Efficacy and Safety of Migalastat, an Oral Pharmacologic Chaperone for Fabry Disease: Results From Two Randomized Phase 3 Studies, FACETS and ATTRACT

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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 a glycosphingolipid A (a-Gal A)1.
- Accumulation of a-Gal A substrate, including glycolipids such as globotriaosylceramide (GL-3) and globotriaosylinositol-glycerol (GL-I-glycosylceramide) (GL-I-glycosylceramide), can lead to multisystem disease and premature death2.
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacologic chaperone approved in the European Union for the treatment of Fabry disease with amenable GLA mutations.
- Migalastat restores lysosomal trafficking and enzyme activity by binding and inducing proper folding of amenable mutant forms of a-Gal A3.
- As an orally administered small molecule, migalastat may obviate the need for lifelong biweekly agalsidase infusions or enzyme replacement therapy (ERT)4.

OBJECTIVE

- To summarize the efficacy and safety of migalastat in patients with Fabry disease with amenable GLA mutations in 2 randomized phase 3 studies.

METHODS

Study Designs

- FACETS (AT1001-011, NCT00895301) is a phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of migalastat in patients with Fabry disease with amenable GLA mutations (Figure 1).
- ATTRACT (AT1001-012, NCT01218659) is a phase 3, randomized, open-label study to compare the efficacy and safety of migalastat and ERT in patients with Fabry disease with amenable GLA mutations who were previously treated with ERT (Figure 2).
- Patients completing either study were eligible to enter an open-label extension (OLE) examining the safety and efficacy of migalastat (AT1001-043, NCT01051329).

Key Inclusion Criteria for FACETS and ATTRACT

- 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 (FACETS).
- Initiated treatment with ERT 3 months before baseline visit and had a stable ERT dose (at ≥80% labeled dose) for 3 months before baseline visit (ATTRACT).
- Patients completing either study were eligible to enter an open-label extension (OLE) examining the safety and efficacy of migalastat (AT1001-043, NCT01051329).

RESULTS

- The FACETS/ATTRACT studies randomized 67/60 patients. Based on the final cell-based GLP HEK assay, 50/50 patients had amenable mutant forms of a-Gal A.

Patients Had Significant Baseline Severity

- In both phase 3 studies, 95% of patients had Fabry disease with involvement in ≥2 organ systems, indicating significant disease burden.
- In FACETS, 90% of patients had renal involvement, 52% had cardiac involvement, and 54% had central nervous system (CNS) involvement.
- In ATTRACT, 75% of patients had renal involvement, 71% had cardiac involvement, and 50% had CNS involvement.

Disease Substrate

- In FACETS, migalastat treatment significantly reduced interstitial capillary GL-3 inclusions and lysosomaal β-galactosidase levels in patients with Fabry disease with amenable mutations (Figures 3 and 4).
- In ATTRACT, plasma lysosomal β-galactosidase levels remained on stable follow-up from ERT to migalastat in patients with amenable mutations. Plasma lysosomal β-galactosidase levels increased in 2 patients with non-amenable mutations following the switch from ERT to migalastat, but did not change in patients with 2 non-amenable mutations who remained on ERT.

Composite Endpoint in ATTRACT

- In the composite clinical endpoint of renal, cardiac, or cerebrovascular events, the frequency of events was 29% and 46% in patients in the migalastat and ERT groups (18 months of treatment), respectively, indicating that the effect of migalastat compares favorably to that of ERT.

Summary of Safety Findings From FACETS and ATTRACT

- Treatment with migalastat was generally safe and well tolerated, with no adverse event (AE) trends attributable to migalastat.
- Most treatment-emergent AEs (TEAs) reported with migalastat use were mild or moderate, and required no intervention or were readily managed in standard clinical practice.
- The profile of TEAs was similar between migalastat and placebo treatment, with headache the most commonly reported TEA.
- There were few severe AEs considered related to migalastat and no deaths during either study.
- There were few discontinuations due to TEAs, and most were related to underlying Fabry disease comorbidities.

CONCLUSIONS

- Migalastat was well tolerated and effective across patient subgroups in both FACETS and ATTRACT.
- In both FACETS and ATTRACT, treatment with migalastat stabilized renal function in male and female patients. In ATTRACT, migalastat and ERT were shown to have comparable effects on renal function.
- The reduction in LVMi by migalastat found in FACETS and ATTRACT is expected to contribute to a decrease in the cardiac complications commonly observed in Fabry disease.
- Based on the findings in FACETS, treatment with migalastat was associated with improvements in several gastrointestinal signs and symptoms and may have a long-term positive effect on quality of life.
- Approved in the European Union, migalastat offers promise as a first-in-class oral treatment for male and female patients with Fabry disease with amenable mutations.

REFERENCES

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DISCLOSURES

Conflicts of Interest

UHP has received research funding from Shire and Genzyme/Sanofi and has served on advisory boards for Amicus Therapeutics. RJS is a consultant and an investigator for Amicus Therapeutics, Biomarin, Genzyme, and Shire; has received educational grants from Ablynx and Urogenax; is a speaker for and has received honoraria from Amicus Therapeutics, Actelion, Biomarin, Genzyme, and Shire; and has received travel support from Shire. DPG and MR have no conflicts of interest to disclose. DHH is a consultant/advisor for Shire, Sanofi, Biomarin, Amicus Therapeutics, Actelion, and Protalix; has received research funding from Shire and Sanofi; and is a speaker for and has received travel support from Shire, Sanofi, Biomarin, Amicus Therapeutics, and Protalix. WJC is a consultant for Amicus Genzyme; has received research funding from Shire and is a member of the Fabry Registry Board of Advisors. IB is a consultant for and has received research funding from Protalex; NethoCorp and Amicus Therapeutics. CGB is an investigator for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. AI has served as a consultant for Genzyme, Shire, and Amicus Therapeutics. JPC, IT, RO, and JB are employees of Amicus Therapeutics.

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