Efficacy of Migalastat in a Cohort of Male Patients With the Classic Fabry Phenotype in the FACETS Phase 3 Study

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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)²
- More than 800 disease-causing mutations in GLA have been identified (>60% missense) that are associated with multigenerational impairment and premature death¹
- 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 binds and reduces proper folding of amenable mutant forms of α-Gal A, restoring lysosomal trafficking and enzyme activity¹

OBJECTIVE

To evaluate the efficacy of migalastat in male patients presenting with the classic phenotype compared with the efficacy of migalastat in male patients with the non-classic phenotype and in female patients, using data from the phase 3 FACETS study in patients with Fabry disease with amenable GLA mutations

METHODS

Study Design

- FACETS (NCT01008530) is a phase 3, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacokinetics of migalastat in patients with Fabry disease and amenable mutations. The study compared 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)

Figure 1. FACETS Study Design

Summary of Analyses

- Post hoc analyses compared male patients with the classic phenotype to an “Other” group, which consisted of male patients with the non-classic phenotype and female patients
- The classic phenotype was defined as multigenerational involvement and white blood cell α-Gal A activity <3%
- Results were compared with those of untreated male patients described in the literature
- Left ventricular mass index (LVMi) (calculated from blinded centralized reads of echocardiograms) was assessed at baseline and months 6, 12, and 24
- Renal function was assessed at baseline and months 1, 6, 7, 9, 12, 18, and 24 with eGFRCKD-EPI, mGFRiohexol assessed at baseline and months 6, 12, 18, and 24
- Plasma globotriaosylsphingosine (Lyso-Gb₃) was measured using the retained iohexol plasma samples taken at baseline and months 6 and 12
- The Gastrointestinal Symptoms Rating Scale (GSRS) was used to assess diarrhea (GSRS-D), a common gastrointestinal sign in patients with Fabry disease

RESULTS

Baseline Measurements

- Male patients enrolled in the FACETS study with the classic phenotype had more severe manifestations of Fabry disease compared with the cohort of male patients with the non-classic phenotype and female patients (Table 1)
- At baseline, 7 of the 14 male patients with the classic phenotype had left ventricular hypertrophy (>125 g/m²)

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>eGFRCKD-EPI</th>
<th>mGFRiohexol</th>
<th>LVMi</th>
<th>Lyso-Gb₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic phenotype</td>
<td></td>
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<tr>
<td>n=14</td>
<td>87.80 (33.59)</td>
<td>78.59 (22.89)</td>
<td>114.33 (27.34)</td>
<td>99.83 (25.28)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=34</td>
<td>95.33 (19.64)</td>
<td>88.17 (21.99)</td>
<td>88.18 (32.32)</td>
<td>30.21 (48.32)</td>
</tr>
</tbody>
</table>

• Amenable patients, n=25
• Other: male patients with the non-classic phenotype and female patients

Renal Assessments

- The benefits of migalastat on eGFRCKD-EPI were found in male patients with the classic phenotype and the subgroup consisting of male patients with the non-classic phenotype and female patients
- Migalastat treatment reduced or stabilized GFR in all patients, male, female, classic, and non-classic

Echocardiology: LVMi

- The benefits of migalastat on LVMi were observed in male patients with the classic phenotype and the subgroup consisting of male patients with the non-classic phenotype and female patients
- Larger effects in the classic male patients were associated with higher baseline values

Gastrointestinal Signs and Symptoms-Diarrhea

- Migalastat produced better outcomes in male patients with the classic phenotype compared with untreated male patients with Fabry disease, based on the literature
- All patients (male, female, classic, and non-classic) with amenable mutations could be expected to benefit from treatment with migalastat

CONCLUSIONS

- The post hoc analyses demonstrated the beneficial effects of migalastat on eGFRCKD-EPI, mGFRiohexol, LVMi, Lyso-Gb₃, and GSRS-D in both males with the classic phenotype, who constitute the population with the most sensitive and severe form of Fabry disease, and the “Other” subgroup consisting of male patients with the non-classic phenotype and female patients
- Migalastat treatment produced better outcomes in male patients with the classic phenotype compared with untreated male patients with Fabry disease, based on the literature
- All patients (male, female, classic, and non-classic) with amenable mutations could be expected to benefit from treatment with migalastat

REFERENCES


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DISCLOSURES

Conflicts of Interest

DPS has no conflicts of interest to disclose. RIG is a consultant and an investigator for Amicus Therapeutics, Bionarm, 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. DGB is an investigator for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. WRR is a consultant for Genzyme; is an investigator for Amicus Therapeutics and Genzyme; has received research funding from Shire; is a member of the Fabry Registry Board of Advisors. DAM is a consultant/advisee for Shire, Sanofi, Amicus Therapeutics, Actelion, and Protalix; has received research funding from Shire and Sanofi; and is a speaker and has received travel support from Shire, Sanofi, Amicus Therapeutics, and Protalix. HMA is a consultant and speaker for Shire and Biomarin and has received research funding from Shire, Amicus Therapeutics, and Biotherdbio. BS has served as a consultant for and received research funding from Protaeg Biotherapeutics and Amicus Therapeutics. CV, NS, IPC, and IAB are employees of Amicus Therapeutics.

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