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Population Pharmacokinetic Modeling of Enzyme Replacement Therapy ATB200 and Pharmacological Chaperone AT2221 in Adult Patients With Pompe Disease and Simulation to Predict Adolescent Exposures

Hajjar JL,[1] Mondick JT,[1] Gastonguay MR,[1] Mulberg AE,[2] Johnson FK[2]

[1]Metrum Research Group, Tariffville, CT, USA; [2]Amicus Therapeutics, Inc., Cranbury, NJ, USA

INTRODUCTION

- Pompe disease is a rare autosomal recessive genetic disorder caused by mutations in the gene that encodes acid α-glucosidase (GAA), the enzyme responsible for breaking down lysosomal glycogen
- Enzyme replacement therapy (ERT) with alglucosidase alfa, the standard of care, may offer improvement in clinical measures for a limited duration (typically 2-3 years) followed by slow decline[1,2]
- An ERT/chaperone (ATB200/AT2221) combination has been proposed as a novel, first-in-class therapy for long-term treatment of late-onset Pompe disease
- ATB200 is a novel human recombinant acid α-glucosidase (rhGAA) administered via intravenous infusion, which is engineered for optimal uptake and targeting to the lysosome, the site of glycogen accumulation in affected tissues
- AT2221 is orally co-administered 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

OBJECTIVES

- Characterize population pharmacokinetics (PK) of ATB200 and AT2221 in adult patients with Pompe disease
- Describe the effects of AT2221 on ATB200 PK
- Perform simulations to compare exposures in adolescents (12 to <18 years old) and adults when co-administered 20 mg/kg ATB200 + 260 mg AT2221

METHODS

Modeling

- The population PK data set was derived from adult patient data from the phase 1/2 study ATB200-02 (NCT02675465):
  - 10 ERT-experienced adult patients who received doses of 5, 10, and 20 mg/kg ATB200, 20 mg/kg ATB200 + 130 mg AT2221, and 20 mg/kg ATB200 + 260 mg AT2221, successively
  - 5 ERT-naive adult patients who received 20 mg/kg ATB200 + 260 mgAT2221
- Plasma samples were collected over 24-hour periods to determine the ATB200 and AT2221 concentrations
- Population PK modeling for each drug was performed using Maximum Likelihood Estimation in NONMEM® version 7.3 with the First Order Conditional Estimation (FOCE) method
- 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 sequential zero and first-order absorption
- Clearance and volume parameters were allometrically scaled by individual weights normalized to 70 kg body weight, with exponents fixed to values of 0.75 and 1, respectively
- A categorical covariate effect model was implemented to estimate the decrease in ATB200 linear clearance (CL) with co-administration of AT2221 doses of 130 mg and 260 mg
  - Fractional changes in CL were modeled as $CL * Eff$, where Eff is the fractional change in CL due to AT2221 dosing
  - A separate Eff parameter was estimated for 130 mg and 260 mg AT2221 doses
- An exploratory covariate analysis was performed for both ATB200 and AT2221 data to investigate the effects of ERT experience on CL
  - Fractional changes in CL were modeled as $CL * \theta^{ERT}$, where ERT = 0 for naive and ERT = 1 for experienced, and θ is the fractional change in CL due to ERT experience

Model Evaluation

- Simulation-based predictive checks were implemented for model evaluation
- 500 replicate trials were generated via Monte Carlo simulation from both the ATB200 and AT2221 models
- The predictive ability of the models was checked with:
  - Quantile-quantile plots of simulated versus observed concentrations
  - Visual predictive check plots of observed concentrations overlaid with simulated 5th, 50th, and 95th percentiles

Adolescent Exposure Simulations

- Population PK simulations were performed using the final ATB200 and AT2221 models to predict likely exposures as measured by the area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$) in adolescents (12 to <18 years old) administered 20 mg/kg ATB200 + 260 mg AT2221
- 500 adolescents were simulated with ages and body weights sampled using the Centers for Disease Control and Prevention distributions
  - Sampling times for PK observations were identical to those used in the adult clinical trial
- 500 typical adults of 70 kg body weight were simulated with the same sampling times and doses
- Boxplots were constructed to compare adolescent and adult AUC distributions

RESULTS

Baseline characteristics

- The baseline characteristics of the patients in the ERT-experienced and ERT-naive cohorts were comparable (**Table 1**)

Table 1. Baseline Characteristics

	ERT-experienced adults (N=11)[a]	ERT-naive adults (N=5)
Age, years, mean (min, max)	49.4 (28, 66)	49.4 (24, 65)
Sex, M:F	9:2	1:4
Time on alglucosidase alfa, years, mean (SD)	4.8 (1.42)	NA
6MWT, meters, mean (SD)	392.0 (93.4)	399.5 (83.5)
FVC Upright, % predicted, mean (SD)	52.3 (13.2)	53.4 (20.3)

6MWT=6-Minute Walk Test; FVC=forced vital capacity; NA=not available; SD=standard deviation.
[a]One patient was excluded from the modeling due to missing PK values.

Population Pharmacokinetic Models

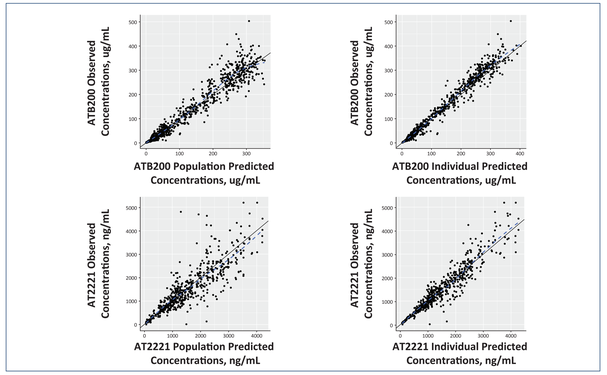
- The relative standard errors (RSEs) for the fixed effects indicated that parameter estimates were relatively precise (**Table 2**)
- Individual and population model predictions indicated a reasonable fit of the model to the data (**Figure 1**)
- Diagnostic plots showed that model fits were reasonable for both enzyme and chaperone, and that no systematic bias was present
- AT2221 doses of 130 mg and 260 mg reduced ATB200 linear clearance by 26.2% and 40.5%, respectively (**Table 2**)
- The analysis of ERT-experienced vs ERT-naive effects on CL indicated that there was not enough information to draw conclusions about the effect of ERT experience
  - The mean ERT covariate effect was 1.16 (95% CI: 0, 2.86) for ATB200 and 0.82 (95% CI: 0.41, 1.23) for AT2221
  - These wide confidence intervals indicated that the small sample size of only 5 ERT-naive individuals was not enough to use in a test for an effect of ERT experience
- Visual predictive checks demonstrated that the model-simulated data were representative of the observed concentrations (**Figure 2**)

Table 2. Population PK Parameter Estimates of ATB200 and AT2221 Models

ATB200 model parameter estimates		
Parameter	**Estimate**	**RSE, %**
Clearance (CL), L/h	0.569 (BSV: 28.35%)	27.2 (93.1)
Central volume of Distribution (Vc), L	2.63 (BSV: 15.48%)	19.1 (68.1)
Intercompartmental Clearance (Q), L/h	0.151	13.3
Peripheral volume of distribution (Vp), L	0.85	8.51
Maximum nonlinear elimination rate (V_{max}), µg/L*h	98.6	16.5
Concentration to reach half V_{max}, (Km), µg/mL	62.4	18.2
Fractional change in ATB200 CL for 130 mg AT2221	0.738	2.80
Fractional change in ATB200 CL for 260 mg AT2221	0.595	4.94
Variance of residual error	0.0317	5.12
AT2221 model parameter estimates		
Parameter	**Estimate**	**RSE, %**
Clearance (CL/F), L/h	8.55 (BSV: 17.50%)	11.6 (90.1)
Central volume of Distribution (Vc), L	36.3	21.3
Intercompartmental Clearance (Q/F), L/h	3.16 (BSV: 43.40%)	26.3 (108)
Peripheral volume of distribution (Vp/F), L	45.6	29.1
Absorption rate Constant (Ka), 1/h	0.485 (BSV: 44.30%)	52.0 (70.8)
Zero order absorption time (D1), h	0.459	27.9
Variance of residual error	0.0408	4.88

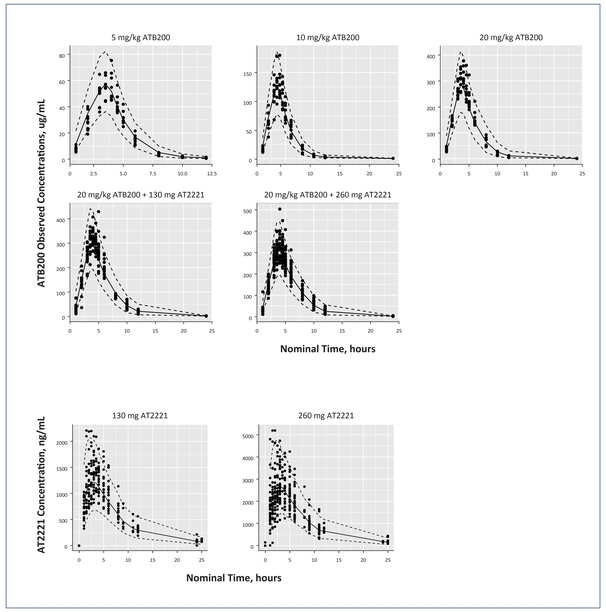
Population PK model parameter estimates for ATB200 (top) and AT2221 (bottom) in adults with Pompe disease. RSE, %=percent relative standard error; BSV=between subject variability, coefficient of variation.

Figure 1. Observed Versus Population and Individual Model Predictions of ATB200 and AT2221 Concentrations



Observed versus population (left) and individual (right) predictions of ATB200 (top) and AT2221 (bottom) concentrations.

Figure 2. Visual Predictive Checks for ATB200 and AT2221 Population PK Models in Adults With Pompe Disease

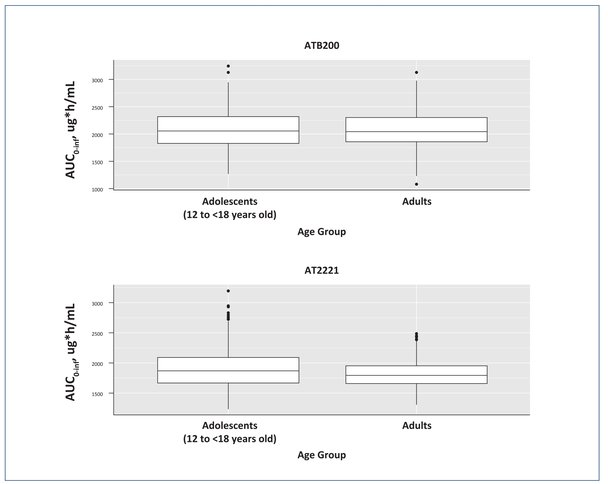


Top: Visual predictive check for ATB200 at 5 dose levels. Bottom: Visual predictive check for AT2221 at 2 dose levels. Dashed lines: top and bottom, 95th and 5th percentiles of simulated concentrations, respectively. Solid line: 50th percentile of simulated concentrations. Solid circles: observed concentrations.

Simulations for Exposure Matching

- Simulations predicted that 20 mg/kg ATB200 + 260 mg AT2221 administration in adolescents and typical adults would yield comparable exposures (**Figure 3**)
- The median (5th percentile; 95th percentile) predicted $AUC_{0\text{-}inf}$ values were:
  - ATB200:
    - Adolescents, mean weight 68.9 kg: 2050 (1510; 2620) µg/mL·h
    - Typical 70 kg adult: 2040 (1530; 2620) µg/mL·h
  - AT2221:
    - Adolescents, mean weight 68.5 kg: 27,300 (19,000; 39,700) ng/mL·h
    - Typical 70 kg adult: 25,900 (19,600; 34,500) ng/mL·h

Figure 3. Comparison of Simulated ATB200 (top panel) and AT2221 (bottom panel) $AUC_{0\text{-}inf}$ Values in Adolescents and Adults Administered 20 mg/kg ATB200 and 260 mg AT2221



Simulated $AUC_{0\text{-}inf}$ distributions of ATB200 (top) and AT2221 (bottom) for adolescents and typical 70 kg adults administered 20 mg/kg ATB200 + 260 mg AT2221.

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 + 260 mg AT2221 in adolescents (12 to <18 years old) will attain exposures comparable to adults administered the same regimen

REFERENCES

1. Toscano A, Schoser B. *J Neurol*. 2013;260(4):951-9.
2. Wyatt K, et al. *Health Technol Assess*. 2012;16(39):1-543.

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DISCLOSURES

Conflict of Interest

AM and FKJ are employees of and hold stock in Amicus. JLH, JTM and MRG are paid consultants for Amicus.

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