Effects of Long-term Migalastat Treatment on Renal Function by Baseline Proteinuria in Patients With Fabry Disease


1. Baylor Research Institute, Dallas, TX, USA; 2. Hôpital du Sacré-Coeur, University of Montreal, Montreal, Quebec, Canada; 3. Division of Medical Genetics, University of Versailles-St. Quentin en Yvelines (UVSQ), Paris, France; 4. Medical Genetics Service, HCPA/UFRPS, Porto Alegre, Brazil; 5. Royal Free NHS Foundation Trust and University College London, London, UK; 6. Royal Melbourne Hospital, Parkville, VIC, Australia; 7. Emory University School of Medicine, Atlanta, GA, USA; 8. Amicus Therapeutics, Inc., Cranbury, NJ, USA

**INTRODUCTION**

- Fabry disease is a rare, devastating, and progressively lethal lysosomal storage disorder caused by a mutation in the GLA gene, resulting in the functional deficiency of α-galactosidase A (α-GalA).
- Accumulation of α-GalA substrates, including glycosphingolipids such as globotriaosylceramide (GL-3), can lead to multisystem disease and progressive decline in renal function.
- Progressive impairment of renal function has been shown to be a major risk factor for cardiovascular events and cardiovascular-related premature death, and the presence and severity of proteinuria has been associated with more rapid loss of renal function in untreated patients with Fabry disease—α-GalA declines of up to 6.9 mL/min/1.73 m²/year have been reported in male patients with untreated Fabry disease and high levels of proteinuria.
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacological chaperone approved in the European Union, Switzerland, Australia, Israel, Republic of Korea, and Japan for long-term treatment of adults and adolescents aged 18 years and older with a confirmed diagnosis of Fabry disease (α-GalA deficiency) who have a missense-amenable GLA mutation.
- Migalastat is also approved in Canada for adults (aged 18 years and older).
- Migalastat binds to and stabilizes amenable mutant forms of α-GalA in the endoplasmic reticulum and facilitates cellular trafficking to lysosomes, whereupon dissociation of migalastat leads to the breakdown of target substrates.

**RESULTS**

### Renal Function Assessed by eGFRMDRD

- **Mean (SD) eGFRMDRD values at baseline were generally similar in migalastat-treated patients and in the Pre-ERT Fabry Cohort.**
  - Migalastat-treated patients: 85.6 (2.9) mL/min/1.73 m² (mean, min: 40.0, 124.8 mL/min/1.73 m²) in the overall group
  - Pre-ERT Fabry Cohort: values ranged from 58.5 (5.5) to 138 (13.3) across the proteinuria and sex-stratified subgroups (overal values not available).
  - **Annexed changes in eGFRMDRD tended to be smaller overall in patients treated with migalastat across proteinuria subgroups (Figure 2).**
  - Nephrological increases were observed with migalastat in patients with baseline proteinuria <100 mg/24 h (males and females) and 100-1000 mg/24 h (males and females) compared with the Pre-ERT Fabry Cohort.

**OBJECTIVE**

To evaluate the long-term effects of migalastat on renal function stratified by baseline proteinuria in patients with Fabry disease and amenable GLA mutations.

**METHODS**

### Study Design

- **Four phase 2, open-label, dose-finding studies of migalastat were conducted in patients with a confirmed diagnosis of Fabry disease.**
- Patients completing any of the 4 phase 2 dose-finding studies were eligible to enroll in and continue migalastat treatment in a phase 2 extension study (LAF-CL-205, NCT001562071).
  - During this study, patients received migalastat 150 mg every other day (QOD), followed by a dose-escalation period (250 mg 3 days on/4 days off) of migalastat 50 mg every other day (QOD).
  - In the phase 3 FACETS trial (NCT00235311), patients were randomly assigned 1:1 to receive migalastat 150 mg QOD or placebo for 6 months; after completing the 6-month double-blind period, patients had the option to receive open-label migalastat 150 mg QOD for an additional year after that (months 12-24). Patients who completed the phase 2 extension study or the FACETS trial could subsequently enroll in and continue migalastat treatment (AT1001-041 extension study).

### Analyses

- **Analyses were restricted to patients with amenable mutations who received migalastat 150 mg QOD for ≥17 months.**
- Patients completing any of the 4 phase 2 dose-finding studies were eligible to enroll in and continue migalastat treatment in a phase 2 extension study and those enrolled in FACETS who may have subsequently enrolled in the AT1001-041 extension study.
- **Annexed changes in eGFRMDRD and eGFRCKD in the migalastat-treated cohort were calculated using simple linear regression and stratified by baseline proteinuria level (<100, 100–1000, >1000 mg/24 h) and sex.**
  - These cut-offs were the same as those used in a previously published analysis of retrospective chart review data in 447 patients with Fabry disease prior to receipt of ERT (Fabry Cohort). In that analysis, annexed changes in eGFRCKD were stratified by baseline proteinuria and sex.
  - eGFRMDRD results from the migalastat-treated cohort were contrasted with the previously published, similar analysis in the Pre-ERT Fabry Cohort.

### Patients

- **A total of 12 patients with amenable mutations received migalastat 150 mg QOD for ≥17 months and are included in these analyses.**
- Most patients (67%) had proteinuria levels between 100–1000 mg/24 h at baseline; 23% of patients had baseline proteinuria levels >1000 mg/24 h, and 10% had levels <100 mg/24 h.
- **Median treatment duration ranged from 5.5 to 4.8 years (maximum, 5.5 years) across baseline proteinuria subgroups.**

### Table 1. Migalastat Treatment Duration by Baseline Proteinuria

<table>
<thead>
<tr>
<th>Baseline 24h urine protein, mg/24 h</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4.8±(4.8, 4.4)</td>
<td>4.2±(4.0, 5.3)</td>
</tr>
<tr>
<td>100-1000</td>
<td>4.3±(4.5, 4.9)</td>
<td>3.5±(3.5, 5.5)</td>
</tr>
<tr>
<td>&gt;1000</td>
<td></td>
<td>3.7±(3.5, 4.1)</td>
</tr>
</tbody>
</table>

### Renal Function Assessed by eGFRCKD

- **eGFRCKD remained stable in most patients [males and females] with baseline proteinuria ≤100 mg/24 h during migalastat treatment (Table 2).**
- Declines in eGFRCKD were observed in patients with proteinuria levels >1000 mg/24 h (Table 2).

### Table 2. Annualized Mean Change in eGFRMDRD With Migalastat by Baseline Proteinuria

<table>
<thead>
<tr>
<th>Baseline 24h urine protein, mg/24 h</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-0.4±(0.5)</td>
<td>1.0±(3.1)</td>
</tr>
<tr>
<td>100-1000</td>
<td>-0.3±(0.9)</td>
<td>1.0±(0.6)</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>-1.1±(0.2)</td>
<td>2.2±(1.4)</td>
</tr>
</tbody>
</table>

**DISCLOSURES**

Conflicts of Interest

RS has received research funding from Amicus, Protalix Biotherapeutics, Sanofi Genzyme, and Shire. DSB has served as a consultant and speaker for Amicus and Sanofi Genzyme, and has received research funding from Amicus, Sanofi Genzyme, and Shire. DPG has received honoraria and research grants from Amicus, Sanofi Genzyme, and Shire. RH has received honoraria from Amicus, Biomarin, Sanofi Genzyme, and Shire. DGH has served as a consultant for and has received research and travel funding from Amicus, Sanofi Genzyme, Shire, Alexion, and Proteouse. KN has served on advisory boards and has received research funding from Amicus, Sanofi Genzyme, and Shire. AWI has received research support from and is employed by Sanofi Genzyme. HW, JY, NS, and JAB are employees of and hold stock in Amicus.

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**REFERENCES**