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.
- More than 50% of patients with Fabry disease report or show gastrointestinal (GI) signs and symptoms, including abdominal pain, diarrhea, constipation, nausea, and vomiting.
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacological chaperone approved in the European Union for the treatment of Fabry disease in patients with amenable GLA mutations.
- 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.
- 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.

OBJECTIVE

- To assess the effects of migalastat relative to placebo on kidney interstitial capillary dissociation of migalastat allows α-Gal A to catabolize accumulated substrates.
- More than 50% of patients with Fabry disease report or show gastrointestinal (GI) signs and symptoms, including abdominal pain, diarrhea, constipation, nausea, and vomiting.

METHODS

- Study Design: FACETS (ATI0101-011, 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 (Figure 1).

RESULTS

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Parameter and Criteria</th>
<th>Odds Ratio</th>
<th>95% CI of Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>GSRD-CFBL &lt; 0.33 (n=67)</td>
<td>4.298</td>
<td>1.155, 15.997</td>
</tr>
<tr>
<td>KIC GL-3 CFBL &lt; 0.01 (n=12)</td>
<td>5.550</td>
<td>1.173, 26.255</td>
<td></td>
</tr>
</tbody>
</table>

| GLS=glomerular sclerosis, GSRD=GI/Somatological Symptoms Rating Scale Drug, ITT=intention to treat, KIC-kidney interstitial capillary. 1-sided values. 2-sided deviation. P value from analysis of covariance, comparing the difference in LS means. The model includes treatment, baseline, and treatment by baseline interaction. |

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).
- The score for the diarrhea domain of the GRS-D was the mean of the 3 related questions (diarrhea, reflux, indigestion).
- A response in the GRS-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.
- Patients with autoimmune disease and with without GI symptoms (MCID=0.33), patients with Fabry disease with amenable mutations (MCID=0.40), patients with Fabry disease with non-amenable mutations (MCID=0.33), and renal transplant patients with and without GI symptoms (MCID=0.40).
- Migalastat 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.
- 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 GRS-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 GSRD 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 GSRD-D.

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 GSRD supports the use of KIC GL-3 as a biomarker that is a predictor of clinical benefit.

ACKNOWLEDGMENTS

The authors acknowledge the patients, their families, and Fabry disease patient organizations, as well as the FACETS study investigators. Third-party medical editing assistance was provided by ApotheCom and was supported by Amicus Therapeutics, Inc.

DISCLOSURES

DPG has no conflicts of interest to disclose. DAH is a consultant/advisor and speaker for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. RS is a consultant for and has received research funding from Protaix Biotechtherapeutics and Amicus Therapeutics. WRW is a consultant for Genzyme and has received research funding from Amicus Therapeutics, Genzyme, and Shire. CV is an employee of and owns stock in Amicus Therapeutics. FH, JY, NS, AM, IPC, and JAB are employees of Amicus Therapeutics.

REFERENCES


The authors acknowledge the patients, their families, and Fabry disease patient organizations, as well as the FACETS study investigators. Third-party medical editing assistance was provided by ApotheCom and was supported by Amicus Therapeutics, Inc.

DISCLOSURES

DPG has no conflicts of interest to disclose. DAH is a consultant/advisor and speaker for and has received research funding and travel support from Shire, Sanofi, and Biomarin. DGB is an investigator for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. RS is a consultant for and has received research funding from Protaix Biotechtherapeutics and Amicus Therapeutics. WRW is a consultant for Genzyme and has received research funding from Amicus Therapeutics, Genzyme, and Shire. CV is an employee of and owns stock in Amicus Therapeutics. FH, JY, NS, AM, IPC, and JAB are employees of Amicus Therapeutics.