Sanofi announces additional data on avalglucosidase alfa in Pompe disease

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- In late-onset Pompe disease (LOPD) patients, data from the ongoing extension study of the Phase 1/2 trial highlight the safety profile, key biomarkers and pulmonary efficacy measures

- In infantile-onset Pompe disease (IOPD) patients, interim safety data for up to six months, from the Phase 2 trial in avalglucosidase alfa are reported

- The Phase 2 IOPD clinical trial and Phase 3 LOPD pivotal trial are on track to complete enrollment in early 2019

Results from multiple studies of the investigational therapy avalglucosidase alfa in patients with Pompe disease were presented this week during the 15th Annual WORLD Symposium™ in Orlando, Florida. Pompe disease is a progressive, debilitating and often fatal neuromuscular disease that affects an estimated 50,000 people worldwide. It can occur at any age from infancy to late adulthood.

NEO-EXT: Ongoing extension study of the Phase 1/2 trial

The safety profile of avalglucosidase alfa was evaluated in 24 patients in the NEO1 study (10 who had not previously been on treatment and 14 who had been treated with alglucosidase alfa) with late-onset Pompe disease (LOPD). After completing NEO1, 19 of 24 patients entered the extension study (NEO-EXT), of which 17 patients are still enrolled. All patients in the NEO-EXT study are currently receiving treatment with avalglucosidase alfa 20 mg/kg once every other week. Results from NEO-EXT for up to 4.5 years remain consistent with the first six months of treatment. Additional key findings from the NEO-EXT trial include:

- No additional participants developed anti-avalglucosidase alfa IgG/IgM antibodies or new allergic reactions since the last safety update (interim data at 3.5 years).
- Among both groups, those who had not previously been on treatment and those who had been treated with alglucosidase alfa, no patient developed IgE antibodies or enzyme-inhibitory antibodies.
- No death or treatment-related life-threatening serious adverse event (AE) has been reported. One patient in the treatment naïve group experienced treatment related serious AEs of shivering and fever (infusion-associated reactions).
- Treatment-related AEs remained unchanged from the 3.5 year analysis. The most common treatment related AEs, were nausea, headache and fatigue, each occurring in 3/24 patients, and dizziness, redness of the skin (erythema), muscle spasm, muscle pain (myalgia), shortness of breath (dyspnea) and rash, each occurring in 2/24 patients.
- One additional patient has discontinued NEO-EXT for personal reasons since the 3.5 year analysis.

All groups demonstrated reductions in two key biomarkers, creatine kinase (CK, marker of muscle damage) and glucose tetrasaccharide (Hex4, marker of disease burden) from baseline to week 208, that have been shown to be elevated in patients with Pompe disease.
Pulmonary function measures, including forced vital capacity (FVC), maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), improved or remained stable in previously treated and treatment-naïve patients while on avalglucosidase alfa at the target dose of 20 mg/kg for up to 4 years (week 208). 20mg/kg is the dose being studied in the Phase 3 clinical trial (COMET) currently recruiting treatment-naïve patients.

Respiratory outcomes in treatment-naïve patients (not previously treated with alglucosidase alfa):

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial dose*</th>
<th>Residual (-1:0, mean ± SD)</th>
<th>Change from baseline, mean ± SD (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Residual (-1:0, mean ± SD)</td>
<td>Week 25</td>
</tr>
<tr>
<td>Uplift</td>
<td>20 mg/kg qw</td>
<td>63.5 ± 17.8 (53.4)</td>
<td>6.3 ± 3.2 (6.4)</td>
</tr>
<tr>
<td>MIP</td>
<td>20 mg/kg qw</td>
<td>50.2 ± 20.0 (40.0)</td>
<td>8.1 ± 16.7 (9.1)</td>
</tr>
<tr>
<td>MEP</td>
<td>20 mg/kg qw</td>
<td>56.6 ± 19.7 (55.0)</td>
<td>12.5 ± 4.2 (11.6)</td>
</tr>
</tbody>
</table>

Respiratory outcomes in patients previously treated with alglucosidase alfa:

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial dose*</th>
<th>Residual (-1:0, mean ± SD)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Residual (-1:0, mean ± SD)</td>
<td>Week 25</td>
</tr>
<tr>
<td>Uplift</td>
<td>20 mg/kg qw</td>
<td>70.8 ± 16.4 (70.6)</td>
<td>1.9 ± 5.7 (6.4)</td>
</tr>
<tr>
<td>MIP</td>
<td>20 mg/kg qw</td>
<td>70.3 ± 17.0 (81.7)</td>
<td>6.0 ± 5.9 (1.0)</td>
</tr>
<tr>
<td>MEP</td>
<td>20 mg/kg qw</td>
<td>85.1 ± 25.2 (82.5)</td>
<td>4.3 ± 21.9 (4.6)</td>
</tr>
</tbody>
</table>

All patients were transitioned to the 20 mg/kg dose in 2016 and have now received the 20 mg/kg dose for at least 2 years.

“The consistency of these results reinforces the long-term safety profile of avalglucosidase alfa as reported in the core study,” said Loren D.M. Pena, M.D., Ph.D, Associate Professor of Pediatrics at University of Cincinnati College of Medicine. “These safety findings, together with the reductions in biomarkers of muscle damage and disease burden associated with improvements in functional pulmonary outcomes, strengthen the body of evidence supporting the development of avalglucosidase alfa as a potential treatment for people living with Pompe disease.”

**mini-COMET Study**

Six month interim data from cohorts 1 and 2 of mini-COMET, a Phase 2 study of avalglucosidase alfa in patients with infantile-onset Pompe disease (iPOMD) who were previously treated with alglucosidase alfa, were also presented at the WORLD Symposium. Patients enrolled in cohorts 1 (n=6) and 2 (n=5) had demonstrated a clinical decline when treated with alglucosidase alfa prior to the study. Key findings include:
Treatment-emergent AEs were mild to moderate and there were no serious AEs that were found to be treatment related. One patient (cohort 2) had an infusion-associated reaction of itchiness/redness of the skin (urticaria). The most frequently reported treatment-related AE was fall in 2/11 patients. No patients tested positive for inhibition of enzyme activity and no patients developed IgE antibodies following treatment.

“These new data from NEO-EXT and mini-COMET are encouraging as we advance avalglucosidase alfa for both late-onset and infantile-onset Pompe disease,” said Gianluca Pirozzi, Head of Development for Rare Diseases and Head of Translational Gene Therapy, Sanofi. “We look forward to completing enrollment in mini-COMET and COMET, our Phase 3 pivotal trial of avalglucosidase alfa, early this year, continuing our efforts to bring this potential new therapeutic option to patients living with Pompe disease.”

Avalglucosidase alfa is an investigational agent and has not been approved by the US Food and Drug Administration (FDA) or any other regulatory agency worldwide for the use under investigation.

Click here for information on the avalglucosidase alfa development program.


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