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

Michael West[1], Ales Linhart[2], Gabriela Dostalova[2], Kathy Nicholls[3], Camilla Tøndel[4], Ana Jovanovic[5], Pilar Giraldo[6], Bojan Vujkovac[7], Tarekegn Hiwot[8], Einat Almon[9], Sari Alon[9], Mali Szlaifer[9], Raul Chertkoff[9], Derralynn Hughes[10]

[1]Dalhousie University, Halifax, Nova Scotia, Canada; [2]General University Hospital and Charles University, Prague, Czech Republic; [3]The Royal Melbourne Hospital and The University of Melbourne, Parkville, Australia; [4]Haukeland University Hospital, Bergen, Norway; [5]Salford Royal, Dept of Inherited Metabolic Disease, Salford, England, UK; [6]Hospital de Dia Quironsalud, Zaragoza, Spain; [7]General Hospital Slovenj Gradec, Slovenia; [8]Endocrinology Dept, University Hospitals Birmingham NHS Foundation Trust, Birmingham, England, UK; [9]Protalix Biotherapeutics, Carmiel, Israel; [10]LSDU, Institute of Immunity and Transplantation, Royal Free London NHS Foundation Trust, London, UK.

Introduction

- Patients with Fabry disease lack lysosomal enzyme a-galactosidase A activity, leading to systemic buildup of globotriaosylceramide (Gb3)
  - 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[1]
    - Therapeutic goals,[2] 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[3]
- Pegunigalsidase alfa is a novel, polyethylene glycosylated, a-galactosidase A enzyme in development for the treatment of patients with Fabry disease, offering enhanced pharmacokinetics compared with current treatments[4,5]

Objective

- 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

Methods

- BRIDGE is a phase 3, multicenter, open-label, single-group, switch-over study (**Figure 1**)
- 22 Adults with Fabry disease (15 males and 7 females)
  - Previously treated with agalsidase alfa 0.2 mg/kg intravenously (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)

Figure 1. Study Design

Safety and Efficacy Endpoints

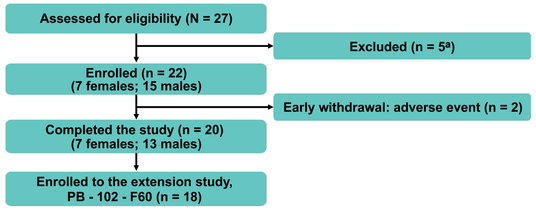
- Key safety endpoints
  - Treatment-emergent adverse events
  - Treatment-emergent anti-pegunigalsidase alfa antibodies
- Key efficacy endpoints
  - Mean annualized change in estimated glomerular filtration rate ($eGFR_{CKD\text{-}EPI}$
  - Fabry disease biomarkers (plasma globotriaosylsphingosine [lyso-Gb3], plasma Gb3, urine lyso-Gb3)

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

Results

Figure 2. Patient Disposition Flowchart



[a]Inclusion/exclusion criteria not met n = 4; health complication unrelated to Fabry disease n = 1.

Table 1. Baseline Characteristics: Efficacy Population

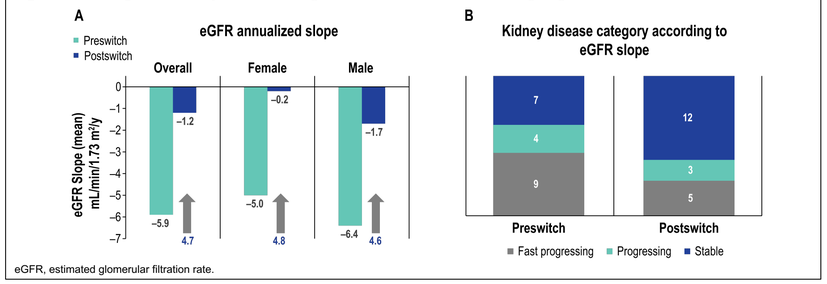
Parameters	Overall	Female	Male
Patients, n	20	7	13
Age, years	45.8 (2.2)	46.7 (4.7)	45.2 (2.5)
Age started ERT, years	36.6 (2.4)	39.4 (4.4)	35.1 (2.9)
Fabry disease classification, n Classic[a] Nonclassic	12 8	0 7	12 1
Patients with significant proteinuria, n (UPCR ≥ 500 mg/g)	4	0	4
eGFR, mL/min/1.73 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-Gb3, nmol/L (normal: ≤ 2.4 nmol/L)	38.5 (9.7)	13.8 (2.3)	51.8 (13.6)
Plasma Gb3, nmol/L (normal: ≤ 4961 nmol/L)	6076 (444)	5468.3 (708.6)	6403.2 (565.2)
Urine lyso-Gb3[b], nmol/L	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 laboratory 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).
ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; ERT, enzyme-replacement therapy; Gb3, globotriaosylceramide; lyso-Gb3, plasma globotriaosylsphingosine; UPCR; urine protein-to-creatinine ratio.

- 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] (**Figure 3A**)
- Following switch to pegunigalsidase alfa, there were fewer patients with progressing or fast progressing kidney disease and the majority of patients achieved stable renal function postswitch[a] (**Figure 3B**)

[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%.[2]

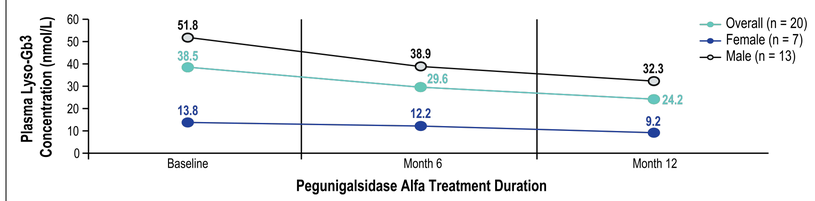
Figure 3. Changes in Kidney Disease Progression After 12 Months of Pegunigalsidase Alfa Treatment



eGFR, estimated glomerular filtration rate.

- Overall, plasma lyso-Gb3 concentrations decreased by 31.5% from a baseline of 38.5 nmol/L to 24.2 nmol/L with treatment at month 12 (**Figure 4**)
- At baseline, males (51.8 nmol/L) had higher plasma lyso-Gb3 levels than females (13.8 nmol/L) and showed greater relative mean reductions from baseline (32.4% for males vs 29.8% for females) with treatment at month 12 (**Figure 4**)

Figure 4. Lyso-Gb3 Plasma Concentration Over 12 Months With Pegunigalsidase Alfa



Lyso-Gb3, plasma globotriaosylsphingosine.

Figure 5. Incidence of Treatment-Emergent Adverse Events: 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

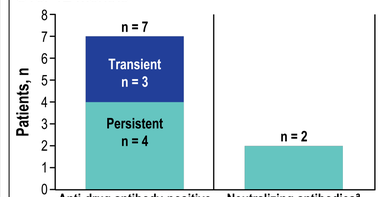
Total: 5/22 patients (22.7%) with any related TEAE

- 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.
TEAE, treatment-emergent adverse event.

- Of 20 patients, 7 (35%) had a positive ADA status at some point during the study (**Figure 6**)
  - Of the 7 ADA-positive patients, 4 (20%) had a persistent positive status and 3 (15%) had a transient positive status
- Of the 4 patients with persistent ADAs, 2 were positive for neutralizing antibodies

Figure 6. Development Anti-Drug Antibodies Over 12 Months



[a]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.
ADA, anti-drug antibody.

Conclusions

- In this analysis of 20 patients (efficacy population) 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
  - The number of patients with moderately progressing or fast progressing kidney disease decreased and most patients achieved a stable status postswitch
  - Compared with baseline, substantial improvements in plasma lyso-Gb3 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)
- Results from this study suggest a potential benefit of pegunigalsidase alfa on renal function for patients with Fabry disease who were previously treated with agalsidase alfa
- Most patients (18/20) who completed the study were enrolled in the long-term extension phase, continuing to receive pegunigalsidase alfa

References

1. Felis A et al. *Kidney Int Rep*. 2020;5:407–413; 2. Wanner C et al. *Mol Genet Metab*. 2018;124:189–203; 3. Schaefer RM et al. *Drugs*. 2009;69:2179–2205; 4. Kizhner T et al. *Mol Genet Metab*. 2015;114:259–267; 5. Ruderfer I et al. *Bioconjug Chem*. 2018;29:1630–1639.

Acknowledgments: The authors thank the patients and their families for participation in the study. This study was sponsored by Protalix. Medical writing support was provided by Oxford PharmaGenesis, Newtown, PA, USA, and funded by Chiesi USA, Inc.

Disclosures: MW: research funding and honoraria from Protalix, Takeda, Sanofi, Amicus; holds patents related to gene therapy and biomarker panels for Fabry disease; **AL:** consultancy and speaker´s honoraria from Amicus Therapeutics, Sanofi, Takeda; **GD:** honoraria, travel and accommodation from Amicus Therapeutics, Greenovation Biotech GmbH, Protalix, Sanofi, Takeda; **KN:** honoraria and grants from Amicus Therapeutics, Sanofi, Idorsia, Protalix, Takeda; **CT:** honoraria, travel support, and/or an investigator in clinical trials supported by Protalix, Sanofi, Takeda, Amicus, Freeline, Avrobio; **AJ:** grant from Amicus; consultancy and speaker's honoraria from Takeda, Sanofi, Amicus; **PG:** honoraria and funding from Sanofi, Takeda, Amicus, Pfizer; **BV:** honoraria, travel and accommodation funding from Greenovation Biotech GmbH, Sanofi, Takeda; member of the EU Advisory Board of Fabry Registry, sponsored by Sanofi; **TH:** no disclosures; **EA**, **SA**, **MS**, and **RC** are full-time employees of Protalix Ltd.; **DH:** consultancy and speaking honoraria from Amicus, Takeda, Sanofi, Freeline, Protalix.