Long-term Safety and Efficacy of Pegunigalsidase Alfa: A Multicenter Extension Study in Adult Patients with Fabry Disease

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Introduction

- Fabry disease (FD) is a rare, X-linked, lysosomal storage disorder caused by mutations in the gene encoding α-galactosidase A (α-GAL-A).
- Mutations associated with lower residual α-GAL-A enzyme activity lead to accumulation of increasingly toxic levels of glycosphingolipids, such as globotriaosylceramide (Gb3), and, ultimately, progressive and organ failure.
- Pegunigalsidase alfa is a novel pegylated α-GAL-A enzyme replacement therapy (ERT) being developed for the treatment of FD.
- Pegunigalsidase alfa has enhanced bioavailability compared with available treatments, and published reports note favorable safety and efficacy for up to 12 months of treatment.

Study F03 (NCT01861720) is the extension of two Phase 1/2 trials of pegunigalsidase alfa, with a combined treatment duration of up to 6 years.

Objective

- To investigate the long-term (up to 6 years) safety, tolerability, and efficacy of pegunigalsidase alfa ERT in adults with FD.

Study Design

- Safety endpoints:
  - Treatment-emergent adverse events (TEAEs): frequency, type, severity, and number of events, and infusion-related reactions (IRR) categorized as mild to moderate severity.
- Main exploratory efficacy endpoints:
  - Reduction from baseline in plasma Gb3 concentration.
- Secondary endpoints:
  - Kidney function, as measured by estimated glomerular filtration rate (eGFR) and annualized slope by BUN.
  - Plasma Gb3 concentrations
  - Myocardial fibrosis assessment, as measured by cardiac MRI
  - Ejection fraction (EF), as measured by cardiac MRI
  - LVM showed a slight increase at month 60 but all values remained within normal ranges.

Endpoints

- Safety endpoints:
  - Treatment-emergent adverse events (TEAEs): frequency, type, severity, and number of events, and infusion-related reactions (IRR)
- Development of antidrug antibodies (ADAs) against pegunigalsidase alfa.

Baseline Characteristics

- Of the cardiac parameters that were assessed by echocardiography (PR, QRS, and QT durations) and stress test (chest pain, dizziness, palpitations, shortness of breath, others), most remained stable and within normal ranges.
- Taken together, these results suggest stability of the cardiac disease involvement.

 Baseline Characteristics at F01 Entry

<table>
<thead>
<tr>
<th>Category</th>
<th>≥ 3 years</th>
<th>≥ 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>37.0 (17–62)</td>
<td>38.5 (17–62)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>9 (60.0)</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td>Women</td>
<td>6 (40.0)</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10 (66.7)</td>
<td>9 (81.8)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (33.3)</td>
<td>2 (18.2)</td>
</tr>
</tbody>
</table>

*All patients: −1.6 (0.8) mL/min/1.73 m²

Cardiac outcomes

- Most TEAEs were mild to moderate in severity.
- No IRRs were serious, severe, or led to withdrawal or death.
- No IRRs were noted in patients of the F02 study.
- The incidence of AF was stable over 60 months of treatment, with a mean (SE) decrease at month 60 of 0.5% (1.4).
- AF was present at month 54 until study completion.

Conclusions

- The results of this study suggest that long-term pegunigalsidase alfa treatment provides continued benefits in patients with FD.
- Most TEAEs were mild to moderate in severity and unrelated to pegunigalsidase alfa.
- ADAs were infrequent and transitory in most patients.
- Cardiac and renal function were stable throughout the follow-up, up to 60 months of treatment.
- Plasma Gb3 concentrations decreased steadily from baseline and remained low throughout the follow-up.

These results are consistent with safety and efficacy findings from other studies with pegunigalsidase alfa.

References


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