**ABSTRACT**

Pegunigalsidase alfa is a novel, Pegylated, α-Galactosidase-A enzyme in development for the treatment of Fabry disease. BRIDGE (PB-102-F30, NCT03018730) is a phase III, open label, switch-over study, designed to assess safety and efficacy of pegunigalsidase alfa (1 mg/kg) administered every other week (EOW) in adult Fabry disease patients previously treated with agalsidase alfa for at least 2 years. This is an interim report of 12-months on treatment data generated from the first 16 patients (9 males and 7 females) out of the 22 adult patients enrolled.

Baseline characteristics: age 24-60 years, the mean estimated Glomerular Filtration Rate (eGFR) 75.5 in males and 85.8 mL/min/1.73m² in females. eGFR slope was -5.2 and -5.0 mL/min/1.73m²/year, respectively, mean residual leukocytes enzymatic activity 5.9% of lab normal mean in males and 27.9% in females, and plasma Lyso-Gb, 53.6 and 13.8 nm, respectively.

After one year, the mean annualized eGFR slope improved from -5.10 mL/min/1.73m²/year (while on agalsidase alfa) to -0.23 mL/min/1.73m²/year on pegunigalsidase alfa. Both disease patients with eGFR slope between -5 and -3 mL/min/1.73m²/year are defined as kidney disease progressing and with eGFR slope < -5 mL/min/1.73m²/year are defined fast progressing, according to Wanner et al. 2018 (1). The therapeutic goal is to reach eGFR slope > -3 mL/min/1.73m²/year for the progressing, and 2.5 mL/min/1.73m²/year or more than 50% decrease in progression for the fast progressing.

In this interim analysis, 100% of the progressing patients and 66.7% in the fast progressing group achieved the proposed therapeutic goals after switching to pegunigalsidase alfa. The switch to pegunigalsidase alfa was safe and well tolerated.

These results suggest a potential benefit of pegunigalsidase alfa on renal function for Fabry disease patients previously treated with agalsidase alfa; this need to be confirmed by long-term data. The majority of the patients who completed the study rolled over to a long-term extension study, continuing receiving pegunigalsidase alfa.

**STUDY DESIGN**

- Multicenter, open label, switch-over study to evaluate the safety and efficacy after switching from agalsidase alfa to pegunigalsidase alfa.
- 22 adult Fabry disease patients (male and female).
- Previously treated with 0.2mg/kg agalsidase alfa for at least 2 years.

**MAIN INCLUSION / EXCLUSION CRITERIA**

- **Main inclusion criteria**
  - Age: 18-60 years
  - A documented diagnosis of Fabry disease
  - Treatment with agalsidase alfa for at least 2 years
  - eGFR < 40 mL/min/1.73 m²
  - At least two historical serum creatinine evaluations since starting agalsidase alfa treatment

- **Main exclusion criteria**
  - History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase alfa/beta
  - History of renal dialysis or transplantation and/or acute kidney injury in the 12 months prior to screening
  - Start or change in dose of ACEi or ARB in the 4 weeks prior to screening
  - UPCR > 0.5 g/g and not treated with ACEi or ARB
  - Cardiovascular and/or Cerebrovascular event in the 6 months before randomization

**MAIN SAFETY AND EFFICACY ENDPOINTS**

- **Safety**
  - Clinical laboratory tests
  - Electrocardiogram
  - Treatment-emergent adverse events

- **Efficacy endpoints**
  - Mean annualized change in eGFR (KD-PII)
  - Biomarkers (Plasma Lyso-Gb3, Plasma GB3, Urine lyso-Gb3)
  - Short Form Brief Pain Inventory (BPI)
  - Mainz Severity Score Index (MSSI)
  - Quality of Life (EQ-5D-5L)

**BASELINE CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
<td>SE</td>
</tr>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age started ERT years</td>
<td>37.5</td>
<td>3.7</td>
<td>39.4</td>
</tr>
<tr>
<td>Residual kidney activity – leukocytes %</td>
<td>15.5</td>
<td>3.3</td>
<td>27.8</td>
</tr>
<tr>
<td>Residual kidney activity – plasma %</td>
<td>14.1</td>
<td>3.9</td>
<td>24.1</td>
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<tr>
<td>Number of patients with proteinuria (UPCR&gt;300/µg)</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Number of patients treated with ACEi/ARB</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Plasma Lyso-Gb3, nM</td>
<td>15.9±5.4</td>
<td>13.5± 5.6</td>
<td>18.4±7.1</td>
</tr>
<tr>
<td>Plasma GB3, nM</td>
<td>354.8±263.7</td>
<td>346.3±212.8</td>
<td>458.6±501.2</td>
</tr>
<tr>
<td>eGFR (baseline)</td>
<td>50.0±7.2</td>
<td>50.8±5.8</td>
<td>49.1±8.7</td>
</tr>
<tr>
<td>Annualized slope on agalsidase alfa (791, excluding V1)</td>
<td>-5.1</td>
<td>1.5</td>
<td>-5.0</td>
</tr>
<tr>
<td>Annualized slope on pegunigalsidase alfa (791)</td>
<td>-4.9</td>
<td>2.0</td>
<td>-4.4</td>
</tr>
</tbody>
</table>

**RESULTS**

**A. eGFR annualized slope**

In Panel A, the overall mean annualized slope at baseline (while on agalsidase alfa pre-switch) was -5.1 mL/min/1.73m²/year, and after 12 months of treatment with pegunigalsidase alfa, the mean annualized eGFR slope improved by 4.9 mL/min/1.73m²/year, similarly for male and female patients (data analysis, Sep 2019).

**B. Kidney Disease (KD) State according to eGFR Slope**

Decrease in progression is also clinically valuable. As shown in Panel B, in this interim analysis, per Wanner et al, 2018 (1), 6 patients started with a stable KD, 4 patients had progressing KD and 6 patients had fast progressing KD according to their historical eGFR data. Of the 16 patients who completed 12 months of pegunigalsidase alfa treatment, the number of patients with stable KD increased to 10, while the number of patients with progressing and fast progressing KD decreased.

**SUMMARY AND CONCLUSIONS**

The current work represents an interim analysis and results of the first 16 patients who completed 12 months of treatment with pegunigalsidase alfa after switching from agalsidase alfa in the BRIDGE trial.

**Kidney disease following pegunigalsidase alfa treatment:**

- Reduction in the annual eGFR loss: the mean annualized eGFR slope improved from -5.1 to -0.23 mL/min/1.73m²/year for both male and female patients.
- The number of patients with stable KD increased from 6 to 10, while the number of patients with progressing and fast progressing KD decreased.

**Fabry disease biomarker:**

- Most of the male patients started with higher levels of Lyso-Gb3 compared to females, resulting in a more substantial improvement compared to the female patients. Female patients continue to be stable with low Lyso-Gb3 levels throughout the study.

The interim study results indicate that switching from agalsidase alfa to pegunigalsidase alfa is safe and well tolerated. These results suggest a potential benefit of pegunigalsidase alfa on renal function for Fabry disease patients previously treated with agalsidase alfa. The majority of the patients who completed the study rolled over to a long-term extension study, continuing receiving pegunigalsidase alfa.

**References:**