Renal Outcomes With Up to 9 Years of Migalastat in Patients With Fabry Disease: Results From an Open-label Extension Study

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INTRODUCTION

• Fabry disease is a rare X-linked lysosomal storage disorder caused by a mutation in the GLA gene, resulting in the functional deficiency of a galactosidase A (α-Gal A)1
• Progressive accumulation of the α-Gal A substrate globotriaosylceramide (GLA-3) and similar glycosphingolipids can lead to multigorgan disease and ultimately organ failure, including end-stage renal disease1
• Untreated patients with Fabry disease have been shown to experience declines in estimated glomerular filtration rates (eGFR) of up to ~12 mL/min per year2
• Progressive impairment of renal function is a major risk factor for cardiac events,3 and end-stage renal disease is the primary cause of death in males with untreated Fabry disease.4 Thus, stabilizing or slowing renal decline is an important treatment goal in Fabry disease5
• Migalastat, a first-in-class, orally administered small molecule, is a pharmacological chaperone approved in the European Union, Switzerland, Australia, Canada, Republic of Korea, and Israel for the treatment of Fabry disease in patients with amenable GLA mutations6
• Migalastat binds to, stabilizes, and facilitates lysosomal trafficking of amenable mutant GLA proteins
• The safety and efficacy of migalastat has been reported in several phase 2 and phase 3 trials

OBJECTIVE

• To evaluate the long-term effects of migalastat on renal function in patients with Fabry disease who completed a phase 2 trial and enrolled in a phase 3 open-label extension study

METHODS

Patients and 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 and could subsequently enroll in and continue migalastat in a phase 3 long-term extension trial (referred to as the 041 extension study hereafter)
• In total, 12 patients originating from 3 of the phase 2 dose-finding studies completed the phase 2 long-term extension and entered into the 041 extension study; an overview of these 3 dose-finding studies, the phase 2 extension study, and the 041 extension study is shown in Figure 1

RESULTS

Analyses

• Linear regression was used to calculate the annualized rate of change in estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR_{\text{CKD-EPI}}) from baseline
• The analyses presented herein were restricted to the 12 patients with amenable mutations who completed phase 2 studies and entered the 041 extension study

Patients

• At the time of this analysis, mean time on migalastat for the 12 patients who continued from a phase 2 trial into the 041 extension study was 8.2 years (standard deviation [SD], 0.83)
• Median time on treatment was 8.4 years (range, 6.3-9.3)
• Eleven patients received migalastat 150 mg every other day (QOD) for >17 months
• Baseline demographics are shown in Table 1

Table 1. Baseline Characteristics (N=12)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Sex</th>
<th>eGFR, mL/min/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>M</td>
<td>100.9</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>M</td>
<td>114.4</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>M</td>
<td>87.1</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>M</td>
<td>84.4</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>M</td>
<td>126.2</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>M</td>
<td>121.7</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>M</td>
<td>92.0</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>M</td>
<td>135.7</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>M</td>
<td>90.1</td>
</tr>
<tr>
<td>10</td>
<td>59</td>
<td>F</td>
<td>76.4</td>
</tr>
<tr>
<td>11</td>
<td>36</td>
<td>F</td>
<td>100.6</td>
</tr>
<tr>
<td>12</td>
<td>43</td>
<td>F</td>
<td>116.0</td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>42.5 (24, 62)</td>
<td></td>
<td>103.8 (18.7)</td>
</tr>
</tbody>
</table>

Renal Function

• Among the 12 patients enrolled in a phase 2 study who continued into the 041 extension study, renal function remained stable (annualized mean change in eGFR_{\text{CKD-EPI}} ~0.67 mL/min/1.73 m² [95% CI, –1.32, –0.02]) during the entire migalastat treatment period (mean exposure, 8.2 years) (Figure 2)
• Renal function also remained stable (annualized mean change in eGFR_{\text{CKD-EPI}} ~0.24 mL/min/1.73 m² [95% CI, –1.74, 2.21]) in an analysis of the 11 patients who received migalastat 150 mg QOD for >17 months (mean exposure, 4.5 years)

Figure 2. Annualized Change in eGFR_{\text{CKD-EPI}} Over the Entire Migalastat Treatment Period (N=12)

CONCLUSIONS

• Renal outcomes by sex and baseline proteinuria levels are shown in Table 2

Table 2. Annualized Change in eGFR_{\text{CKD-EPI}} by Baseline Proteinuria Levels and Sex in Patients Who Received Migalastat 150 mg QOD for >17 months (N=11)

<table>
<thead>
<tr>
<th>Sex</th>
<th>Baseline 24-hour Urine Protein, mg/24 h</th>
<th>n</th>
<th>Annualized Rate of Change in eGFR_{\text{CKD-EPI}}, mL/min/1.73 m², Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td>11</td>
<td>+0.2 (-1.7, 2.2)</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td>3</td>
<td>+0.4 (-4.1, 4.9)</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td>4</td>
<td>+2.4 (-4.0, 8.8)</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td>2</td>
<td>-1.6 (-2.4, -0.9)</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td>2</td>
<td>-1.7 (-2.0, -1.3)</td>
</tr>
</tbody>
</table>

REFERENCES

5. Germain DP. Orphanet J Rare Dis. 2010;5:30.

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DISCLOSURE

Conflicts of Interest

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