**INTRODUCTION**

- Pompe disease is a rare autosomal recessive genetic disorder caused by mutations in the gene that encodes acid alpha-glucosidase (GAA), the enzyme responsible for breaking down lysosomal glycogen.
- Enzyme replacement therapy (ERT) with alglucosidase alfa, the standard of care, offers improvement in clinical measures for a limited duration (typically 2-3 years) following slow decline in enzyme activity.
- A phase IIb/III expansion study of ATB200 (ATB200/AT2221) combinations has been proposed as a novel, first-in-class therapy for long-term treatment of late-onset Pompe disease.
- AT2221 is a novel human recombinant acid-alpha-glucosidase (HAGA) administered intramuscularly, which is engineered for optimal uptake and targeting to the lysosomes, the site of glycogen accumulation in affected tissues.
- AT2221 is co-synthesized with ATB200 to stabilize ATB200, preventing it from denaturation while in systemic circulation and enhancing the delivery of ATB200 to muscle and lysosomes.
- ATB200 and AT2221 clinical trials have been conducted in adult patients, but neither drug has been studied in pediatric patients.

**METHODS**

- **Modeling**
  - The population PK data set was derived from adult patient data from the phase 1-2 study ATB200-02 (NCT02465459).
  - 154 ERT-experienced adult patients who received doses of 5, 10, 20 mg/kg ATB200, 20 mg/kg ATB200 + 130 mg AT2221, and 20 mg/kg ATB200 + 260 mg AT2221, respectively.
  - 191 ERT-naive adult patients who received 20 mg/kg ATB200 + 260 mg AT2221.

- **Population Pharmacokinetic Models**
  - **ATB200** disposition was described by a 2-compartment model with parallel linear and nonlinear clearance.
  - **AT2221** disposition was described by a 2-compartment model with parallel linear and nonlinear clearance.
  - **First Order Conditional Estimation (FOCE)** method was used in NONMEM version 7.3 with the FOCE method.

- **Population PK simulations** were performed using the final ATB200 and AT2221 models to predict likely concentration time profiles of both drugs in adolescents.

- **Diagnostic plots** showed that model fits were reasonable for both enzyme and chaperone, and that no systematic bias was present.

- **Population covariate analysis** was performed to determine the effect of ERT experience on ATB200 and AT2221.

- **Random effects** were estimated for both ATB200 and AT2221.

- **Co-administration of 130 mg and 260 mg AT2221 resulted in decreases in ATB200 linear clearance by 26.2% and 40.5%, respectively.**

- **Simulation-based predictive checks** were implemented for model evaluation.

- **Visual predictive check plots** of observed concentrations overlaid with simulated 5th, 50th, and 95th percentiles of simulated concentrations, respectively.

**RESULTS**

- **Baseline characteristics**

<table>
<thead>
<tr>
<th>Age, years, mean (SD)</th>
<th>ATB200 observed adults (n=191)</th>
<th>ATB200 mean adults (n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.1 (10.8)</td>
<td>32.3 (11.3)</td>
<td>32.1 (10.8)</td>
</tr>
</tbody>
</table>

- **ATB200 disposition** was described by a 2-compartment model with parallel linear and nonlinear clearance.

- **AT2221 disposition** was described by a 2-compartment model with parallel linear and nonlinear clearance.

- **Fractional changes in CL** were modeled as

\[
\text{CL} \times \text{Eff}
\]

- **Estimated parameters**

<table>
<thead>
<tr>
<th>ATB200 model//parameter estimate</th>
<th>Estimate</th>
<th>95% CI</th>
<th>RSE %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (CL), L/h</td>
<td>0.149 (0.21, 0.08)</td>
<td>27.9 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Central volume distribution (Vc), L</td>
<td>2.61 (1.96, 3.48)</td>
<td>191 (86.8)</td>
<td></td>
</tr>
<tr>
<td>Intercompartmental Clearance (CL), L/h</td>
<td>0.115</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>Peripheral volume of distribution (Vp), L</td>
<td>0.05</td>
<td>8.51</td>
<td></td>
</tr>
<tr>
<td>Maximum nonlinear elimination rate (Vmax), μg/L · h</td>
<td>98.6</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>Concentration to reach half (C50), μg/mL</td>
<td>8.64</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>Fractional change in CL, %</td>
<td>20.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Population Pharmacokinetic Models**

- **Simulation-based predictive checks** were implemented for model evaluation.

- **Visual predictive check plots** of observed concentrations overlaid with simulated 5th, 50th, and 95th percentiles of simulated concentrations, respectively.

**CONCLUSIONS**

- The population PK models provided a reasonable description of ATB200 and AT2221 disposition in adults.

- Co-administration of 130 mg and 260 mg AT2221 resulted in decreases in ATB200 CL of 26.2% and 40.5%, respectively.

- Simulations suggest that a dose of 20 mg/kg ATB200 + 300 mg AT2221 in adolescents (12 to <18 years old) will attain exposure comparable to adults administered the same regimen.

**REFERENCES**


**ACKNOWLEDGMENTS**

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**DISCLOSURES**

Conflict of Interest

Amicus and FMI are employees of and hold stock in Amicus, JMS, JMIR and MIR are paid consultants for Amicus.

Hajjar JL et al. Population pharmacokinetic modeling of enzyme replacement therapy ATB200 and pharmacological chaperone AT2221 in adult patients with Pompe disease and simulation to predict adolescent exposures.

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