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pegunigalsidase alfa for Fabry disease

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Disclosures

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Alexion
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Excelsior Pharma
Idorsia
Protalix
Sanofi-Genzyme
Shire
Sumitomo Pharma
Pegunigalsidase alfa - Novel Enzyme Replacement Therapy for the Treatment of Patients with Fabry Disease

- A recombinant PEGylated enzyme expressed by Protalix’s proprietary plant cell-based expression system, ProCellEx®.

- Phase I/II in naïve Fabry patients has successfully completed
  - B-102-F01/F02- NCT01678898/NCT01769001

- Phase III program – 3 studies are on going world wide
  - PB-102-F20 NCT02795676
  - PB-102-F30 NCT03018730
  - PB-102-F50 NCT03180840

- Has received
  - FDA - Fast Track Designation - 2018
  - EMA - Orphan Drug Designation - 2017
Pegunigalsidase alfa: PEGylated, Chemically Modified α-Gal-A Enzyme

Subunits linked through a 2KDa PEG cross-linker resulting in 114 kDa enzyme. Contains additional PEG moieties bound to only one subunit through a lysine residue.

Extended stability in plasma and in target cells lysosomal condition.

PEG moieties are masking some enzyme epitope which could be recognized by the immune system → Potentially reducing the immune response to the enzyme plus reduced cross reactivity to pre-existing ADA.
Prolonged Stability in Biological Matrices – *in vitro*
Compared to Other ERTs-Quantified by an Activity Assay

**Stability in human plasma at 37°C (pH=7.4)**

- *P=0.02

**Stability in lysosomal-like conditions (pH=4.6)**

- **P<<0.01

Prolonged stability in plasma and lysosomal-like conditions implicating for higher potential to deliver an active long-functional enzyme to its site of action.

**Ex Vivo:** Internalization and lysosomal localization of pegunigalsidase alfa into skin fibroblasts derived from Fabry patients

α pegunigalsidase alfa  |  α LAMP-2  |  Overlay + DAPI

**Control**

Panel A: **α pegunigalsidase alfa**

Panel B: **α LAMP-2**

Panel C: **Overlay + DAPI**

**Treated with pegunigalsidase alfa**

Panel D: **α pegunigalsidase alfa**

Panel E: **α LAMP-2**

Panel F: **Overlay + DAPI**

Localization of the exogenous pegunigalsidase alfa enzyme into the lysosome of Fabry skin fibroblasts

Cells were incubated for 24 h in the absence (panels A–C) or presence (panels D–F) of PRX-102 (160 μg/mL). PRX-102 was labeled with anti PRX-102 antibodies (red fluorophore). Lysosome labeling was achieved with anti LAMP-2 antibody (green fluorophore). Cellular nuclei were labeled using DAPI (blue fluorophore). The overlap is represented in yellow when the images are superimposed (panel F).
Pharmacokinetics: pegunigal sidingase alfa
Longer half life and higher exposure compared to other ERT

Plasma drug concentration vs. time

- **agalsidase beta time frame**
- **pegunigal sidingase alfa time frame**

Up to 14 days

<table>
<thead>
<tr>
<th>Concentration (ng/mL)</th>
<th>Time (hours) - 14 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>100,000</td>
<td>PRX-102 1mg/Kg</td>
</tr>
<tr>
<td>10,000</td>
<td>Fabrazyme 1mg/Kg</td>
</tr>
<tr>
<td>1,000</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**T½: Approx. 80 hours**

- ** pegunigalsidase alfa (1mg/Kg)**: 78.9
- ** agalsidase beta (1mg/Kg)**: 2
- ** agalsidase alfa (0.2mg/Kg)**: 1.8

**AUC (0-∞):**

- **>35 fold from current ERTs**
  - pegunigalsidase alfa (1mg/Kg): 23,454
  - agalsidase beta (1mg/Kg): 649

*agalsidase beta – USPI ; ** agalsidase alfa - SMPC
Phase I/II- Naïve Fabry Patients
Stabilization of renal parameters & Reduction of Gb3 inclusion in Kidney Peritubular Capillaries

Renal Function- 24M

Kidney Biopsies- 6M

Hughes, LDN 2017; Schiffmann New Horizons in Fabry Disease 2017
Study Objective and Design
PB-102-F30 NCT03018730- Ongoing in Canada, Europe and Australia (Ex-US Study)

- Multicenter, open label switch over study to evaluate the safety and efficacy of switching from agalsidase alfa to pegunigalsidase alfa
  - 22 adult FD patients (male and female)
  - Previously treated with agalsidase alfa for at least 2 years

Main Safety and efficacy endpoints

- Safety
  - Clinical laboratory tests
  - Electrocardiogram
  - Treatment-emergent adverse events
  - Ability to taper off infusion premedication throughout the first 2 months of the study
  - Requirement for use of premedication overall to manage infusion reactions
  - Treatment-emergent anti-PRX-102 antibodies

- Efficacy
  - Mean annualized change in eGFR_{CKD-EPI}
  - Biomarkers (Plasma Lyso-Gb3, Plasma Gb3, Urine Lyso-Gb3)
  - Frequency of pain medication use
  - Short Form Brief Pain Inventory (BPI)
  - Mainz Severity Score Index (MSSI)
  - Quality of life EQ-5D-5L

[Diagram showing the study timeline with phases for agalsidase alfa and pegunigalsidase alfa, including screening, switch, 3 months, 12 months, and extension study phases.]
Study Main Inclusion and Exclusion Criteria

Main inclusion criteria

- Age: 18-60 years
- A documented diagnosis of Fabry disease.
- Treatment with agalsidase alfa for at least 2 years and on a stable dose for at least 6 months
- eGFR ≥ 40 ml/min/1.73 m² by CKD-EPI
- Availability of at least 2 historical serum creatinine evaluations since starting agalsidase alfa treatment and not more than 2 years

Main exclusion criteria

- History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase alfa/beta
- History of renal dialysis or transplantation
- History of 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
- Urine protein to creatinine ratio (UPCR) > 0.5 g/g and not treated with ACEi or ARB
- Cardiovascular and/or Cerebrovascular event in the 6 months before randomization
- Congestive heart failure NYHA Class IV
# Baseline characteristics of first 16 patients (9 males and 7 females)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ALL (Mean)</th>
<th>ALL (SD)</th>
<th>Female (Mean)</th>
<th>Female (SD)</th>
<th>Male (Mean)</th>
<th>Male (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>n=16</td>
<td></td>
<td>n=7</td>
<td></td>
<td>n=9</td>
<td></td>
</tr>
<tr>
<td>Age at screening years</td>
<td>46.3</td>
<td>10.1</td>
<td>47.1</td>
<td>12.4</td>
<td>45.7</td>
<td>8.6</td>
</tr>
<tr>
<td>Age started ERT years</td>
<td>37.9</td>
<td>10.9</td>
<td>39.9</td>
<td>11.5</td>
<td>36.4</td>
<td>10.9</td>
</tr>
<tr>
<td>Residual enzyme activity – leucocytes %</td>
<td>15.5</td>
<td>13.1</td>
<td>27.9</td>
<td>10.2</td>
<td>5.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Residual enzyme activity – plasma %</td>
<td>14.1</td>
<td>15.6</td>
<td>28.5</td>
<td>12.7</td>
<td>2.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Number of patients with proteinuria UPCR≥500 mg/gr</td>
<td>3</td>
<td></td>
<td>1</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Number of patients treated with ACEi/ARB</td>
<td>8</td>
<td></td>
<td>4</td>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Plasma Lyso-Gb$_3$ nM; (normal ≤ 2.4 nM)</td>
<td>36.18</td>
<td>47.16</td>
<td>13.81</td>
<td>6.11</td>
<td>53.57</td>
<td>58.01</td>
</tr>
<tr>
<td>Plasma Gb$_3$ nM; (normal ≤ 4961 nM)</td>
<td>6049</td>
<td>2219</td>
<td>5468</td>
<td>1875</td>
<td>6501</td>
<td>2464</td>
</tr>
<tr>
<td>Urine Lyso-Gb$_3$, pM/mM creatinine; (normal-0 pM/mM)</td>
<td>47.29</td>
<td>40.99</td>
<td>45.48</td>
<td>31.11</td>
<td>49.11</td>
<td>51.63</td>
</tr>
<tr>
<td>eGFR$_{CKD-EPI}$ at Baseline (V1) - mL/min/1.73m$^2$</td>
<td>80.0</td>
<td>21.8</td>
<td>86.0</td>
<td>17.8</td>
<td>75.4</td>
<td>24.5</td>
</tr>
<tr>
<td>Annualized Slope on Replagal (~2Y, including V1) - mL/min/1.73m$^2$/year</td>
<td>-6.8</td>
<td>7.4</td>
<td>-5.1</td>
<td>4.4</td>
<td>-8.0</td>
<td>9.2</td>
</tr>
</tbody>
</table>
Individual eGFR values

- Pt. #1 (M)
- Pt. #2 (M)
- Pt. #3 (M)
- Pt. #4 (M)
- Pt. #8 (M)
- Pt. #11 (M)
Individual eGFR values (continued)
Individual eGFR values (continued)

Pt. #7 (F)

Pt. #6 (F)

Pt. #5 (F)

Pt. #9 (F)

Pt. #12 (F)

Pt. #14 (F)
Mean and individual annualized eGFR slopes pre- and post-treatment with pegunigalsidase alfa (6 M on Unigal; n=16)-preliminary results

* Based on available historical serum creatinine for approximately 2 years and study 3 month screening period values

eGFR mL/min/1.73 m² is calculated using CKD-EPI formula

eGFR Slope = mL/min/1.73 m²/year
Summary

- Pegunigalsidase alfa is a PEGylated enzyme with unique biochemical characteristics
  - Higher stability in plasma and lysosomal-like conditions
  - Prolonged half-life and higher exposure in FD patients
- Reduction of Gb3 inclusion in PTC derived from kidney biopsies was observed in Naïve treated Fabry patients
- Preliminary results from BRIDGE study indicate improvement in kidney function in patients switched from agalsidase alfa
Acknowledgements

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