Efficacy and Safety of Migalastat, an Oral Pharmacal Chaperone for Fabry Disease: Renal Findings From Two Randomized Phase 3 Studies (FACETS and ATTRACT)

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INTRODUCTION

- Fabry disease is a devastating, rare, and progressive lysosomal storage disorder caused by a mutation in the GLA gene, resulting in the functional deficiency of α-galactosidase A (α-Gal A).
- Accumulation of α-Gal A substrates, including glycosphingolipids such as globotriaosylceramide (GL-3) and globotriaosylganglioside (Globo-G), can lead to multiorgan system dysfunction and premature death.
- 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.
- Migalastat increases lysosomal enzyme induction 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 offer the need for lifelong biweekly agalsidase infusions or enzyme replacement therapy (ERT).

OBJECTIVE

To summarize renal findings from 2 randomized phase 3 studies of migalastat in patients with Fabry disease.

METHODS

Study Designs

- FACETS (NCT013101-127, NCT02930255) was a phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of migalastat in patients with Fabry disease with amenable GLA mutations (Figure 1).
- ATTRACT (NCT01112060) 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 (Figure 2).

RESULTS

- The FACETS and ATTRACT studies randomized 87 and 60 patients, respectively, of which 50 and 56 patients, respectively, had amenable mutations.
- Patients in both studies had significant baseline disease severity. 94% and 88% of patients in the FACETS and ATTRACT studies, respectively, had Fabry disease in ≥2 organ systems.
- 90% and 75% of patients in the FACETS and ATTRACT studies, respectively, had renal involvement.

Disease Substrate

In FACETS, migalastat treatment significantly reduced interstitial capillary G3-J3 inclusion volume and G3-lys>G4 levels in patients with Fabry disease with amenable mutations.

In ATTRACT, plasma G3-lys>G4 levels remained stable and following the switch from ERT to migalastat, but did not change in 2 patients with non-amenable mutations who remained on ERT.

Renal Function

FACETS

- From baseline to month 24, renal function was stable in patients with amenable mutations treated with migalastat in the FACETS study (Figure 3).
- Stabilization of renal function was observed regardless of baseline eGFR.

Figure 3. FACETS Study Design

![FACETS Study Design](image)

- **Baseline**
- **Double-Blind**
  - Placebo
  - Migalastat 150 mg QOD
- **Randomized Open-Label Extension**
  - Migalastat 150 mg QOD
  - ERT
- **Completed Study:**
  - All patients, n=27
  - Amenable patients, n=22

Figure 4. FACETS Study Results

<table>
<thead>
<tr>
<th>Month</th>
<th>Placebo</th>
<th>Migalastat 150 mg QOD</th>
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<th>ERT</th>
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<tbody>
<tr>
<td>12</td>
<td>-0.06 mL/min/1.73 m²</td>
<td>0.05 mL/min/1.73 m²</td>
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Amended rates based on the subset of patients who received at least 11 months of treatment with migalastat (n=26) or ERT (n=21) at month 24.

- Migalastat restored lysosomal trafficking and enzyme activity by binding and inducing proper folding of amenable mutant forms of GLA.
- Migalastat is well tolerated and continues to be tested in phase 3 studies.
- Migalastat has demonstrated safety and efficacy in phase 1 studies.

ATTACH

- In the ATTACK study, migalastat and ERT had comparable favorable effects on renal function at month 18 using both GFR methods (Figure 4).
- Migalastat restored renal function in 18 months regardless of baseline eGFR (Figure 5).

Figure 4. FACETS Study Results

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Amended rates based on the subset of patients who received at least 11 months of treatment with migalastat (n=25) or ERT (n=20) at month 24.

- Migalastat offered promise as a treatment option for Fabry disease with amenable mutations.
- Migalastat was well tolerated and continued to be studied in phase 3 studies.

CONCLUSIONS

- Migalastat was generally well tolerated and effective in patients with amenable mutations in the FACETS and ATTRACT studies.
- In both FACETS and ATTACK, treatment with migalastat stabilized renal function.
- There were few discontinuations due to TEAEs, and most were related to underlying Fabry disease comorbidities.
- Predefined renal AKI during the 18-month comparison stage of ATTACK occurred in 24% and 33% of patients receiving migalastat and ERT, respectively.
- No patients progressed to end-stage renal disease.

REFERENCES

5. Protalix. VJ, JY, JPC, NS, and JAB are employees of and own stock in Amicus Therapeutics.
7. UFR serves on advisory boards for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. AJ has no conflicts of interest to disclose. RS has received research funding from Amicus Therapeutics, Inc.

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DISCLOSURE

Conflicts of Interest

All authors declared conflicts of interest to disclose. RS has received research funding from Amicus Therapeutics, Protalix Biotherapeutics, Shire, and Genzyme. KN serves on advisory boards for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. SJR has received honoraria from Amicus Therapeutics, Shire, Genzyme, and Shire. DS services as a consultant and speaker for and has received funding from Amicus Therapeutics, Roche, and has received funding from Genzyme. JY has received research funding from Shire. SJR is consultant for and has received research and travel funding from Amicus Therapeutics, Shire, Genzyme, Astellas, and Protein. ML, JF, JR, and JAB are employees of and own stock in Amicus Therapeutics, Inc.

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