INTRODUCTION

- Pompe disease is an inherited metabolic disease of lysosomal glycogen clearance due to acid alpha-glucosidase (GAA) deficiency, which leads to accumulation of the substrate most prominently in the heart, skeletal muscle, and smooth muscle.
- Progressive accumulation of glycogen results in a spectrum of disease severity, often leading to organ failure and/or death.
- Skeletal muscle weakness and progressive respiratory involvement are predominant manifestations of late-onset Pompe disease.
- AT2221 is a next-generation recombinant human GAA (rGAA) enzyme replacement therapy (ERT) designed with optimized glycosylation and high levels of mannose 6-phosphate receptors for better uptake in target muscle tissues.
- The pharmacological chaperone AT2221 is coadministered with AT2221 to minimize denaturation of the enzyme in blood and maintain catalytic activity to deliver active ERT to lysosomes.

OBJECTIVE

To assess the safety, pharmacodynamics, and efficacy of AT2221 coadministered with AT2221 in patients with Pompe disease enrolled in the phase 1/2 AT200-02 study (NCT02075465).

METHODS

- **Study Design**
  - Data are from interim analysis 5 and include all 12-month data that were available as of the data cutoff (n=81 for Cohort 1; n=54 for Cohort 2; n=25 for Cohort 3).
  - Safety analyses include all data up to 20 months.

- **RESULTS**
  - **Sixteen clinical sites in 5 countries participated in the AT200-02 trial**
  - **Patients were representative of the overall LOPA population**, with significant impairment at baseline (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics</th>
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<tr>
<td>Patient</td>
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<td>---------</td>
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<tr>
<td>Age, years</td>
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<tr>
<td>Body weight, kg</td>
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<td>6MWT, meters</td>
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- **Efficacy**
  - **Improvements in 6MWT and other motor function tests** were consistent with an overall improvement in motor performance for ambulatory ERT-switch patients and ERT-naive patients over 12 months (Table 3).

- **Patient-Reported Outcomes**
  - **All cohorts were significantly impacted by fatigue at baseline**, and demonstrated a mean improvement in their Fatigue Severity Scale (FSS) after receiving AT200/AT2221 (Table 6).

- **Markers of Muscle Injury**
  - **All cohorts demonstrated persistent improvement in biomarkers of muscle damage** (creatinic kinase and CD) and disease substrate (urine hexosaminidase/1-acidic protein).

- **Safety**
  - **At the data cutoff, the longest duration on treatment** was 20 months.
  - **AEs** were generally mild and transient.
  - **The most common AE s reported as treatment-related were upper and lower abdominal pain (8/20), diarrhea (8/20), nasopharyngitis (8/20), nasoconjunctivitis (2/20), headache (5/20), and upper respiratory tract infection (3/20).
  - **There were 3 incidents of injection-associated reactions (IARs)** (hypotension and pruritus, erythema and burning sensation).

- **CONCLUSIONS**
  - **Muscle function**
    - **GMT** distance continued to improve in ambulatory ERT-switch and ERT-naive patients out to Month 12.
    - **Other motor function tests** were consistent with 6MWT results in both ambulatory cohorts.
  - **Pulmonary function**
    - **FVC** and MEP were generally stable in ambulatory ERT-switch patients.
    - **FVC** and MEP increased generally in ERT-naive patients.
  - **Fatigue Severity Scale**
    - **Improvements in fatigue score** were observed in all cohorts.
  - **Biopsies and safety**
    - **CT and Hoehn levels decreased in all cohorts**.
  - **AT200/AT2221 was generally well tolerated**.

- **REFERENCES**
  - 4. Khanna R et al. Presented at the 12th Annual WORLDSymposium™; February 29-March 4, 2016; San Diego, CA, USA.