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Migalastat Improves Gastrointestinal Signs and Symptoms in Patients With Fabry Disease: Patient-Level Responder Analyses From the Double-Blind, Placebo-Controlled Phase 3 Trial (FACETS)

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INTRODUCTION

- Fabry disease is a devastating, rare, and progressive X-linked lysosomal storage disorder caused by the functional deficiency of α-galactosidase A (α-Gal A) as a result of mutation in the *GLA* gene[1]
- More than 50% of patients with Fabry disease report or show gastrointestinal (GI) signs and symptoms, including abdominal pain, diarrhea, constipation, nausea, and vomiting[2]
- 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[3]
- Migalastat restores lysosomal trafficking and enzyme activity by binding and inducing proper folding of amenable mutant forms of α-Gal A[3,4]
- As an orally administered small molecule, migalastat may obviate the need for lifelong biweekly agalsidase infusions or enzyme replacement therapy (ERT)[5,6]

OBJECTIVE

- To further assess the effects of migalastat on diarrhea relative to placebo, using a new patient-level responder analysis based on the minimal clinically important difference (MCID)

METHODS

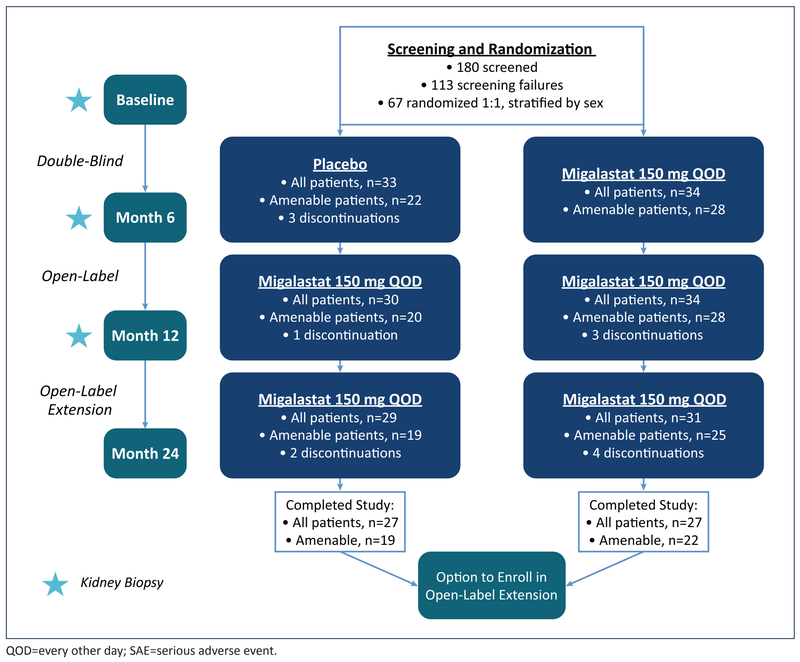
Study Design: FACETS

- FACETS (AT1001-011, NCT00985301) is a phase 3, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of migalastat in patients with Fabry disease with amenable mutations; the study consisted of 6 months of double-blind treatment with migalastat or placebo and 6 months of open-label migalastat, followed by a 12-month open-label extension (AT1001-041, NCT01458119) (**Figure 1**)

Key Inclusion Criteria

- Male and female patients aged 16-74 years with a diagnosis of Fabry disease with amenable *GLA* mutations
- Naive to ERT or had not received ERT for ≥6 months before screening
- $eGFR_{MDRD}$ of ≥30 mL/min/1.73 m^2 at screening
- Urine globotriaosylceramide 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

Figure 1. FACETS Study Design



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

Gastrointestinal Assessments

- The Gastrointestinal Symptoms Rating Scale (GSRS) contains 15 items to assess the severity of 5 domains: abdominal pain, reflux, diarrhea, indigestion, and constipation
  - Each domain consists of 2-4 questions, scored on a 7-point Likert scale (ranging from 1-absence of burden to 7-severe discomfort)
- Scores were determined by calculating the mean of the items completed within an individual subscale
- GSRS scores were collected at baseline and months 6, 12, 18, and 24
- Subanalyses measured GSRS results in patients presenting with GI signs and symptoms at baseline and in patients with non-amenable mutations

Minimal Clinically Important Difference for GSRS-Diarrhea

- Post hoc patient-level responder analyses of the FACETS study using the MCID between 0.33 and 0.66 were based on estimates from the literature for several non-Fabry GI disorders in which diarrhea is prominent[7-9]
  - MCIDs are derived from anchor-based methodologies from liver transplant patients with GI symptoms (MCID=0.33),[7] patients with autoimmune disease with and without GI symptoms (MCID=0.33),[8] and renal transplant patients with and without GI symptoms (MCID=0.40)[9]
- Distribution-based estimates of MCID in Fabry disease were based on the change from baseline data in the placebo arm of the FACETS study. The MCID of 0.35 was based on half the standard deviation, and the MCID of 0.43 was based on the standard error of measurement[7,8]
- Based on these analyses, 0.33 was determined to be the best estimate of MCID for the diarrhea domain of the GSRS (GSRS-D)

RESULTS

Summary of GSRS Findings

- More than 50% of patients enrolled in FACETS with baseline values on the GSRS-D reported baseline GI signs and symptoms, including diarrhea, indigestion, constipation, and abdominal pain (**Table 1**)
- GI signs and symptoms improved in 3 of 5 domains (diarrhea, reflux, and indigestion) within the first 6 months of treatment in patients receiving migalastat
- Patients with baseline symptoms had larger improvements in GSRS-D between baseline and month 6 (*P*=0.06) compared with all patients (baseline vs month 6; *P*=0.03) (**Table 1**)
- In patients presenting with GI signs and symptoms at baseline, migalastat significantly improved scores in the reflux domain after 6 months of treatment (*P*=0.047)
- After 24 months, there were significant improvements in the indigestion and diarrhea domains in the intention-to-treat (ITT)–amenable population and in the subset of patients presenting with GI signs and symptoms at baseline (*P*<0.05). There was also a trend toward improvement in the constipation domain

Table 1. Baseline and Change From Baseline in GSRS-D

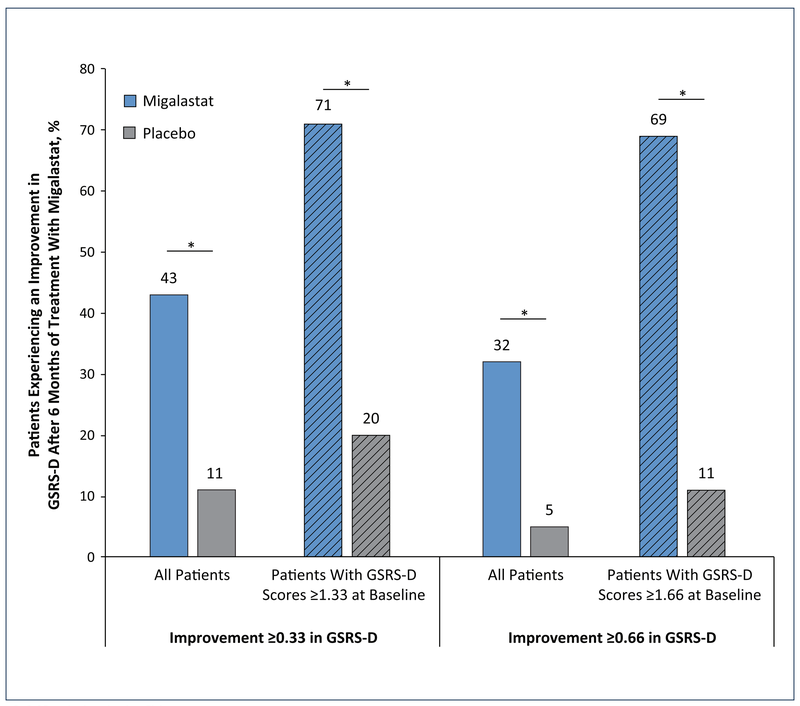
	Mean Baseline Values		Mean Change From Baseline to Month 6		Mean Change From Baseline/Month 6 (placebo) to Month 24 (OLE migalastat treatment)	
	All Patients, Mean (n)	Patients With Symptoms at Baseline, Mean (n)	All Patients, Mean	Patients With Symptoms at Baseline, Mean	All Patients, Mean (95% CI) n=40	Patients With Symptoms at Baseline, Mean (95% CI) n=24
Migalastat	2.3 (28)	3.2 (17)	−0.3[a]	−0.6	−0.5 (−0.9, −0.1)[b]	−1.0 (−1.5, −0.4)[b]
Placebo	2.1 (22)	3.1 (11)	0.2	0.2		

CI=confidence interval; GSRS-D=diarrhea domain of the Gastrointestinal Symptoms Rating Scale; OLE=open-label extension.
[a]*P*≤0.05 based on analysis of covariance (ANCOVA).
[b]Statistically significant based on 95% CIs >0.

Summary of GSRS-D Findings Using MCID

- A significant percentage of patients in the ITT-amenable population experienced an MCID ≥0.33 in GSRS-D (**Figure 2**)
  - After 6 months, 43% of the migalastat-treated patients experienced an MCID ≥0.33 compared with 11% of patients receiving placebo (*P*=0.02)
  - Approximately 50% of patients presented with diarrhea at baseline (baseline GSRS-D scores ≥1.33); of this subgroup, 71% of the migalastat-treated patients experienced an MCID ≥0.33 compared with 20% of placebo-treated patients (*P*=0.02)
- After 6 months of treatment, 69% of patients with baseline GSRD-D scores ≥1.66 given migalastat had an improvement ≥0.66, compared with 11% of patients given placebo (*P*=0.012); similar results were found in sensitivity analyses using a higher threshold (**Figure 2**)

Figure 2. Sensitivity Analysis: Patients Experiencing Improvement of ≥0.33 or ≥0.66 in GSRS-D After 6 Months of Treatment With Migalastat



*P<0.05, calculated using Fisher's exact test.

Mean Change From Baseline in GSRS-D in Patients With Amenable vs Non-amenable Mutations

- While there was a significant decrease in GSRS-D between baseline and month 6 in the ITT-amenable population, patients with non-amenable mutations did not demonstrate improvement in diarrhea when treated with migalastat (**Table 2**)

Table 2. Mean Change in GSRS-D From Baseline to Month 6 in the ITT-amenable Population Compared With the ITT Non-amenable Population

Population	Treatment Group	Baseline GSRS-D Score, Mean (SD)	Change From Baseline to Month 6, Mean (SD)	Difference Between Treatment Groups at Month 6: Migalastat-Placebo (95% CI)	*P*-Value
ITT-amenable (n=50)	Migalastat	2.3 (1.6)	−0.3 (0.9)	−0.52 (−1.0, −0.1)	0.03[a]
	Placebo	2.1 (1.5)	0.2 (0.8)		
Patients with non-amenable mutations (n=17)	Migalastat	2.4 (2.2)	−0.1 (1.4)	0.4 (−0.8, 1.7)	0.47
	Placebo	1.8 (1.3)	−0.1 (0.5)		

Higher GSRS scores indicate greater severity of symptoms. *P*-value is calculated from ANCOVA, comparing the difference in LS means. The model includes treatment, baseline, and treatment by baseline interaction.
LS=least-squares; SD=standard deviation.
[a]*P*≤0.05 based on ANCOVA.

- In patients with non-amenable mutations, the proportion achieving an MCID ≥0.33 in GSRS-D was similar between the migalastat and placebo treatment groups (**Table 3**)

Table 3. Patients With Non-amenable Mutations Experiencing Improvement in MCID of ≥0.33 in GSRS-D From Baseline to Month 6

Population	Migalastat, % (n/N)	Placebo, % (n/N)	Difference, %	*P*-Value
Non-amenable mutations (n=17)	17 (1/6)	13 (1/8)	4	1.0[a]

All patients with non-amenable mutations presented with GI signs and symptoms at baseline.
[a]*P*-value was calculated using Fisher's exact test.

CONCLUSIONS

- Treatment with migalastat was associated with improvement in GI signs and symptoms,[10] with migalastat-treated patients achieving greater improvements in the GSRS-D than placebo-treated patients
- Improvements in GI signs and symptoms were seen after both 6 and 24 months of treatment with migalastat
- Analyses using the estimated MCID of 0.33 also demonstrated that treatment with migalastat was associated with a clinically relevant improvement in diarrhea signs, as assessed by the GSRS-D
- Improvements in GI signs and symptoms with migalastat treatment were observed in all patients with amenable mutations and were largest in those who presented with GI signs and symptoms at baseline
- Migalastat-associated improvements in GI signs and symptoms may have a long-term positive effect on quality of life

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ACKNOWLEDGMENTS

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

DISCLOSURES

RS has served as a consultant for and 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. 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. RG is a consultant and an investigator for Amicus Therapeutics, Biomarin, Genzyme, and Shire; has received educational grants from Alexion and Ultragenyx; is an investigator for Amicus Therapeutics, Biomarin, Genzyme, and Shire; is a speaker for and has received honoraria from Amicus Therapeutics, Actelion, Biomarin, Genzyme, and Shire; and has received travel grants from Alexion. 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. SPS is an investigator for Amicus Therapeutics, Biomarin, Genzyme/Sanofi, Protalix/Pfizer, Shire, and Actelion. DPG has no conflicts of interest to disclose. CV, JPC, NS, and JAB are employees of Amicus Therapeutics.

http://bit.ly/2958kHL

Supported by Amicus Therapeutics, Inc.

Presented at the 13th Annual WORLD*Symposium*™; February 13-17, 2017; San Diego, CA, USA