SP004

Effects of Long-term Migalastat Treatment on Renal Function by Baseline Proteinuria in Patients With Fabry Disease

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INTRODUCTION

- Fabry disease is a rare, devastating, and progressive X-linked lysosomal storage disorder caused by a mutation in the *GLA* gene, resulting in the functional deficiency of α-galactosidase A (α-Gal A)[1]
- Accumulation of α-Gal A substrates, including glycosphingolipids such as globotriaosylceramide (GL-3), can lead to multiorgan disease and progressive decline in renal function[1]
- Progressive impairment of renal function has been shown to be a major risk factor for cardiovascular events and cardiovascular-related premature death,[2] and the presence and severity of proteinuria has been associated with more rapid loss of renal function in untreated patients with Fabry disease—eGFR declines of up to 6.9 mL/min/1.73 m^2/year have been reported in male patients with untreated Fabry disease and high levels of proteinuria[3]
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacological chaperone approved in the European Union, Switzerland, Australia, Israel, Republic of Korea, and Japan for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-Gal A deficiency) who have a migalastat-amenable *GLA* mutation[4,5]
- Migalastat is also approved in Canada for adults (aged 18 years and older)
- Migalastat binds to and stabilizes amenable mutant forms of α-Gal A in the endoplasmic reticulum and facilitates cellular trafficking to lysosomes, whereupon dissociation of migalastat leads to the breakdown of target substrates[6,7]
- Previous analyses have demonstrated renal function remained stable (mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ was –0.7 mL/min/1.73 m^2 [95% CI, −1.83, 0.46]) during 48 months of migalastat treatment in enzyme replacement therapy (ERT)-naive patients with Fabry disease and amenable *GLA* mutations[8,9]

OBJECTIVE

- To evaluate the long-term effects of migalastat on renal function stratified by baseline proteinuria in patients with Fabry disease and amenable *GLA* mutations

METHODS

Study Design

- Four phase 2, open-label, dose-finding studies of migalastat were conducted in patients with a confirmed diagnosis of Fabry disease
- Patients completing any of the 4 phase 2 dose-finding studies were eligible to enroll in and continue migalastat treatment in a phase 2 extension study (FAB-CL-205; NCT00526071)
  - During this study, patients received migalastat 150 mg every other day (QOD), followed by a dose-escalation period (250 mg 3 days on/4 days off → 500 mg 3 days on/4 days off), followed by migalastat 150 mg QOD
- In the phase 3 FACETS trial (NCT00925301), patients were randomly assigned 1:1 to receive migalastat 150 mg QOD or placebo for 6 months; after completing the 6-month double-blind period, patients had the option to receive open-label migalastat for an additional 6 months (months 6-12) and for an additional year after that (months 12-24)[8]
- Patients who completed the phase 2 extension study or the FACETS trial could subsequently enroll in and continue to receive migalastat 150 mg QOD in the phase 3, open-label, long-term extension AT1001-041 study (NCT01458119; referred to as the AT1001-041 extension study herein)

Analyses

- Analyses were restricted to patients with amenable mutations who received migalastat 150 mg QOD for ≥17 months; this includes patients who entered the AT1001-041 extension study from the phase 2 open-label extension study and those enrolled in FACETS who may have subsequently enrolled in the AT1001-041 extension study
- Annualized change rates in $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$ in the migalastat-treated cohort were calculated using simple linear regression and stratified by baseline proteinuria level (<100, 100-1000, >1000 mg/24 h) and sex
  - These cut-offs were the same as those used in a previously published analysis of retrospective chart review data in 447 patients with Fabry disease prior to receipt of ERT (Pre-ERT Fabry Cohort). In that analysis, annualized changes in $eGFR_{MDRD}$ were stratified by baseline proteinuria and sex[3]
- $eGFR_{MDRD}$ results from the migalastat-treated cohort were contrasted with the previously published, similar analysis in the Pre-ERT Fabry Cohort[3]

RESULTS

Patients

- A total of 52 patients with amenable mutations received migalastat 150 mg QOD for ≥17 months and are included in these analyses
- Most patients (67%) had proteinuria levels between 100-1000 mg/24 h at baseline; 23% of patients had baseline proteinuria levels <100 mg/24 h, and 10% had levels >1000 mg/24 h (**Table 1**)
- Median treatment duration ranged from 3.5 to 4.8 years (maximum, 5.3 years) across baseline proteinuria subgroups (**Table 1**)

Table 1. Migalastat Treatment Duration by Baseline Proteinuria

Baseline 24 h urine protein, mg/24 h	Males		Females	
	n	Duration, Years, Median (min, max)	n	Duration, Years, Median (min, max)
<100	3	4.8 (4.8, 4.8)	9	4.2 (2.0, 5.3)
100-1000	16	4.3 (1.5, 4.9)	19	3.5 (1.5, 5.0)
>1000	2	3.6 (3.0, 4.3)	3	3.7 (1.5, 4.1)

Max=maximum; min=minimum.

Renal Function Assessed by $eGFR_{CKD\text{-}EPI}$

- $eGFR_{CKD\text{-}EPI}$ remained stable in most patients (males and females) with baseline proteinuria ≤1000 mg/24 h during migalastat treatment (**Table 2**)
- Declines in $eGFR_{CKD\text{-}EPI}$ were observed in patients with proteinuria levels >1000 mg/24 h at baseline (**Table 2**)

Table 2. Annualized Mean Change in $eGFR_{CKD\text{-}EPI}$ With Migalastat by Baseline Proteinuria

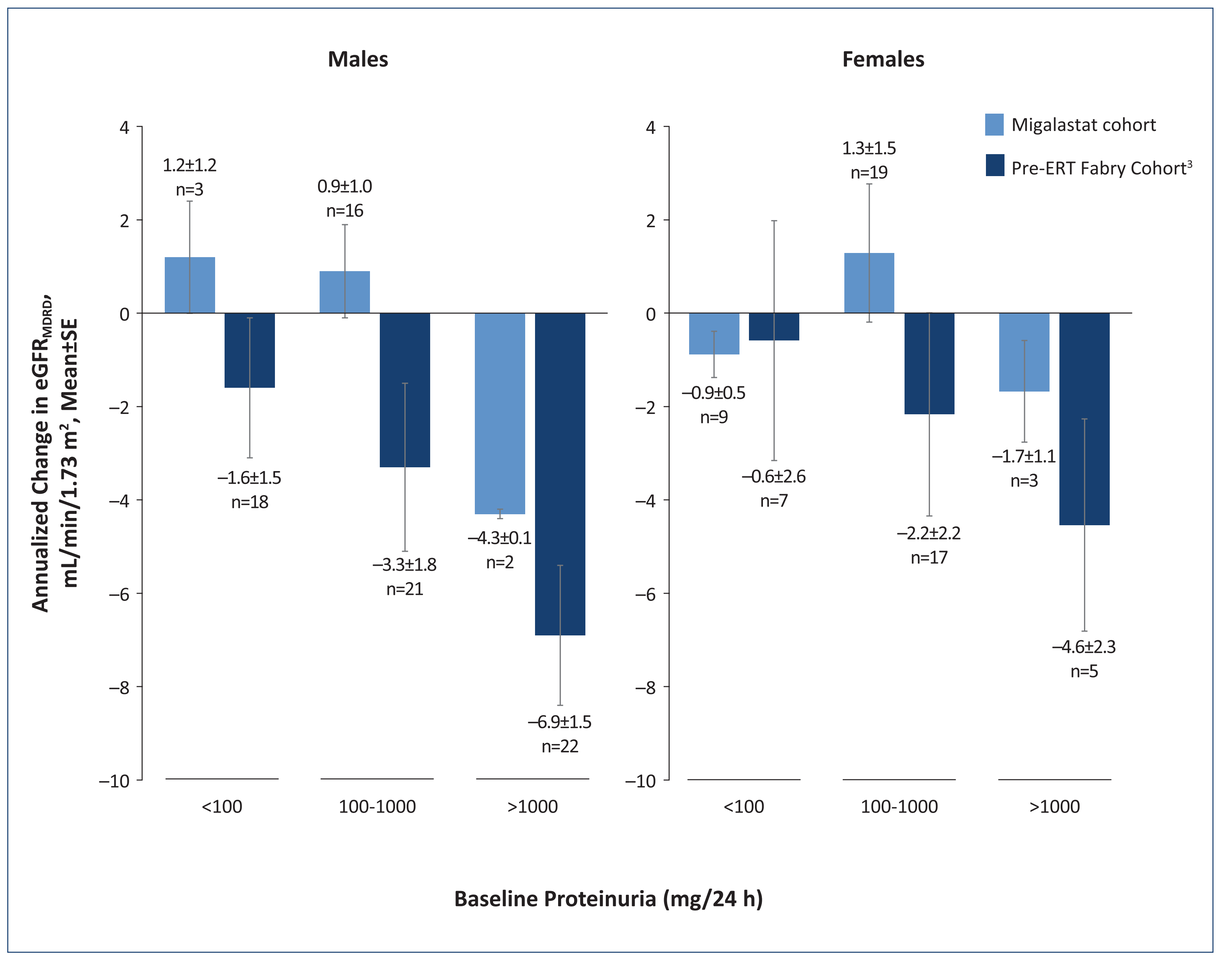
Baseline 24 h urine protein, mg/24 h	Males		Females	
	n	Annualized $eGFR_{CKD\text{-}EPI}$ Change Rate, mL/min/1.73 m^2, Mean (SE)	n	Annualized $eGFR_{CKD\text{-}EPI}$ Change Rate, mL/min/1.73 m^2, Mean (SE)
<100	3	0.4 (1.0)	9	−0.9 (0.4)
100-1000	16	0.2 (0.8)	19	−0.3 (1.0)
>1000	2	−5.1 (0.1)	3	−2.2 (1.4)

SE=standard error of the mean.

Renal Function Assessed by $eGFR_{MDRD}$

- Mean (SE) $eGFR_{MDRD}$ values at baseline were generally similar in migalastat-treated patients and in the Pre-ERT Fabry Cohort
  - Migalastat-treated patients: 85.6 (2.9) mL/min/1.73 m^2 (min, max: 40.0, 128.4 mL/min/1.73 m^2) in the overall group
  - Pre-ERT Fabry Cohort: values ranged from 58.5 (5.5) to 138 (13.3) across the proteinuria and sex-stratified subgroups (overall values not available)
- Annualized changes in $eGFR_{MDRD}$ tended to be smaller overall in patients treated with migalastat across proteinuria subgroups (**Figure 1**)
  - Numeric increases were observed with migalastat in patients with baseline proteinuria <100 mg/24 h (males) and 100-1000 mg/24 h (males and females)
  - Numeric decreases were reported in all proteinuria and sex-stratified subgroups in the Pre-ERT Fabry Cohort

Figure 1. Annualized Mean Change in $eGFR_{MDRD}$ by Sex and Baseline Proteinuria



Pre-ERT Fabry Cohort reported in Schiffmann R et al. *Nephrol Dial Transplant*. 2009;24(7):2102-2111.

LIMITATIONS

- In the Pre-ERT Fabry Cohort, patients were not previously treated with ERT; however, other treatments were not controlled for (eg, angiotensin-converting enzyme inhibitors in patients with chronic kidney disease) and the mutations were not specified but would include those with non-amenable mutations
- The numbers of patients in some subgroups were small, thus limiting the interpretation of these results

CONCLUSIONS

- Long-term treatment with migalastat was associated with generally stable renal function in Fabry disease patients with amenable mutations regardless of baseline proteinuria
- Male and female patients with baseline proteinuria of ≤1000 mg/24 h did not have further decline in renal function during the treatment period of 3-4 years with migalastat

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DISCLOSURES

Conflicts of Interest

RS has received research funding from Amicus, Protalix Biotherapeutics, Sanofi Genzyme, and Shire. DGB has served as a consultant and speaker for Amicus and Sanofi Genzyme, and has received research funding from Amicus, Sanofi Genzyme, and Shire. DPG has received honoraria and research grants from Amicus, Sanofi Genzyme, and Shire. RG has received honoraria from Amicus, Biomarin, Sanofi Genzyme, and Shire. DAH has served as a consultant for and has received research and travel funding from Amicus, Sanofi Genzyme, Shire, Actelion, and Protalix. KN has served on advisory boards for and has received research funding from Amicus, Sanofi Genzyme, and Shire. WRW has received research support from Amicus, Sanofi Genzyme, Shire, and Protalix, and honoraria from Sanofi Genzyme. HW, JY, NS, and JAB are employees of and hold stock in Amicus.

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