFR_{CKD\text{-}EPI}$, estimated glomerular filtration rate Chronic Kidney Disease-Epidemiology collaboration equation (formula used for calculating eGFR); EQ-5D-5L, 5-dimension EuroQol questionnaire; MRI, magnetic resonance imaging.

Inclusion and Exclusion Criteria

Main Inclusion criteria

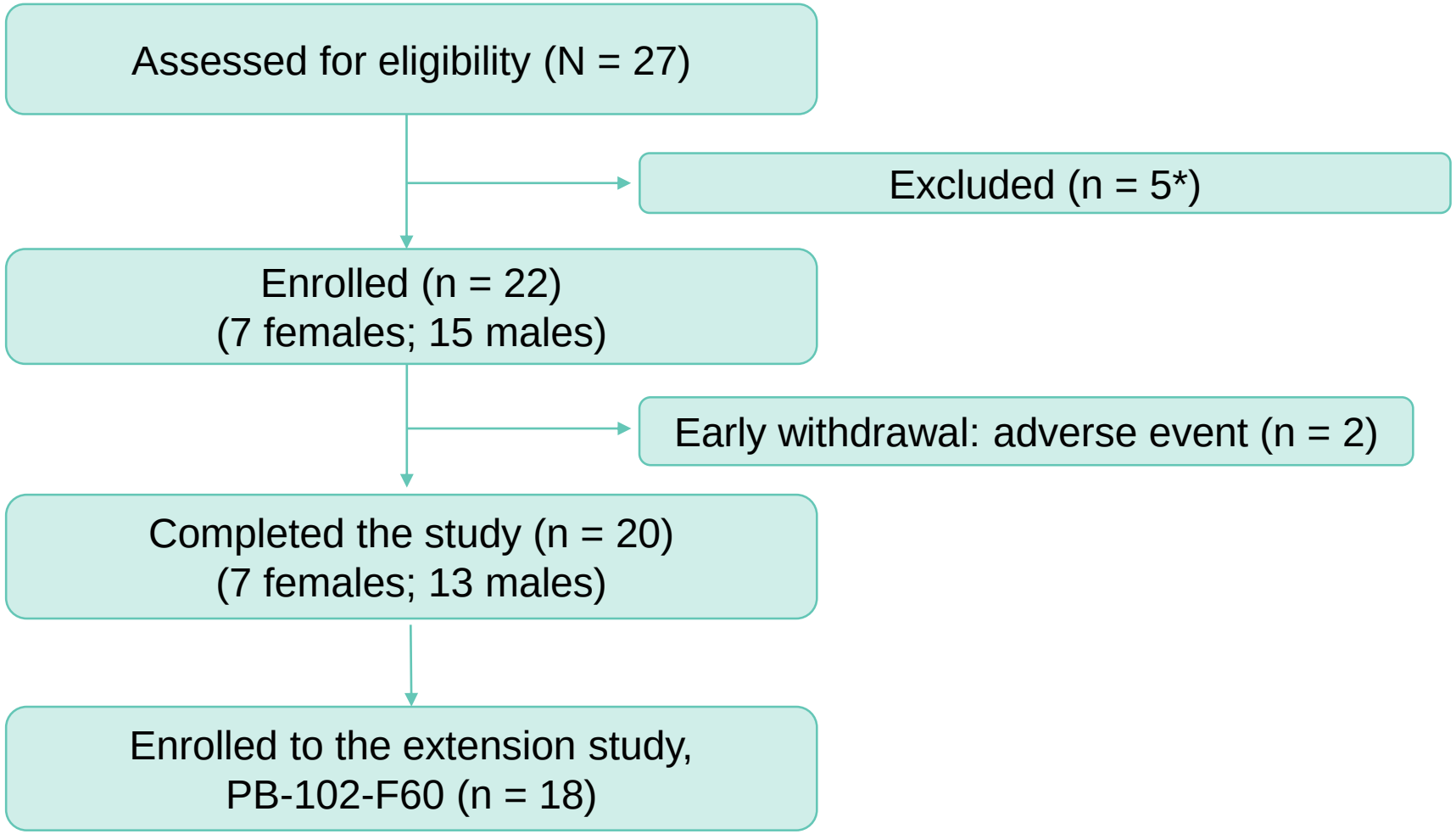
- ✓ Age: 18–60 years
- ✓ Documented diagnosis of Fabry disease
- ✓ Treated with agalsidase alfa for ≥ 2 years
- ✓ $eGFR_{CKD\text{-}EPI}$ ≥ 40 mL/min/1.73 m^2
- ✓ ≥ 2 Historical serum creatinine evaluations since starting agalsidase alfa treatment collected ≤ 2 years before enrollment

Main Exclusion criteria

- x History of anaphylaxis or type 1 hypersensitivity reaction to agalsidase alfa
- x History of renal dialysis or transplantation
- x History of acute kidney injury within 12 months before screening
- x Start, or change, in ACEi or ARB dose within 4 weeks before screening
- x UPCR > 0.5 g/g and not treated with ACEi or ARB
- x Cardiovascular and/or cerebrovascular event within 6 months of randomization

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

CONSORT Diagram



*inclusion/exclusion criteria not met n = 4, health complication un-related to Fabry disease n = 1

Baseline Characteristics: Efficacy Population

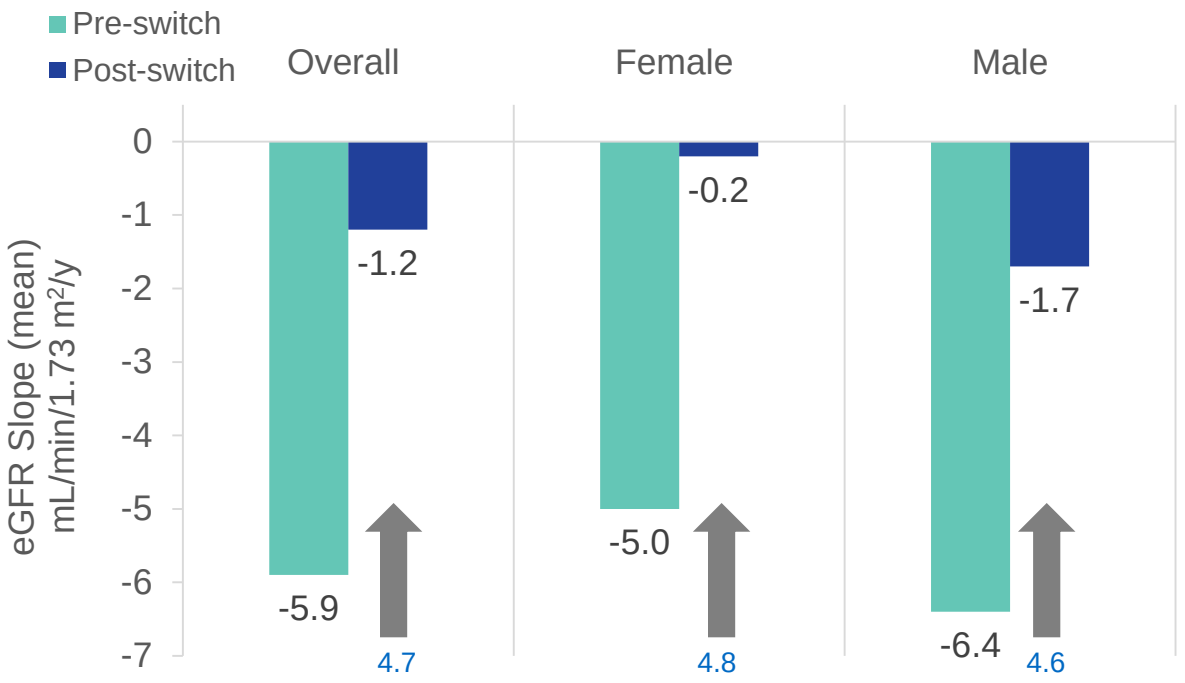
Parameters	Overall	Female	Male
Patients, n	20	7	13
Age, years	45.8 (2.2)	46.7 (4.7)	45.2 (2.5)
Age started ERT, years	36.6 (2.4)	39.4 (4.4)	35.1 (2.9)
Fabry disease classification, n [a]Classic Nonclassic	 12 8	 0 7	 12 1
Patients with significant proteinuria (UPCR ≥ 500 mg/g)	4	0	4
eGFR, mL/min/1.73 m^2	79.5 (4.9)	86.1 (6.7)	75.9 (6.6)
Annualized slope with agalsidase alfa ~2 years, including eGFR baseline; mL/min/1.73 m^2/y	-5.9 (1.3)	-5.0 (1.7)	-6.4 (1.9)
Patients treated with ACEi / ARB, n	11	4	7
Plasma lyso-Gb_3, nmol/L (normal: ≤ 2.4 nmol/L)	38.5 (9.7)	13.8 (2.3)	51.8 (13.6)
Plasma Gb_3, nmol/L (normal: ≤ 4961 nmol/L)	6076 (444)	5468.3 (708.6)	6403.2 (565.2)
[b]**Urine lyso-Gb_3**, pM/mM	58.4 (12.1)	45.4 (11.8)	66 (17.9)[b]

Values shown as mean (standard error) unless otherwise stated. Data are a subset of collected baseline characteristics

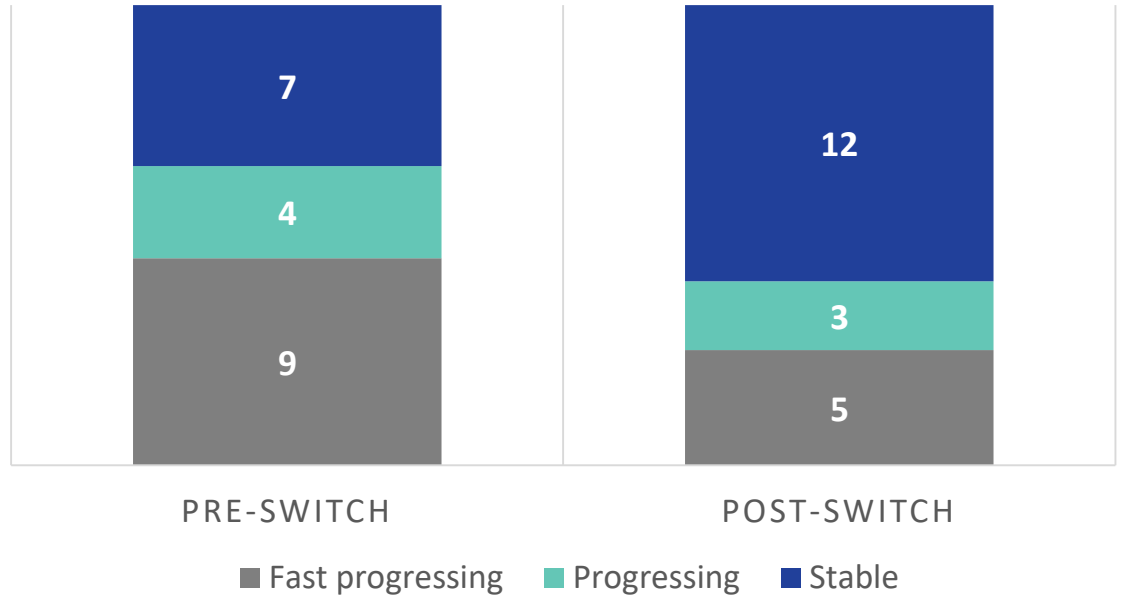
[a] classic defined as ≤ 5% mean of lab normal ranges residual enzymatic activity in plasma or leukocytes and ≥1 Fabry specific symptom at baseline.

[b] Urine lyso-Gb3 (N= 19 patients; n=12 males)

Changes in Kidney Disease Progression After 12 Months of Pegunigalsidase Alfa Treatment



- After 12 months of pegunigalsidase alfa treatment, mean annualized eGFR slope improved by 4.7 mL/min/1.73 m^2/y, from -5.9 to -1.2 mL/min/1.73 m^2/y[a]

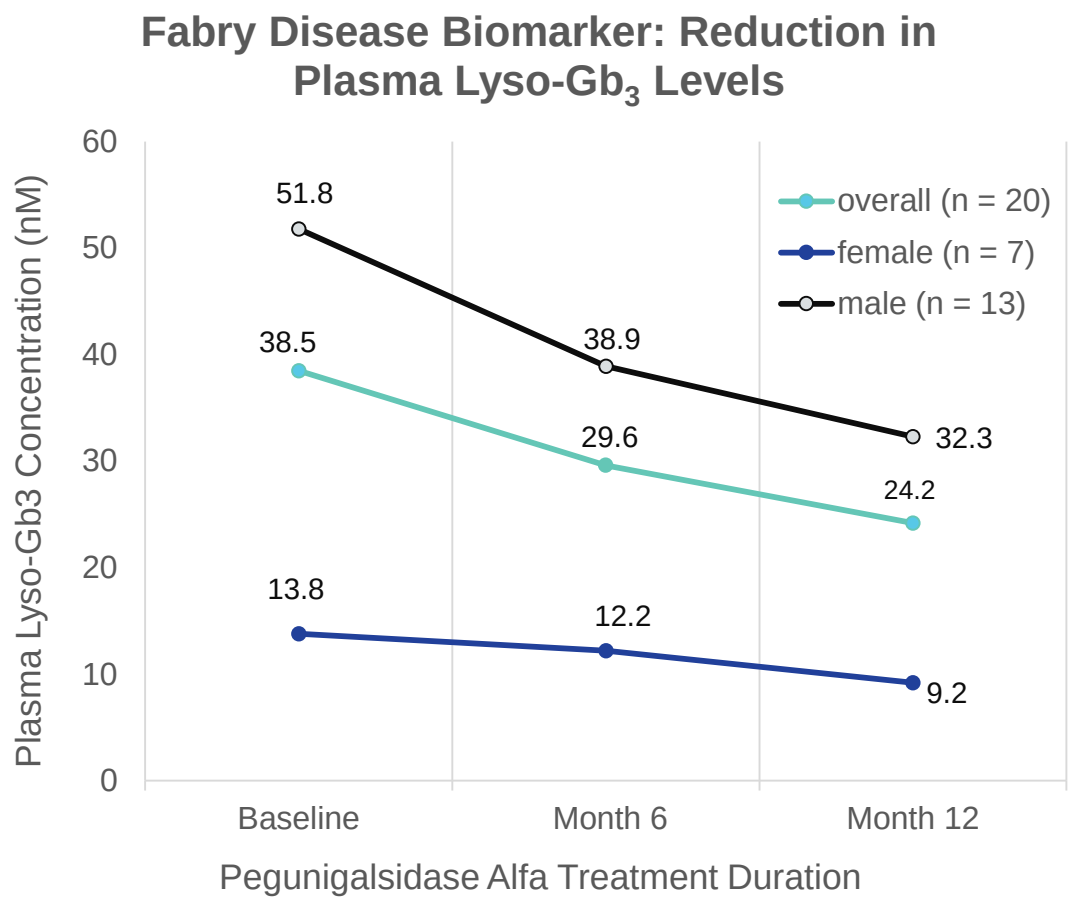


- Following switch to pegunigalsidase alfa, there were fewer patients with progressing or fast progressing kidney disease and the majority of patients achieved a stable status post-switch[a]

[a]According to a European expert consensus statement on therapeutic goals, treatment with ERT should aim at keeping or reducing the annual slope loss to < 3 mL/min/1.73 m^2/y for stable and progressing patients, and for patients with fast renal progression, the goal is slowing the decrease to < 5 mL/min/1.73 m^2/y, by more than 50%.

1. Wanner C et al. *Mol Genet Metab.* 2018;124:189-203.

Lyso-Gb_3 Plasma Concentration Over 12 Months With Pegunigalsidase Alfa



- Overall, plasma lyso-Gb_3 concentrations decreased by 31.5% from a baseline of 38.5 nM to 24.2 nM with treatment at month 12.
- At baseline, males (51.8 nM) had higher plasma lyso-Gb_3 levels than females (13.8 nM) and showed greater relative mean reductions from baseline (32.4% for males vs 29.8% for females) with treatment at month 12.

Incidence of Treatment-Emergent Adverse Events (TEAEs): Safety Population

TEAEs	Patients, n (%)	Events, n
Total	21 (95.5)	127
Moderate severity	19 (86.4)	123
Most common (reported in ≥3 patients)		
Nasopharyngitis	7 (31.8)	9
Headache	5 (22.7)	5
Dyspnea	3 (13.6)	3
Severe	**4 (18.2)**	**4**
Infectious mononucleosis	1 (4.5)	1
Urinary tract infection	1 (4.5)	1
Type-I hypersensitivity[a]	2 (9.1)	2
Infusion-related reaction	5 (22.7)	9
Injection-site reaction	3 (13.6)	4
Fatal	0	0

Total: 21/22 patients (95.5%) with any TEAE

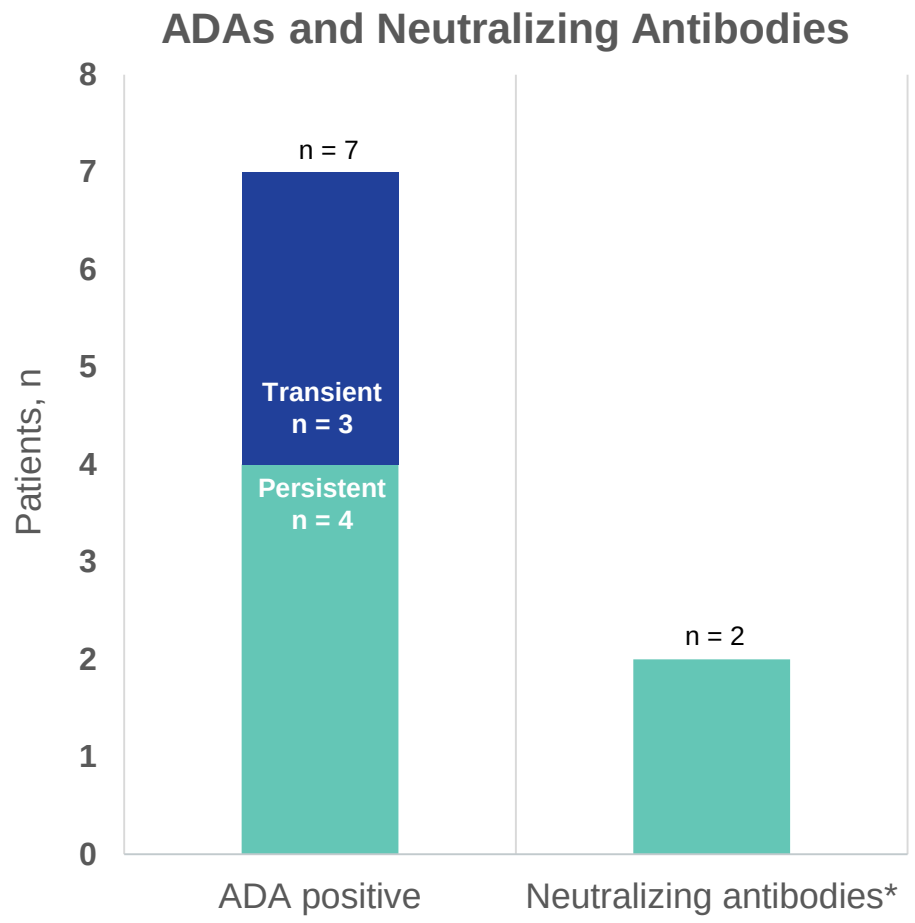
- **4 (18.2%) Patients with severe TEAEs**
- **4 (18.2%) Patients with serious TEAEs**
- **2 (9.1%) Patients with TEAEs leading to withdrawal**

Total: 5/22 patients (22.7%) with any related TEAE

- **2 (9.1%) Patients with related severe TEAEs**
- **2 (9.1%) Patients with related serious TEAEs**
- **2 (9.1%) Patients with related TEAEs leading to withdrawal**

[a]TEAE during first infusion that resulted in withdrawal from study.

Development of Anti-Drug Antibodies (ADA) Over 12 Months



- Of 20 patients, 7 (35%) had a positive ADA status at some time points during the study
  - Of the 7 ADA-positive patients, 4 (20%) had a persistent positive status and 3 (15%) had a transient positive status
- Only patients (n = 2) with pre-existing ADAs were positive for neutralizing antibodies

*Neutralizing ADAs tested only in patients with a positive IgG antibody response. The assays were validated according to United States' Food and Drug Administration and European Medicines Agency immunogenicity guidelines and performed centrally, in accordance with the Good Laboratory Practices. Methods were either a solid-phase enzyme-linked immunosorbent assay or an in vitro enzymatic activity procedure.

Conclusions

- 22[a] Patients with Fabry disease were enrolled in the BRIDGE study
- In this analysis of 20[b] patients who completed 12 months of treatment with pegunigalsidase alfa after switching from agalsidase alfa, we observed:
  - Mean overall annualized eGFR slope improved from −5.9 to −1.2 mL/min/1.73 m^2/y
  - Results suggest a potential benefit of pegunigalsidase alfa on renal function for patients with Fabry disease who were previously treated with agalsidase alfa
  - The number of patients with moderately progressing or fast progressing kidney disease decreased and most patients achieved a stable status post-switch
  - Compared with baseline, substantial improvements in plasma lyso-Gb_3 levels were observed after 12 months of treatment in male patients, and levels improved or remained stable throughout the study in female patients
- In the safety population (22 patients), most TEAEs were mild or moderate in severity, with 2 patients (9.1%) withdrawing from treatment because of hypersensitivity reaction (that resolved following withdrawal)
- Most patients (18/20) who completed the study were enrolled in the long-term extension phase, continuing to receive pegunigalsidase alfa

[a]n = 22 patients in the safety population. [b]n = 20 patients in the efficacy population

Co-Authors and Acknowledgments

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