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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Supported by Amicus Therapeutics, Inc.

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 a glycosphingolipid α-galactosidase A (α-Gal A).
- Accumulation of glycosphingolipids such as globotriaosylceramide (Gb3) and globotriaosylganglioside, can lead to multiorgan disease and progressive decline in renal function.
- Accumulation of Gb3 in the kidney is a known consequence of Fabry disease.
- Progressive impairment of renal function has been shown to be a major risk factor for cardiac events and premature death. Thus, stabilizing or slowing renal decline is an important treatment goal in Fabry disease.
- Migalastat, a small-molecule, orally administered pharmacophore compound approved in the European Union, Switzerland, and Israel, for the treatment of Fabry disease in patients with amenable GLA mutations.
- Amenable is determined via the Migalastat Amenability Assay by measuring migalastat-induced changes in HEK cells that are transfected with GLA mutated for Fabry disease.
- 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.
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- or slowing renal decline is an important treatment goal in Fabry disease.
- The long-term effect of migalastat on renal function was assessed by calculating the annualized rate of change in eGFRCKD-EPI in patients who received at least 17 months of treatment with migalastat (n=41).
- Based on GFR assessments, renal function remained stable over 18 and 24 months of migalastat treatment in patients with amenable mutations (Figure 1).
- Patients who completed 24 months of treatment in FACETS had the option to enroll in the 041 extension study and receive open-label migalastat.
- 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 eGFRCKD-EPI of −3.0 mL/min/1.73 m2 and −2.6 mL/min/1.73 m2 have been reported for 2 large cohorts of untreated female and male patients with Fabry disease.

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 9-36) for an additional year after that (months 12-36).
- 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.

Key Inclusion Criteria
- Male and female patients aged ≥16 years diagnosed with Fabry disease with amenable GLA mutations.
- Naïve to ERT or had not received ERT for ≥6 months before screening.
- Patients aged ≥16 years with Fabry disease with amenable mutations.
- Patients aged ≥16 years with Fabry disease9,10

RESULTS

- Of 57 patients (39% of whom had amenable mutations) randomly assigned in the phase 3 FACETS trial, 54 patients (91% of whom had amenable mutations) completed the study, and 48 patients (95% of whom had amenable mutations) entered the 041 extension study. Among patients with amenable mutations, renal function remained stable for up to approximately 5 years of treatment with migalastat (n=19).
- Patients who completed FACETS were eligible for enrollment in the phase 3, open-label, long-term extension AT1001-011 study (NCT01451110), referred to as the 041 extension study herein.
- A total of 14 patients (19% of whom had amenable mutations) were enrolled in the 041 extension study; 12 patients completed 24 months of treatment in the 041 extension study; and 11 patients completed at least 36 months of treatment (Figure 1).

Analyses
- All patients: eGFRCKD-EPI was calculated using simple linear regression.
- Patients with amenable mutations: eGFRCKD-EPI was calculated using the mean annualized rate of change in eGFRCKD-EPI from baseline to month 48 was −0.49 mL/min/1.73 m2 (95% confidence interval (CI): −0.55, 0.44) in female patients and −0.32 mL/min/1.73 m2 (95% CI: −0.78, 0.15) in male patients.
- The long-term effect of migalastat on renal function compared favorably with the decline reported in untreated patients with Fabry disease.
- Average annualized declines in eGFRCKD-EPI of −3.0 mL/min/1.73 m2 and −2.6 mL/min/1.73 m2 have been reported for 2 large cohorts of untreated female and male patients with Fabry 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.

REFERENCES


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.
- The most common TEAEs were mild or moderate, and required no intervention or were readily managed in standard medical practice.
- Among patients with amenable mutations, renal function remained stable for up to approximately 5 years of treatment with migalastat (n=19).
- Two deaths were reported during the extension study; neither was considered related to migalastat treatment.

DISCLOSURES

The authors thank the patients and their families, as well as the FACETS and AT1001-041 investigators. Third-party medical editing assistance was provided by ApexCom and was supported by Amicus Therapeutics, Inc.

ACKNOWLEDGMENTS

Conflicts of Interest

D has known economic interests. D has received research funding from Amicus Therapeutics, Protea Biotherapeutics, Genzyme, and Shire. 2 is an advisor to and has received research funding from Amicus Therapeutics, Genzyme, and Shire. 3 is an advisor to and has received research funding from Amicus Therapeutics, Genzyme, and Shire. 4 is a consultant for and has received research and travel funding from Amicus Therapeutics, Genzyme, Shire, Astellas, and Pfizer. 5, 6, 7, and 8 are employees of and own stock in Amicus Therapeutics.

Presented at the 13th International Congress of Inborn Errors of Metabolism; September 5-8, 2017; Rio de Janeiro, Brazil

Supported by Amicus Therapeutics, Inc.