INTRODUCTION

Cardiac complications are uncommon in Fabry disease, a rare X-linked disorder of lysosomal α-galactosidase A deficiency, and are the main cause of death in patients with this condition.1–7 Left ventricular hypertrophy (LVH) is the hallmark of Fabry cardiomyopathy and is the main risk factor for Fabry disease-related cardiac complications (ie, heart failure, myocardial infarction, sudden cardiac death).8–10 A progressive decline in midwall fractional shortening (MFS) may be observed in earlier stages of Fabry disease and is one of the first signs of systolic impairment.11–13 Studies assessing left ventricular mass (LVM) in untreated patients with Fabry disease reported a progressive increase in LVM index (LVMi) of 1.52–4.07 g/m²/year; progression occurred regardless of disease phenotype.14 While reductions in LVM have been observed in patients with Fabry disease following treatment with enzyme replacement therapy (ERT), the effect of ERT on LVM has been inconsistent, per the published literature.15–17 Migalastat, a first-in-class, orally administered small molecule, is a pharmacological chaperone approved in the European Union, Switzerland, Israel, and Australia for the treatment of Fabry disease in patients with amenable GLA mutations.18,19 Migalastat restores lysosomal trafficking and enzyme activity by binding, inducing proper folding, and stabilizing amenable mutant forms of α-galactosidase A.20

OBJECTIVE

To summarize the effects of long-term migalastat treatment on cardiac outcomes in patients with Fabry disease and amenable mutations who were enrolled in two randomized two-phase 3 studies.

METHODS

Study Designs

• FACETS (AT1001-01, NC07025101) was a phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of migalastat 150 mg every other day in ERT-naive patients with Fabry disease with amenable GLA mutations.21

• ATTRACT (AT1001-02, NC10123859) was a phase 3, randomized, open-label study to compare the efficacy and safety of migalastat and ERT in patients with Fabry disease with amenable GLA mutations who were previously treated with ERT.

• Patients completing either FACETS or ATTRACT were eligible to enter an open-label extension (OLE) study examining the long-term efficacy and safety of migalastat. [AT1001-04, NC10845819]

Key Inclusion Criteria for FACETS and ATTRACT

• Male and female patients aged 18–74 years diagnosed with Fabry disease with amenable GLA mutations.

• Naive to ERT or had not received ERT for 6 months before screening (FACETS).

• Initiated treatment with ERT ≤12 months before baseline visit and had a stable ERT dose (±20% label dose) for 3 months before baseline visit (ATTRACT).

• eGFRMDRD of ≥30 mL/min/1.73 m² at screening.

• 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.

Analyses

• Cardiac echocardiograms were evaluated (blinded, central review) by a single reader specialized in echocardiography.

• Cardiac echocardiographic findings were used to assess changes in LVH and LVM with migalastat or ERT over time.

• The analyses performed herein were restricted to patients with amenable mutations per the Migalastat Amenable Mutations Assay (MAA).

Patients

• The FACETS trial randomised 67 patients, 50 of whom had amenable mutations. Forty-one patients with amenable mutations continued the study, 35 of whom continued into the OLE extension.

• The ATTRACT trial randomised 60 patients, 56 of whom had amenable mutations.

Cardiac Mass

FACETS

At baseline, mean LVMi was 95.9 ± 26.5 g/m² (standard deviation [SD], 32.8 ± 44) at baseline. A statistically significant mean change from baseline in LVMi was observed after 18/24 months of migalastat treatment (–7.7 ± 9.3 g/m²) at 12 months; 5% patients were randomized to placebo and 24 months for patients randomized to migalastat (Figure 1).21

Further reductions in LVMi were observed at month 30/36 in patients from FACETS who entered the OLE study (change from baseline, −7.0 ± 9.6 g/m² [95% CI, −9.2 to −4.8, −7.0 to −4.1]) (Figure 1).21

TABLE 1. Changes From Baseline in LVMi (g/m²) With 18 Months of Migalastat Treatment in Patients With Amenable Mutations and ERT at Baseline (FACETS; mean values ± 1SD)

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>BL</th>
<th>M6</th>
<th>M12</th>
<th>M18</th>
<th>M6/M18 (95% CI)</th>
<th>M12/M18 (95% CI)</th>
<th>M18/M12 (95% CI)</th>
<th>M18/LOCF (95% CI)</th>
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<tbody>
<tr>
<td>N</td>
<td>44</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>–12.0 (–20.9, 29.9)</td>
<td>2.1 (–14.9, 19.2)</td>
<td>–2.1 (–8.5, 4.3)</td>
<td>–1.6 (–6.3, 3.1)</td>
</tr>
<tr>
<td>Mean change</td>
<td>–36.0</td>
<td>–12.0</td>
<td>–10.0</td>
<td>–8.4</td>
<td>–8.4 (–11.9, –4.9)</td>
<td>–3.2 (–6.2, –0.2)</td>
<td>–1.4 (–4.3, 1.5)</td>
<td>0.5 (–2.8, 3.7)</td>
</tr>
<tr>
<td>N</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>13</td>
<td>–10.0 (–16.2, –3.8)</td>
<td>0.3 (–7.1, 7.7)</td>
<td>–3.8 (–9.9, 2.3)</td>
<td>–2.4 (–8.6, 3.7)</td>
</tr>
<tr>
<td>Mean change</td>
<td>–36.0</td>
<td>–10.0</td>
<td>–6.4</td>
<td>–4.0</td>
<td>–4.0 (–6.9, –1.1)</td>
<td>–0.4 (–4.4, 3.6)</td>
<td>0.4 (–4.4, 5.2)</td>
<td>0.4 (–3.5, 4.4)</td>
</tr>
</tbody>
</table>

Figure 1. Mean Change From Baseline in LVMi (g/m²) Over Time With Migalastat Treatment (FACETS; patients with amenable mutations)

CONCLUSIONS

• Migalastat treatment resulted in increases in MWFS, a measure of systolic function, in a majority of patients in FACETS with abnormal LVH at baseline.

• These beneficial long-term effects on LVMi and LVH suggest that migalastat has the potential to reduce the risk of cardiac complications associated with Fabry disease.

REFERENCES