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 α-galactosidase A (α-Gal A)[1]
- Accumulation of α-Gal A substrates, including glycosphingolipids such as globotriaosylceramide (GL-3) and globotriaosylsphingosine (lyso-Gb_3), can lead to multisystem disease and premature death[1]
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacologic chaperone approved in the European Union for the treatment of Fabry disease in patients with *amenable GLA* mutations[2]
- Migalastat restores lysosomal trafficking and enzyme activity by binding and inducing proper folding of amenable mutant forms of α-Gal A[1,3]
- As an orally administered small molecule, migalastat may obviate the need for lifelong biweekly agalsidase infusions or enzyme replacement therapy (ERT)[4,5]

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

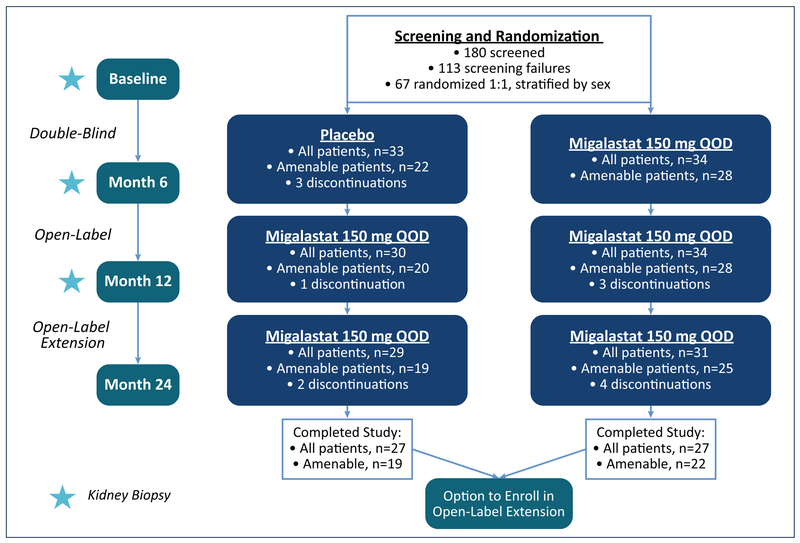
Study Designs

- FACETS (AT1001-011, NCT00985301) 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 (AT1001-041, NCT1458119)

Key Inclusion Criteria for FACETS and ATTRACT

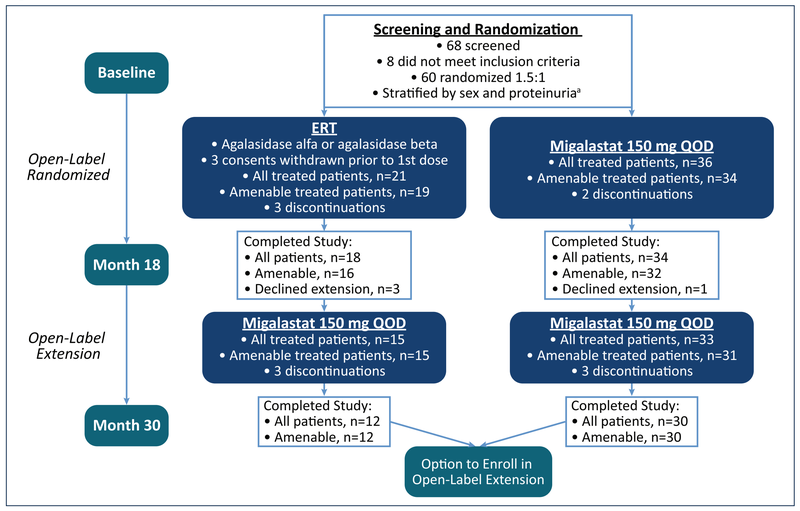
- Male and female patients aged 16-74 years diagnosed with Fabry disease with amenable *GLA* mutations
- Naive to ERT or had not received ERT for ≥6 months before screening (FACETS)
- Initiated treatment with ERT ≥12 months before baseline visit and had a stable ERT dose (at ≥80% labeled dose) for 3 months before baseline visit (ATTRACT)
- $eGFR_{MDRD}$ at screening ≥30 mL/min/1.73 m^2
- Urine GL-3 at screening ≥4× the upper limit of normal (24-hour collection) (FACETS)
- 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

Figure 1. FACETS Study Design



QOD=every other day; SAE=serious adverse event.

Figure 2. ATTRACT Study Design



ERT=enzyme replacement therapy.
[a]Proteinuria stratification: high (≥0.1 g/24 h); low (<0.1 g/24 h).

RESULTS

- The FACETS/ATTRACT studies randomized 67/60 patients. Based on the final cell-based GLP HEK assay, 50/56 patients had amenable mutant forms of α-Gal A

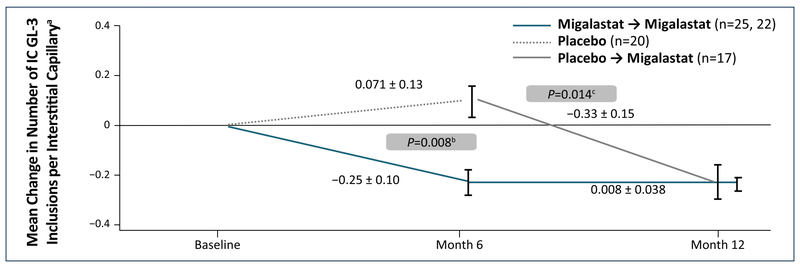
Patients Had Significant Baseline Disease Severity

- In both phase 3 studies, 91% 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

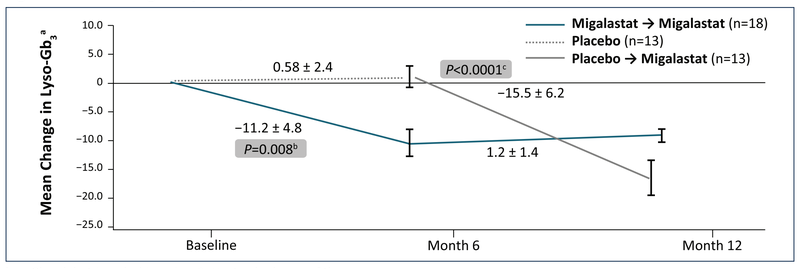
- In FACETS, migalastat treatment significantly reduced interstitial capillary GL-3 inclusions and lyso-Gb_3 levels in patients with Fabry disease with amenable mutations (**Figures 3** and **4**)
- In ATTRACT, plasma lyso-Gb_3 levels remained low and stable following the switch from ERT to migalastat in patients with amenable mutations. Plasma lyso-Gb_3 levels increased in 2 patients with non-amenable mutations following the switch from ERT to migalastat, but did not change in 2 patients with non-amenable mutations who remained on ERT

Figure 3. Mean Change in IC GL-3 Inclusions in the FACETS ITT-Amenable Population



GL-3=globotriaosylceramide; IC=interstitial capillary; ITT=intention-to-treat.
[a]Data are baseline corrected.[b]Analysis of covariance (ANCOVA) model with covariate adjustment for baseline value and factors for treatment group and treatment by baseline interaction. *P* value corresponds to least-squares mean difference between migalastat and placebo.
[c]Mixed-effects model for repeated measures was used for the change from months 6 to 12 (placebo to migalastat).
The model used fixed effects for treatment group and time, time by treatment interaction, and baseline GL-3 inclusions.

Figure 4. Mean Change in Lyso-Gb_3 Levels in the FACETS ITT-Amenable Population



lyso-Gb_3=globotriaosylsphingosine; SEM=standard error of the mean.
[a]Data are baseline corrected and represent mean (± SEM) change from baseline or month 6. [b]ANCOVA comparing migalastat to placebo from baseline to month 6. [c]ANCOVA comparing change from months 6 to 12 in patients switching from placebo to migalastat. ANCOVA used covariate adjustment for baseline value and factors for treatment group and treatment by baseline interaction. *P* values correspond to least squares mean difference between migalastat and placebo. Of the 44 patients who consented to the plasma lyso-Gb_3 analyses, 31 had amenable mutations.

Summary of Renal and Echocardiology Assessments

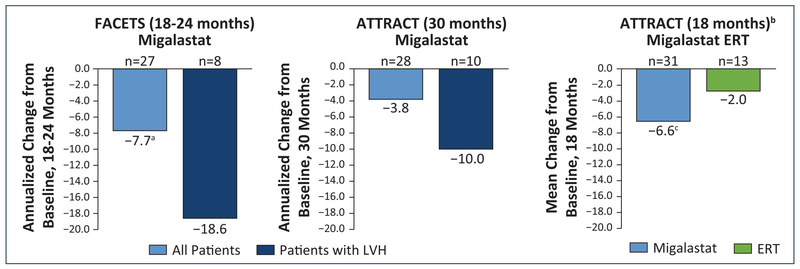
- In both FACETS and ATTRACT, treatment with migalastat stabilized renal function and reduced left ventricular mass index (LVMi) in patients with amenable mutations (**Table 1** and **Figure 5**)
- In FACETS, renal function remained stable for the 41 patients who continued into the OLE study (average of 36 months), with an annualized rate of change in $eGFR_{CKD-EPI}$ of −0.77 mL/min/1.73 m^2 (95% CI −1.9, 0.39)
- In ATTRACT, migalastat and ERT were shown to have comparable effects on renal function following 18 months of treatment (**Table 1**)
- In both FACETS and ATTRACT, the LVMi change from baseline for migalastat-treated patients was largest for patients with left ventricular hypertrophy (**Figure 5**)

Table 1. Summary of Renal Function Results From FACETS and ATTRACT in Patients With Amenable Mutations

Population	Treatment	Measurement	$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	$mGFR_{iohexol}$ (mL/min/1.73 m^2)
FACETS	Migalastat	Annualized mean, 24 months (SEM)	−0.30 (0.66), n=41	−1.51 (1.33), n=37
ATTRACT	Migalastat	Annualized mean, 18 months (95% CI)	−0.4 (−2.27, 1.48), n=34	−4.35 (−7.65, −1.06), n=34
	ERT		−1.03 (−3.64, 1.58), n=31	−3.24 (−7.81, 1.33), n=18
	Migalastat	Annualized mean change from baseline, 18 months (95% CI)	−1.1 (−2.2, 0.1), n=31	−5.0 (−8.5, 1.5), n=31
	Migalastat	Annualized mean change from baseline, 30 months (95% CI)	−1.7 (−2.7, −0.8), n=31	−2.7 (−4.8, −0.7), n=31

CI=confidence interval; $eGFR_{CKD-EPI}$=estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration Equation; $mGFR_{iohexol}$=measured GFR using iohexol clearance.

Figure 5. Summary of LVMi Results From FACETS and ATTRACT in Patients With Amenable Mutations

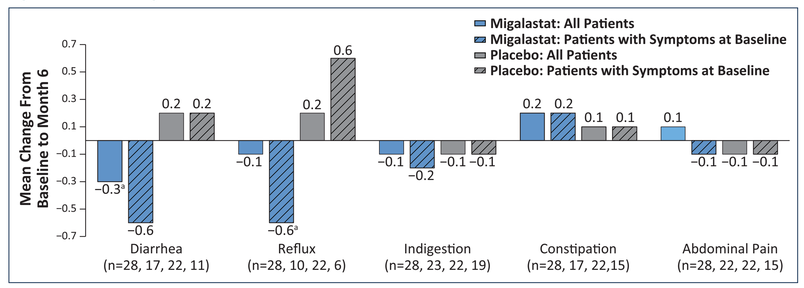


LVH=left ventricular hypertrophy.
[a]*P*<0.05. [b]All patients. [c]Statistically significant (95% CI does not overlap zero).

Summary of Gastrointestinal Signs and Symptoms From FACETS

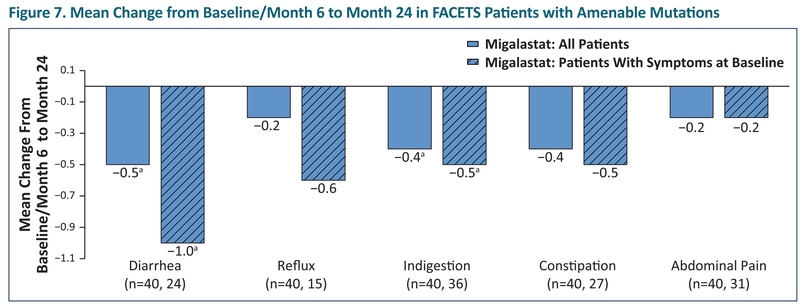
- In FACETS, 6 months of treatment with migalastat was associated with improvement in the diarrhea domain of the Gastrointestinal Symptom Rating Scale, compared with placebo (**Figure 6**)
- Improvements were seen in several of the domains over 24 months, indicating that migalastat may have a long-term positive effect on quality of life (**Figure 7**)

Figure 6. Mean Change from Baseline to Month 6 in FACETS Patients with Amenable Mutations



[a]*P*≤0.05 based on ANCOVA.

Figure 7. Mean Change from Baseline/Month 6 to Month 24 in FACETS Patients with Amenable Mutations



[a]Statistically significant based on 95% CIs <0.

Composite Endpoint in ATTRACT

- In the composite clinical endpoint of renal, cardiac, or cerebrovascular events, the frequency of events was 29% and 44% of 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 (TEAEs) reported with migalastat use were mild or moderate, and required no intervention or were readily managed in standard clinical practice
- The profile of TEAEs was similar between migalastat and placebo treatment, with headache the most commonly reported TEAE
- There were few serious AEs considered related to migalastat and no deaths during either study
- There were few discontinuations due to TEAEs, and most were related to underlying Fabry disease comorbidities

CONCLUSIONS

- Migalastat was well tolerated and effective across patient subgroups in both FACETS[6] 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

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DISCLOSURES

Conflicts of Interest

UFR has received research funding from Shire and Genzyme/Sanofi and has served on advisory boards for Amicus Therapeutics. RG is a consultant and an investigator for Amicus Therapeutics, Biomarin, Genzyme, and Shire; has received educational grants from Alexion and Ultragenyx; is a speaker for and has received honoraria from Amicus Therapeutics, Actelion, Biomarin, Genzyme, and Shire; and has received travel grants from Alexion. DPG and DB have no conflicts of interest to disclose. DAH 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. WRW is a consultant for Genzyme; is an investigator for Amicus Therapeutics and Genzyme; has received research funding from Shire; and is a member of the Fabry Registry Board of Advisors. RS is a consultant for and has received research funding from Protalix Biotherapeutics and Amicus Therapeutics. DGB is an investigator for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. AJ has served as a consultant for Genzyme, Shire, and Amicus Therapeutics. JPC, JY, NS, and JAB are employees of Amicus Therapeutics.

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