INTRODUCTION

- Fabry disease is a devastating, rare, and progressive X-linked lysosomal storage disorder caused by the functional deficiency of a galactosylceramide 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, indigestion, constipation, nausea, and vomiting.  
- 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.
- Migalastat restores lysosomal trafficking and enzyme activity by binding and inducing proper folding of amenable mutant forms of α-Gal A.  
- As an orally administered small molecule, migalastat may obviate the need for lifelong biweekly agalsidase infusions or enzyme replacement therapy (ERT).  

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, NCT01695501] 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.
- None to < 25% of free erythrocyte protoporphyrin (FEP) above 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 24 weeks before the screening visit.

RESULTS

Summary of GSRS Findings

- A significant percentage of patients in the ITT-population experienced an MCID ≥0.33 in GSRS-D.
- After 6 months, 43% of the migalastat-treated patients experienced an MCID ≥0.33 compared with 11% of patients receiving placebo.
- Approximately 50% of patients presented with diarrhea at baseline (Baseline GSRS-D score ≥1.33); 71% of the migalastat-treated patients experienced an MCID ≥0.33 compared with 20% of placebo-treated patients.
- After 6 months of treatment, 69% of patients with baseline GSRS-D scores ≥1.66 given migalastat had an improvement ≥0.66, compared with 15% of patients given placebo (P=0.02); similar results were found in sensitivity analyses using a higher threshold (Figure 2).

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment Group</th>
<th>Mean Baseline</th>
<th>Change from Baseline</th>
<th>Difference</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, Mean (SD)</td>
<td>Migalastat</td>
<td>3.0 (1.9)</td>
<td>0.6 (1.0)</td>
<td>1.6 (2.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.1 (2.5)</td>
<td>0.1 (1.3)</td>
<td>-0.3 (1.9)</td>
<td>-1.6 (3.0)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment Group</th>
<th>Change from Baseline</th>
<th>Difference</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, Mean (SD)</td>
<td>Migalastat</td>
<td>0.3 (0.3)</td>
<td>-0.3 (0.7)</td>
<td>-0.6 (1.0)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.2 (0.4)</td>
<td>0.0 (0.1)</td>
<td>-0.4 (1.0)</td>
<td>-0.7 (1.5)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

- Treatment with migalastat was associated with improvement in GI signs and symptoms, 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 NMC 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 larger 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.

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.

REFERENCES


DISCLOSURES

RI has served as a consultant for and received research funding from Protalix Biotherapeutics and Amicus Therapeutics. DGB is an investigator and has received research funding from Amicus Therapeutics, Biogen, and Shire. WRW is a consultant for Alexion; an investigator for Amicus Therapeutics, Biogen, Genzyme, Sanofi, Protalix/Biopharm, Shire, and Akcea. DPG has no conflicts of interest to disclose. CV, JPC, NS, and JAB are employees of Amicus Therapeutics.