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Long-Term Migalastat Treatment Stabilizes Renal Function in Patients With Fabry Disease: Results From a Phase 3 Clinical Study (AT1001-041)

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INTRODUCTION

- Fabry disease is a devastating, rare, 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) and globotriaosylsphingosine, can lead to multiorgan disease and progressive decline in renal function[1]
  - Accumulation of GL-3 in the kidney is a known consequence of Fabry disease[2]
- Progressive impairment of renal function has been shown to be a major risk factor for cardiac events and premature death[3]; 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, and Israel for the treatment of Fabry disease in patients with *amenable GLA* mutations[4]
  - Amenability is determined via the Migalastat Amenability Assay by measuring migalastat-induced changes in HEK cells that are transfected with cDNA from Fabry disease–associated *GLA* mutations. Criteria include a relative increase in α-Gal A activity ≥1.2-fold above baseline and an absolute increase in α-Gal A ≥3.0% of wild type after incubation with 10 μM of migalastat[5]
  - Patients do not have to be individually tested for amenability; the http://galafoldamenabilitytable.com website can be used to identify whether a specific mutation has been found to be amenable or non-amenable in the assay
- Migalastat restores lysosomal trafficking and enzyme activity by binding and inducing proper folding of amenable mutant forms of α-Gal A[6,7]
- FACETS (AT1001-011, NCT00925301) was a phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of migalastat in enzyme replacement therapy (ERT)–naive patients with Fabry disease with amenable *GLA* mutations[8]
- Patients completing FACETS were eligible for enrollment in the phase 3, open-label, long-term extension AT1001-041 study (NCT01458119; referred to as the 041 extension study herein)

OBJECTIVE

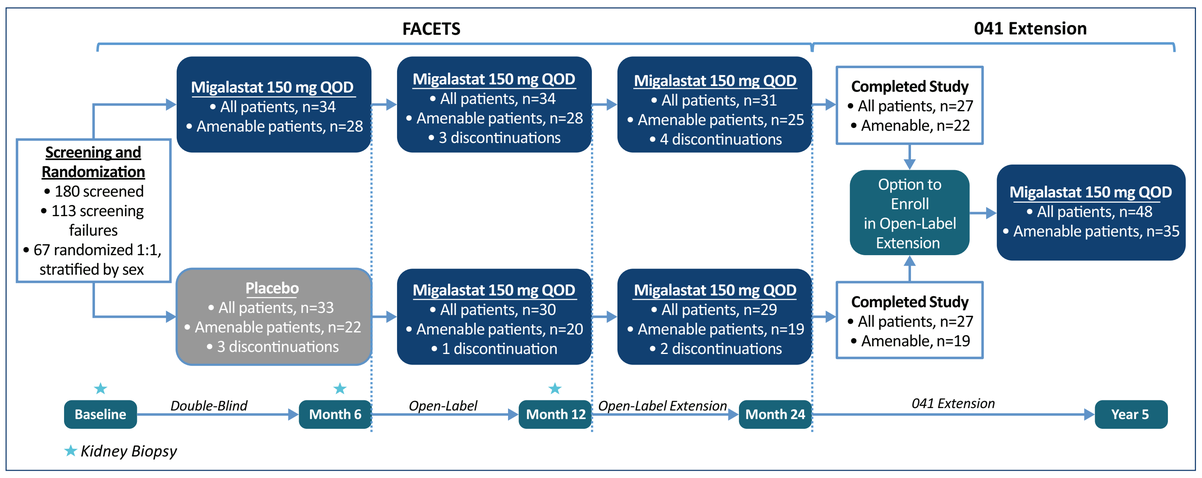
- To evaluate the long-term effects of migalastat on renal function in patients with Fabry disease completing the FACETS study who enrolled in the 041 extension study

METHODS

Study Design

- In FACETS, eligible patients were randomly assigned 1:1 to receive migalastat 150 mg or placebo every other day for 6 months (**Figure 1**)
- 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)
- Patients who completed 24 months of treatment in FACETS had the option to enroll in the 041 extension study and receive open-label migalastat for up to 5 years (**Figure 1**)
- The effect of migalastat on renal function was a secondary objective of both FACETS and the 041 extension study

Figure 1. FACETS and 041 Extension Study Designs



QOD=every other day.

Key Inclusion Criteria

- Male and female patients aged 16-74 years diagnosed with Fabry disease with amenable *GLA* mutations
- Naive to ERT or had not received ERT for ≥6 months before screening
- $eGFR_{MDRD}$ at screening ≥30 mL/min/1.73 m^2
- Urine GL-3 at screening ≥4× the upper limit of normal (24-hour collection)
- Patients taking angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or renin inhibitors had to be on a stable dose for ≥4 weeks before the screening visit

Analyses

- In FACETS, eGFR was calculated using $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$
  - A post hoc analysis examined $eGFR_{CKD\text{-}EPI}$ annualized rate of change in subgroups based on eGFR at baseline (30 to <60 mL/min/1.73 m^2, 60 to <90 mL/min/1.73 m^2, and ≥90 mL/min/1.73 m^2)
- mGFR was assessed based on plasma clearance of unlabeled iohexol ($mGFR_{iohexol}$)
- The long-term effect of migalastat on renal function was assessed by calculating the annualized rate of change in $eGFR_{CKD\text{-}EPI}$ in patients who received at least 17 months of treatment with migalastat (n=41)
- Annualized change rates were calculated using simple linear regression
- The analyses presented herein were restricted to patients with amenable mutations per the Migalastat Amenability Assay

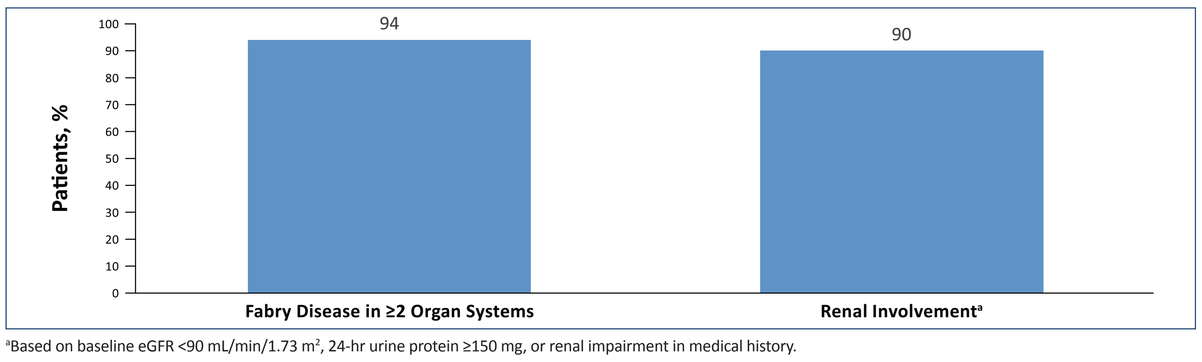
RESULTS

- Of 67 patients (50 of whom had amenable mutations) randomly assigned in the phase 3 FACETS trial, 54 patients (41 of whom had amenable mutations) completed the study, and 48 patients (35 of whom had amenable mutations) entered the 041 extension study
- At the time of these analyses, patients with amenable mutations had received treatment for a median of 3.5 years (range, 1.5-4.9)

Baseline Disease Severity

- Disease severity at baseline was significant among the 50 randomized patients who had amenable mutations (**Figure 2**)

Figure 2. Baseline Disease Severity Per Organ System (patients with amenable mutations; n=50)

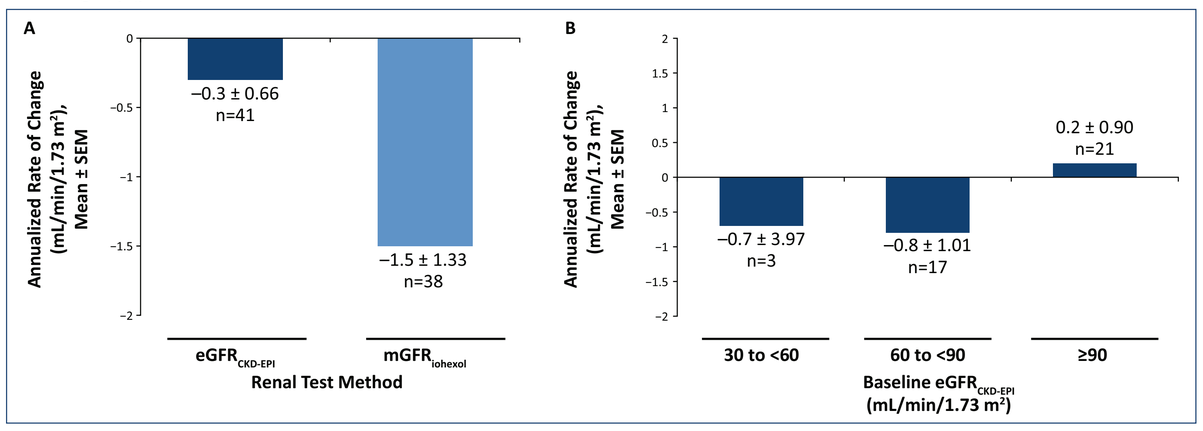


[a]Based on baseline eGFR <90 mL/min/1.73 m^2, 24-hr urine protein ≥150 mg, or renal impairment in medical history.

Renal Function (FACETS study)

- Based on GFR assessments, renal function remained stable over 18 and 24 months of migalastat treatment in patients with amenable mutations treated with placebo and migalastat, respectively, during the double-blind period (**Figure 3A**)
- Stabilization of renal function with migalastat treatment was observed regardless of baseline eGFR (**Figure 3B**)

Figure 3. Annualized Mean Change From Baseline to Month 24 in (A) $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ in All Patients and (B) $eGFR_{CKD\text{-}EPI}$ by Baseline eGFR Subgroup (patients with amenable mutations)

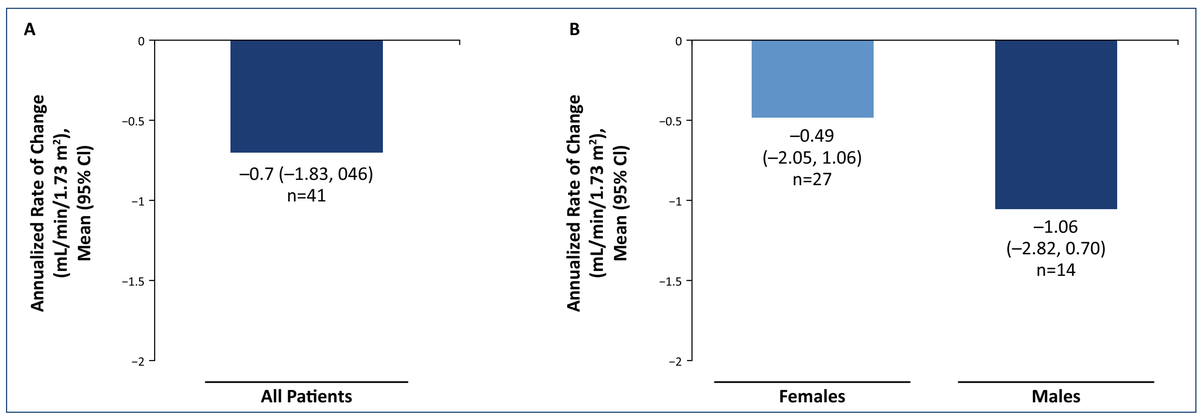


$eGFR_{CKD\text{-}EPI}$=estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; $mGFR_{iohexol}$=measured glomerular filtration rate using iohexol clearance; SEM=standard error of the mean.

Renal Function (041 extension study)

- Among patients with amenable mutations, renal function remained stable for up to approximately 5 years of treatment with migalastat (min, 1.5 years; max, 4.9 years) (**Figure 4A**)
- Long-term stabilization of renal function with migalastat was observed regardless of sex (**Figure 4B**)
  - The mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ from baseline to month 48 was −0.49 mL/min/1.73 m^2 (95% confidence interval [CI] −2.05, 1.06) in female patients and −1.06 mL/min/1.73 m^2 (95% CI −2.82, 0.70) in male patients
  - The long-term effect of migalastat on renal function compares favorably with the decline reported in untreated patients with Fabry disease. Average annualized declines in eGFR of −3.0 mL/min/1.73 m^2 and −2.6 mL/min/1.73 m^2 have been reported for 2 large cohorts of untreated female and male patients with Fabry disease[9,10]

Figure 4. Annualized Mean Change in $eGFR_{CKD\text{-}EPI}$ From Baseline to Month 48 in (A) All Patients and (B) Patients By Sex (patients with amenable mutations)



Rate of change calculated using simple linear regression.
CI=confidence interval.

Summary of Safety Findings From FACETS and the 041 Extension Study

- In FACETS and the 041 extension study, migalastat was generally safe and well tolerated over 48 months of treatment
- During the double-blind period of FACETS, the profile of treatment-emergent adverse events (TEAEs) was similar between migalastat and placebo
  - Headache was the most common TEAE (migalastat, 35%; placebo, 21%) followed by nasopharyngitis (migalastat, 18%; placebo, 6%)
- Most TEAEs reported with migalastat were mild or moderate, and required no intervention or were readily managed in standard clinical practice
- During FACETS, 1 patient experienced 2 serious adverse events (AEs; fatigue and paresthesia) considered possibly related to migalastat; both events resolved
- In FACETS and the 041 extension study, there were no discontinuations due to migalastat-related AEs, including serious AEs
- Two deaths were reported during the extension study; neither was considered related to migalastat treatment

Renal-Specific Safety

- Between months 12 and 24 in the FACETS study, 4 of 50 (8%) patients with amenable mutations experienced treatment-emergent proteinuria
  - For 1 of these patients, proteinuria was considered possibly related to migalastat
- No patient in FACETS or the 041 extension study progressed to end-stage renal disease

CONCLUSIONS

- In both FACETS and the 041 extension study, treatment with migalastat stabilized renal function regardless of baseline renal function level
- In FACETS, migalastat was generally well tolerated and effective in patients with amenable mutations
- Approved in the European Union, Switzerland, and Israel, migalastat offers promise as a first-in-class oral treatment for male and female patients aged ≥16 years with Fabry disease with amenable mutations

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DISCLOSURES

Conflicts of Interest

CL has no conflicts of interest to disclose. RS has received research funding from Amicus Therapeutics, Protalix Biotherapeutics, Genzyme, and Shire. KN serves on advisory boards for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. DGB serves as a consultant and speaker for Amicus Therapeutics and Genzyme, and has received research funding from Amicus Therapeutics, Genzyme, and Shire. UFR serves on advisory boards for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. DAH is a consultant for and has received research and travel funding from Amicus Therapeutics, Genzyme, Shire, Actelion, and Protalix. JY, JPC, NS, and JAB are employees of and own stock in Amicus Therapeutics.

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