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Effects of Treatment With Migalastat on the Combined Endpoint of Kidney Globotriaosylceramide Accumulation and Diarrhea in Patients With Fabry Disease: Results From the Phase 3 FACETS Study

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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 pharmacological chaperone approved in the European Union, Switzerland, and Israel for the treatment of Fabry disease in patients with *amenable GLA* mutations[3-5]
- The binding of migalastat to the active site of α-Gal A stabilizes certain mutant enzymes (referred to as amenable), thus facilitating proper trafficking to lysosomes, where dissociation of migalastat allows α-Gal A to catabolize accumulated substrates[6-11]
- As an orally administered small molecule, migalastat may obviate the need for lifelong biweekly agalsidase infusions or enzyme replacement therapy (ERT) in patients with amenable mutations[5,12]

OBJECTIVE

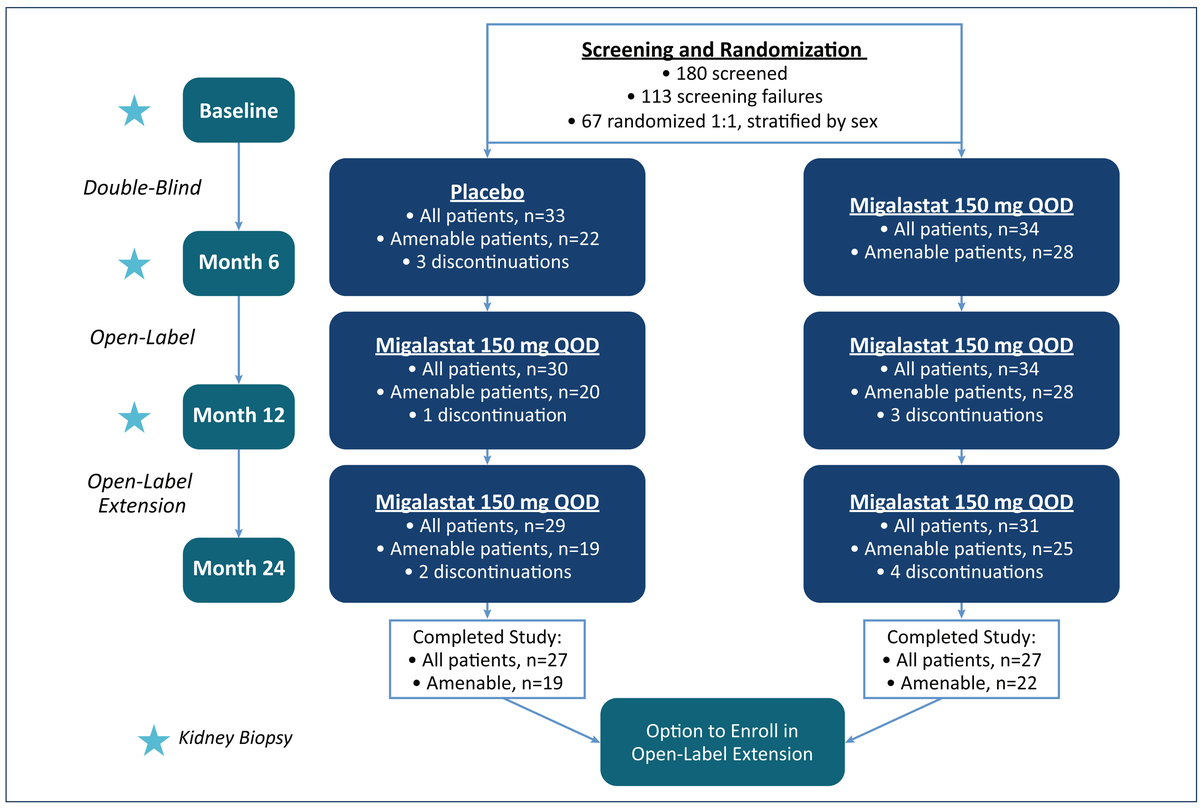
- To assess the effects of migalastat relative to placebo on kidney interstitial capillary globotriaosylceramide (KIC GL-3) content, changes in diarrhea, and the combined endpoint of changes in KIC GL-3 and diarrhea in patients in the phase 3 FACETS study

METHODS

Study Design

- FACETS (AT1001-011, NCT00925301) 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 (**Figure 1**)

Figure 1. FACETS Study Design and Disposition



QOD=every other day.

Key Inclusion Criteria

- Male and female patients aged 16-74 years with a diagnosis of Fabry disease with responsive *GLA* mutations based on a preliminary human embryonic kidney 293 cell assay
- Naive to ERT or had not received ERT for ≥6 months before screening
- $eGFR_{MDRD}$ ≥30 mL/min/1.73 m^2 at screening
- 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

Amenability of Mutant α-Gal A Forms

- Amenability was determined using a GLP-validated assay, which became available after study initiation[7]
- Testing was completed before unblinding of the data

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[13]
- Each domain consists of 2-4 questions, scored on a 7-point Likert scale (ranging from 1-absence of burden to 7-severe discomfort)
- The score for the diarrhea domain of the GSRS (GSRS-D) was the mean of the 3 related questions (diarrhea, reflux, indigestion)
- A response in the GSRS-D was defined as a reduction >0.33 (estimated minimal clinical important difference; MCID), which was derived using distribution-based methods and/or anchor-based methodologies from liver transplant patients with GI symptoms (MCID=0.33),[14] patients with autoimmune disease with and without GI symptoms (MCID=0.33),[15] and renal transplant patients with and without GI symptoms (MCID=0.40)[16]
- GSRS scores were collected at baseline and months 6, 12, 18, and 24

KIC GL-3 Inclusion Assessments

- Renal biopsies were collected at baseline and months 6 and 12. The number of KIC GL-3 inclusions was quantitatively measured using digital images[17]
- Response to migalastat was defined as a reduction of >0.1 inclusions per capillary (above background staining)

Statistical Analysis

- The number of patients demonstrating a response in KIC GL-3 and/or GSRS-D from baseline to month 6 was compared between the migalastat and placebo groups
- A retrospective analysis using Xu's statistic, evaluated if treatment had an effect on changes in KIC GL-3 and GSRS-D simultaneously from baseline to month 6 in the intention-to-treat (ITT) amenable population
- Logistic regression assessed the correlation between changes in KIC GL-3 and GSRS-D

RESULTS

Summary of Baseline and Change from Baseline for KIC GL-3 and GSRS-D in FACETS

- Sixty-seven patients were randomized in FACETS; 50 treated patients had amenable mutations
- After 6 months, in all patients with amenable mutations, migalastat treatment reduced KIC GL-3 inclusions and GSRS-D scores, while placebo did not (**Table 1**)
- Eighty-three percent (15/18) of migalastat-treated patients with amenable mutations demonstrated a response in KIC GL-3 and/or MCID in GSRS-D when either or both were elevated at baseline, compared with 33% (5/15) of patients treated with placebo

Table 1. Change From Baseline to Month 6: GSRS-D and KIC GL-3 Inclusions (ITT-Amenable Population)[3]

	Migalastat	Placebo
Baseline GSRS-D, mean ± SD (n)	2.3 ± 1.61 (28)	2.1 ± 1.47 (22)
Mean change from baseline	−0.3	0.2
Difference (migalastat-placebo)	−0.5 (*P*=0.03)[a]	
Baseline KIC GL-3 inclusions, mean ± SD (n)	0.649 ± 1.23 (25)	0.493 ± 0.594 (20)
Change from baseline, mean ± SD	−0.25 ± 0.51	0.071 ± 0.56
Difference (migalastat-placebo)	−0.3 (*P*=0.008)[a]	

GL-3=globotriaosylceramide; GSRS-D=Gastrointestinal Symptoms Rating Scale-Diarrhea; ITT, intention-to-treat; KIC=kidney interstitial capillary; SD=standard deviation.
[a]*P* value/least squares (LS) mean from analysis of covariance, comparing the difference in LS means. The model includes treatment, baseline, and treatment by baseline interaction.

Xu's Statistic and Logistic Regression for KIC GL-3 and GSRS-D

- Xu's statistic revealed a significant difference between treatments from baseline to month 6 for the combined endpoint of KIC GL-3 and GSRS-D (*P*=0.009; 1-sided) (**Table 2**)

Table 2. Xu's Statistic on Combined Changes in KIC GL-3 and GSRS-D in FACETS

Population	1-sided *P*-Value	1-sided *P*-Value	*Bona Fide* 1-sided *P*-Value
	KIC GL-3	GSRS-D	KIC GL-3 and GSRS-D Combined
ITT-amenable	0.021	0.029	0.009

- Patients with a reduction in KIC GL-3 were 4.3 to 5.6 times more likely to show improvement in GSRS-D than patients who did not have a reduction in KIC GL-3 (**Table 3**)

Table 3. Logistic Regression Between Reductions in KIC GL-3 and Improvement in GSRS-D in the ITT and ITT-Amenable Populations

Population	Parameter and Criteria	Odds Ratio[a]	95% CI of Odds Ratio[a]
ITT	GSRS-D CFBL ≤ −0.33 (n=67) KIC GL-3 CFBL < −0.1	4.298	1.155, 15.997
ITT-amenable	GSRS-D CFBL ≤ −0.33 (n=50) KIC GL-3 CFBL < −0.1	5.550	1.173, 26.255

CFBL=change from baseline; CI=confidence interval.
[a]Odds ratios and 95% CIs are based on logistic regression that includes the KIC GL-3 and treatment groups.

CONCLUSIONS

- Migalastat simultaneously reduces the disease substrate and improves GI symptoms in patients with Fabry disease with amenable mutations
- Reductions in KIC GL-3 are associated with improvements in diarrhea
- The significant correlation between KIC GL-3 and the GSRS-D supports the use of KIC GL-3 as a biomarker that is a predictor of clinical benefit

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DISCLOSURES

Conflicts of Interest

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