Renal Outcomes With Up to 9 Years of Migalastat in Patients With Fabry Disease: Results From an Open-label Extension Study

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INTRODUCTION

- Fabry disease is a rare 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]
- Progressive accumulation of the α-Gal A substrate globotriaosylceramide (GL-3) and similar glycosphingolipids can lead to multiorgan disease and ultimately organ failure, including end-stage renal disease[1]
- Untreated patients with Fabry disease have been shown to experience declines in estimated glomerular filtration rates (eGFR) of up to −12.2 mL/min per year[2,3]
- Progressive impairment of renal function is a major risk factor for cardiac events,[4] and end-stage renal disease is the primary cause of death in males with untreated Fabry disease.[5] Thus, stabilizing or slowing renal decline is an important treatment goal in Fabry disease
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacological chaperone approved in the European Union, Switzerland, Australia, Canada, Republic of Korea, and Israel for the treatment of Fabry disease in patients with *amenable GLA* mutations[6]
- Migalastat binds to, stabilizes, and facilitates lysosomal trafficking of amenable mutant forms of α-Gal A[7,8]
- The safety and efficacy of migalastat has been reported in several phase 2 and phase 3 clinical trial manuscripts[9-12]

OBJECTIVE

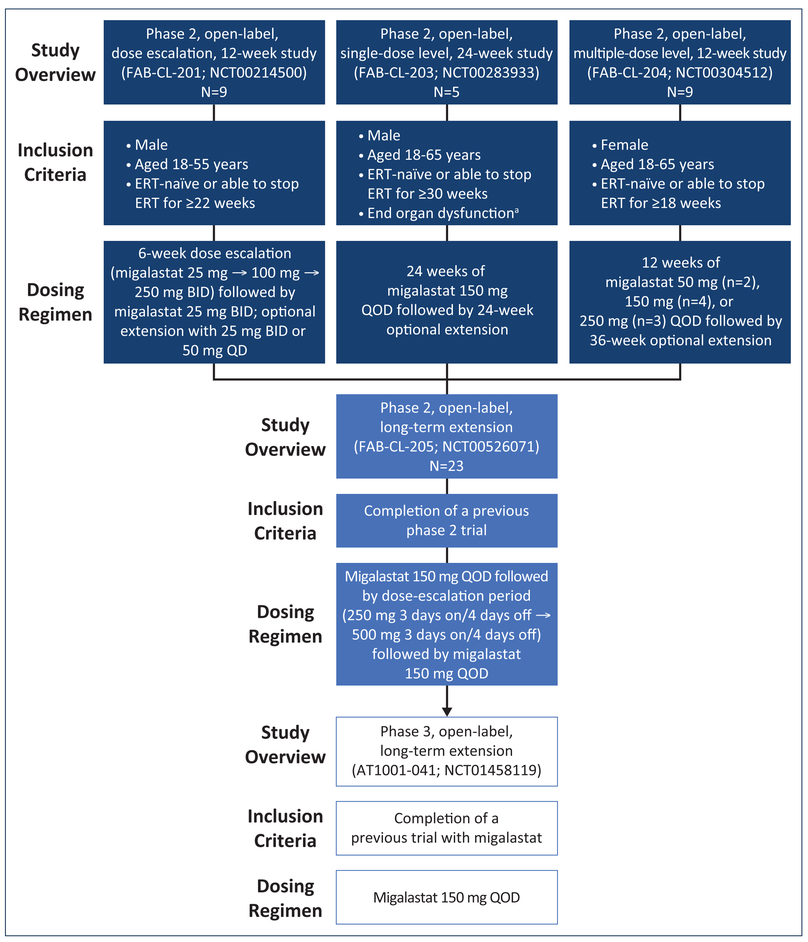
- To evaluate the long-term effects of migalastat on renal function in patients with Fabry disease who completed a phase 2 trial and enrolled in a phase 3 open-label extension study

METHODS

Patients and 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 and could subsequently enroll in and continue migalastat in a phase 3 long-term extension trial (referred to as the 041 extension study herein)
- In total, 12 patients originating from 3 of the phase 2 dose-finding studies completed the phase 2 long-term extension and entered into the 041 extension study; an overview of these 3 dose-finding studies, the phase 2 extension study, and the 041 extension study is shown in **Figure 1**

Figure 1. Study Designs and Flow of the 5 Studies



BID=twice daily; ECG=electrocardiogram; ERT=enzyme replacement therapy; QD=every day; QOD=every other day.
[a]End organ dysfunction characterized as abnormal ECG, left ventricular hypertrophy, or renal insufficiency.

Analyses

- Linear regression was used to calculate the annualized rate of change in estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation ($eGFR_{CKD\text{-}EPI}$) from baseline
- The analyses presented herein were restricted to the 12 patients with amenable mutations who completed phase 2 studies and entered the 041 extension study

RESULTS

Patients

- At the time of this analysis, mean time on migalastat for the 12 patients who continued from a phase 2 trial into the 041 extension study was 8.2 years (standard deviation [SD], 0.83)
  - Median time on treatment was 8.4 years (range, 6.3-9.3)
  - Eleven patients received migalastat 150 mg every other day (QOD) for ≥17 months
- Baseline demographics are shown in **Table 1**

Table 1. Baseline Characteristics (N=12)

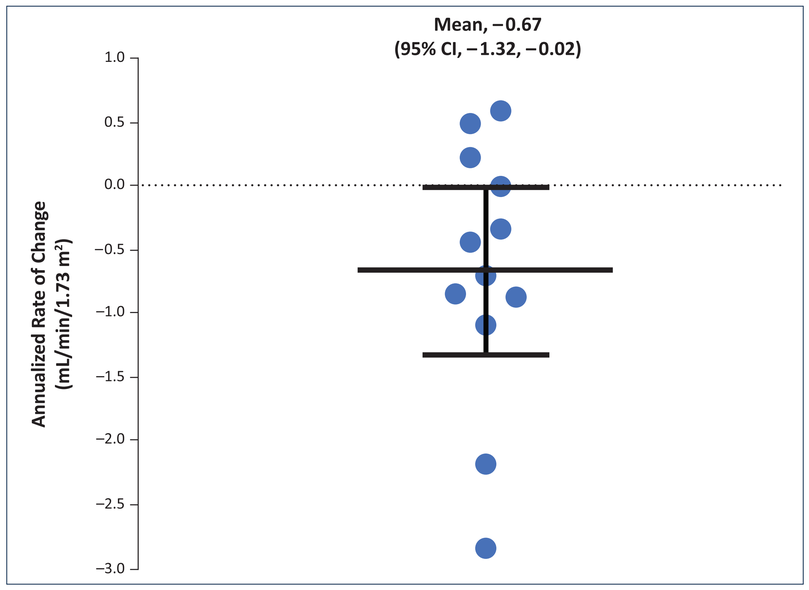
Patient	Age, years	Sex	eGFR, mL/min/1.73 m²
1	37	M	100.9
2	39	M	114.4
3	42	M	87.1
4	49	M	84.4
5	24	M	126.2
6	39	M	121.7
7	55	M	92.0
8	47	M	135.7
9	62	F	90.1
10	59	F	76.4
11	36	F	100.6
12	43	F	116.0
Mean (SD)	44.3 (10.7)	—	103.8 (18.7)
Median (min, max)	42.5 (24, 62)	—	100.8 (76, 136)

eGFR=estimated glomerular filtration rate; SD=standard deviation.

Renal Function

- Among the 12 patients enrolled in a phase 2 study who continued into the 041 extension study, renal function remained stable (annualized mean change in $eGFR_{CKD\text{-}EPI}$, −0.67 mL/min/1.73 m² [95% CI, −1.32, −0.02]) during the entire migalastat treatment period (mean exposure, 8.2 years) (**Figure 2**)
- Renal function also remained stable (annualized mean change in $eGFR_{CKD\text{-}EPI}$, 0.24 mL/min/1.73 m² [95% CI, −1.74, 2.21]) in an analysis of the 11 patients who received migalastat 150 mg QOD for ≥17 months (mean exposure, 4-5 years)

Figure 2. Annualized Change in $eGFR_{CKD\text{-}EPI}$ Over the Entire Migalastat Treatment Period[a] (N=12)



CI=confidence interval.
Baseline characteristics of the 2 patients showing declines >-2.0 mL/min/1.73 m²: male, eGFR 87 mL/min/1.73 m², proteinuria 270 mg/24 hr and male, eGFR 122 mL/min/1.73 m², proteinuria 0.1 g/L.
[a]The entire duration of migalastat treatment, including periods during the phase 2 trials when patients received various dosing regimens of migalastat and periods during the phase 2 trials and the 041 extension study when patients received migalastat 150 mg QOD.
Blue circles indicate individual patient data. Mean (95% CI) is shown with black horizontal bar and error bars, respectively.

- Renal outcomes by sex and baseline proteinuria levels are shown in **Table 2**

Table 2. Annualized Change in $eGFR_{CKD\text{-}EPI}$ by Baseline Proteinuria Levels and Sex in Patients Who Received Migalastat 150 mg QOD for ≥17 months (n=11)

Sex	Baseline 24-hour Urine Protein, mg/24 h[a]	n	Annualized Rate of Change in $eGFR_{CKD\text{-}EPI}$, mL/min/1.73 m², Mean (95% CI)
All	All	11	+0.2 (−1.7, 2.2)
Males	<100	3	+0.4 (−4.1, 4.9)
Males	100-1000	4	+2.4 (−4.0, 8.8)
Females	<100	2	−1.6 (−2.4, −0.9)
Females	100-1000	2	−1.7 (−2.0, −1.3)

[a]No patients had baseline 24-hour urine protein >1000 mg/24 h.

CONCLUSIONS

- Stabilization of renal function was demonstrated in male and female patients with Fabry disease and amenable mutations treated with migalastat for up to 9 years
- The effects were observed over a wide baseline proteinuria range
- Stabilization of renal function may prevent or delay renal and cardiac complications associated with the disease

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DISCLOSURE

Conflicts of Interest

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