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First-in-Human Preliminary Pharmacokinetic and Safety Data on a Novel Recombinant Acid α-Glucosidase, ATB200, Co-administered With the Pharmacological Chaperone AT2221 in ERT-Experienced Patients With Pompe Disease

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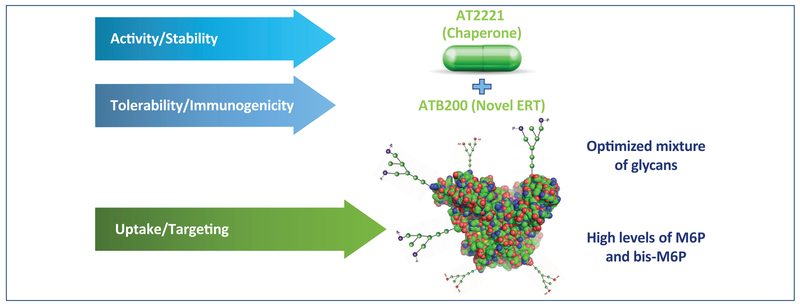
INTRODUCTION

- Pompe disease is an inherited metabolic disease of impaired lysosomal glycogen clearance due to acid α-glucosidase (GAA) deficiency, which leads to accumulation of the substrate most prominently in the heart, skeletal muscle, and smooth muscle[1,2]
- Progressive accumulation of glycogen results in a spectrum of disease severity, often leading to organ failure and/or death. Muscle weakness and progressive respiratory involvement are predominant manifestations of late-onset Pompe disease (LOPD)[1,2]
- Current management of LOPD includes enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA), in association with cardiopulmonary and gastrointestinal support, musculoskeletal and functional rehabilitation, and dietary therapy[1]
- ATB200 is a next-generation rhGAA ERT designed with optimized glycosylation and high levels of mannose 6-phosphate residues for better uptake to target tissues (**Figure 1**). The pharmacological chaperone AT2221 is co-administered with ATB200 to stabilize the enzyme in blood and maintain catalytic activity to deliver active ERT to lysosomes[3,4]
- Study ATB200-02 was designed to primarily evaluate the safety, tolerability, and pharmacokinetics (PK) of ATB200 co-administered with AT2221
- A PK/pharmacodynamic (PD) translational model from *Gaa* knockout mice predicted that a combination of ATB200 20 mg/kg with a high dose of AT2221 in humans would provide optimal glycogen reduction[5]

Figure 1. Representative Schematic of ATB200/AT2221



ERT=enzyme replacement therapy; M6P=mannose 6-phosphate.

OBJECTIVE

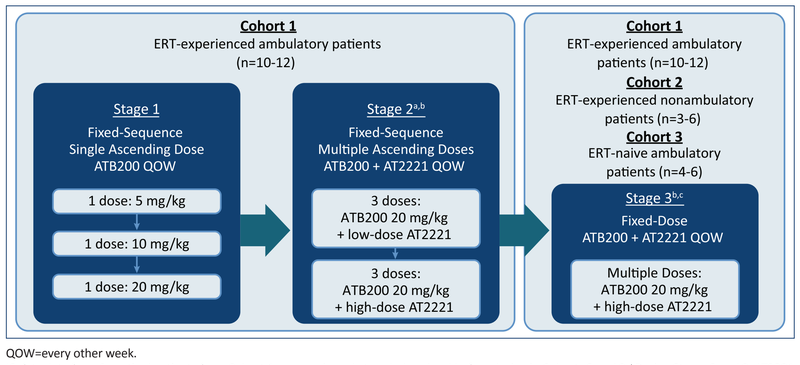
- To evaluate preliminary total GAA protein, ATB200 and AT2221 PK data, and safety markers from 10-13 patients in the phase 1/2 study ATB200-02

METHODS

- ATB200-02 (NCT02675465) is an open-label, fixed-sequence, ascending-dose, first-in-human, phase 1/2 study to assess the safety, tolerability, PK, PD, and efficacy of intravenous infusions of ATB200 co-administered with oral AT2221 in adults with Pompe disease (**Figure 2**)

Study Design

Figure 2. ATB200-02 Study Design



QOW=every other week.
[a]Safety data from 2 sentinel patients from Cohort 1 were reviewed at each dose level before dosing in Cohorts 2 and 3. [b]During Stages 2 and 3, AT2221 was orally administered prior to the start of ATB200 intravenous infusion. For all doses, ATB200 was intravenously infused for a 4-hour duration. [c]The first 2 patients in Cohorts 2 and 3 served as sentinel patients for their respective cohorts.

Key Inclusion Criteria

- Males and females aged 18-65 years who were diagnosed with Pompe disease based on documented deficiency of GAA enzyme activity or by GAA genotyping
  - Received ERT with alglucosidase alfa for 2-6 years (or ≥2 years for Cohort 2) prior to trial initiation (Cohort 1)
  - Currently receiving alglucosidase alfa at a frequency of every other week and completed the last 2 infusions without a drug-related adverse event (AE) resulting in dose interruption (Cohorts 1 and 2)
  - Must be able to walk between 200 and 500 meters on the 6-Minute Walk Test (Cohorts 1 and 3)
  - Upright forced vital capacity must be 30%-80% of predicted normal value (Cohorts 1 and 3)
  - Must be wheelchair-bound and unable to walk unassisted (Cohort 2)

PK and PD Analysis

- Mean total GAA protein (T09) and AT2221 PK results from the first 8 Cohort 1 patients through visit 9 and the first 2 Cohort 3 patients were assessed
- Blood samples for plasma total GAA protein and activity concentration were collected
  - Stage 1: prior to start of ATB200 infusion and 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hour(s) post-start of infusion
  - Stages 2 and 3: 0 (before start of infusion) and 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hour(s) after start of infusion
- Blood samples for plasma AT2221 concentrations were taken just prior to AT2221 oral administration (time 0) and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 11, and 25 hour(s) after AT2221 oral administration. Plasma AT2221 is determined by a validated LC-MS/MS assay
- Total GAA protein concentrations in plasma for ATB200 5, 10, and 20 mg/kg were determined by a validated LC-MS/MS quantification of rhGAA-specific "signature" peptide(s) (T09 [primary] and T50 [confirmatory])
- Biomarkers of muscle injury (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and creatine phosphokinase [CPK]) and disease substrate (urine glucose tetrasaccharide [Hex4]) were assessed

RESULTS

- A preliminary analysis was completed in 8 patients in Cohort 1 who completed Stages 1 and 2 and 2 patients in Cohort 3 who started Stage 3
  - Initial ERT-switch patients are representative of the Pompe disease population, with a mean of 5.02 years on ERT (**Table 1**)
- A preliminary safety analysis was completed in 13 patients, including the 10 patients assessed in the PK/PD analysis as well as 3 additional patients (1 patient in Cohort 2 and 2 patients in Cohort 1)

Table 1. Baseline Characteristics

Baseline Characteristics (N=12[a])	ERT-Experienced Ambulatory (n=10)	Naive (n=2)
Time on ERT (Lumizyme®/Myozyme®), years, mean (SD)	5.02 (1.20)	N/A
Age, years, mean (min, max)	47.7 (28, 59)	33.0 (24, 42)
Age at Pompe diagnosis, years, mean (min, max)	40.1 (25.0, 47.6)	29.8 (20.2, 39.4)
Sex, M/F, %	80/20	0/100
6MWT, meters, mean (SD)	398.4 (95.92)	432.1 (67.81)
Upright FVC, mean % predicted (SD)	51.9 (13.84)	51.0 (26.87)

6MWT=6-Minute Walk Test; FVC=forced vital capacity; N/A=not available; SD=standard deviation.
[a]n=10 from Cohort 1 (ambulatory ERT-switch) through interim data analysis (data cut December 20, 2016); n=2 from Cohort 3 (naive).

Total GAA Protein

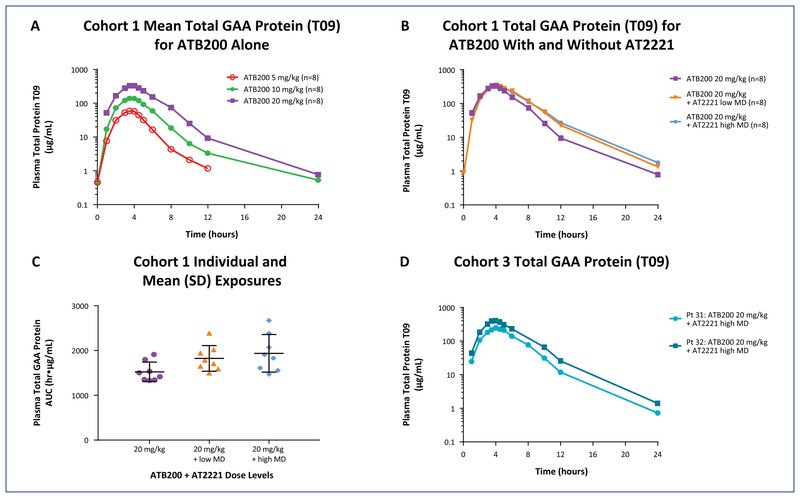
- The PK disposition of signature peptide T50 did not differ from T09 (area under the curve ratio [AUC]: 1.00)
- When given alone, ATB200 increases in a slightly greater-than-dose-proportional manner (**Table 2** and **Figure 3A**)
  - Variability appears to increase with AT2221 dose (**Table 2**)
- Co-administration of ATB200 20 mg/kg with the high dose of AT2221 increased total GAA protein exposure (AUC) by approximately 25% relative to ATB200 alone at 20 mg/kg (**Table 2** and **Figure 3C**)
  - The distribution half-life (α-phase) increased by 45%, consistent with high-dose AT2221 stabilizing ATB200 in plasma (**Figure 3B**)
  - An increase in the distribution half-life is accompanied by an increase in AUC from time to maximum plasma concentration to approximately 12 hours post-dose (**Table 2** and **Figure 3B**)
- The increases in AUC and half-life can be observed on the log scale, during the terminal elimination phase (**Figure 3B**)
- ATB200 demonstrated a relatively high volume of distribution (**Table 2**)
- The disposition of plasma total GAA protein appears similar between ERT-naive (Cohort 3) and ERT-experienced patients (Cohort 1) (**Figures 3B** and **3D**)

Table 2. Total GAA Protein (T09)

Cohort	Treatment	C_{max} (ng/mL)[a]	t_{max} (hr)[b]	$AUC_{0\text{-}t}$ (ng*hr/mL)[a]	$AUC_{0\text{-}\infty}$ (ng*hr/mL)[a]	$\beta t_{½}$ (hr)[c]	$\alpha t_{½}$ (hr)[c]	CL_T (L/hr)[c]	V_{ss} (L)[c]
1	5 mg/kg alone[d]	61 (18.1)	3.8 (3.0-4.0)	215 (16.7)	218 (16.4)	1.9 (16.7)	1.1 (10.2)	2.1 (16.9)	4.62 (12.7)
1	10 mg/kg alone[d]	144 (16.6)	4.0 (3.5-4.0)	578 (20.3)	584 (20.4)	1.6 (46.1)	1.3 (10.5)	1.59 (25.4)	3.87 (16.5)
1	20 mg/kg alone[d]	345 (10.1)	4.0 (3.5-4.0)	1508 (14.5)	1512 (14.4)	2.1 (29.7)	1.5 (6.5)	1.22 (21.7)	3.52 (12.4)
1	ATB200 20 mg/kg + AT2221 low MD[d]	353 (13.7)	4.0 (3.5-5.0)	1804 (15.7)	1808 (15.8)	2.5 (8.1)	1.9 (21.8)	1.02 (21.4)	3.73 (12.3)
1	ATB200 20 mg/kg + AT2221 high MD[d]	356 (20.2)	4.0 (3.5-4.0)	1886 (21.3)	1901 (21.7)	2.5 (20.5)	2.1 (16.1)	0.98 (27.3)	3.6 (18.7)
3	ATB200 20 mg/kg + AT2221 high MD[e]	291 (21.6)	4.3 (4.0-4.5)	1597 (34.8)	1600 (34.9)	2.4 (5.4)	2 (14.5)	0.69 (28.9)	2.61 (17.3)

AUC=area under the curve; CL_T=total body clearance; C_{max}=maximum drug concentration; CV=coefficient of variability; MD=multiple doses; $t_{1/2}$=half-life; t_{max}=time to maximum drug concentration; V_{ss}=apparent volume of distribution in steady state.
[a]Geometric mean (CV%). [b]Median (min-max). [c]Arithmetic mean (CV%). [d]n=8. [e]n=2.

Figure 3. Total GAA Protein by Cohort



Pt=patient.

AT2221 Pharmacokinetics

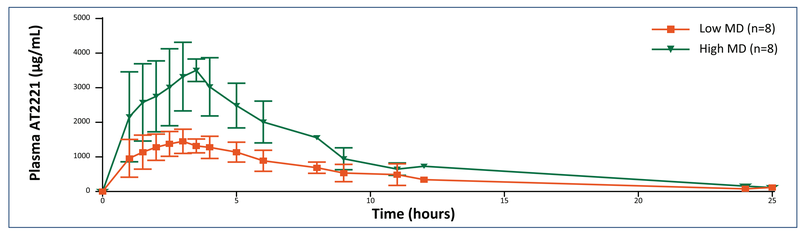
- AT2221 demonstrated dose-proportional kinetics (**Table 3** and **Figure 4**), consistent with the profile for miglustat, an active ingredient in AT2221[5]

Table 3. AT2221 PK Summary

Treatment	C_{max} (ng/mL)[a]	t_{max} (h)[b]	$AUC_{0\text{-}t}$ (ng*h/mL)[a]	$AUC_{0\text{-}\infty}$ (ng*h/mL)[a]	$t_{1/2}$ (h)[c]	CL/F (L/h)[c]	V_z/F (L)[c]
Low MD	1518 (27.6)	3.0 (1.5-3.5)	12,254 (26.4)	13,094 (28.3)	5.9 (32.1)	10.2 (23.9)	86.7 (43.9)
High MD	3569 (25.5)	3.0 (1.0-4.0)	24,970 (24.1)	25,972 (23.0)	5.3 (15.6)	10.3 (26.4)	81.0 (41.8)

CL/F=plasma clearance adjusted for AT2221 oral bioavailability; V_z/F =apparent terminal phase volume of distribution adjusted for AT2221 oral bioavailability. [a]Geometric mean (CV%). [b]Median (min-max). [c]Arithmetic mean (CV%).

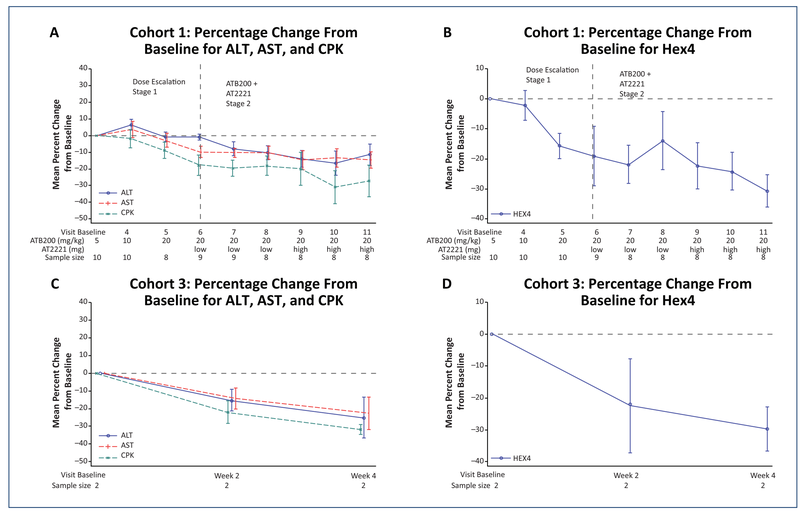
Figure 4. Mean (SD) AT2221 Concentration by Dose Regimen



Pharmacodynamics

- By the 11th visit (18 weeks) in ERT-experienced patients from Cohort 1 (**Figures 5A** and **5B**):
  - ALT decreased in 5 of 8 patients; 4/4 patients with elevated baseline levels normalized
  - AST decreased in 6 of 8 patients; 3/4 patients with elevated baseline levels normalized
  - CPK decreased in 6 of 8 patients; 2/6 patients with elevated baseline levels normalized
  - Urine Hex4 levels decreased in 8 of 8 patients; overall reduction approximately 30%
  - In patients not exhibiting decreases, biomarkers were generally stable
- By week 4 in ERT-naive patients from cohort 3 (**Figures 5C** and **5D**):
  - ALT, AST, CK, and urine Hex4 decreased in 2 of 2 patients

Figure 5. Pharmacodynamics



Data are represented as mean ± standard error.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; Hex4=urine glucose tetrasaccharide.

Safety

- No serious AEs or infusion-associated reactions were reported after 150+ total infusions in all patients (as of February 7, 2017)
- Treatment-emergent AEs, reported in 11/13 (84%) patients, were generally mild and transient
- Treatment-related AEs reported in 7/13 (53%) patients: nausea (n=1), fatigue (n=1), headache (n=1), tremor (n=2), acne (n=1), tachycardia (n=1), and hypotension (n=1)

CONCLUSIONS

- ATB200 alone and in combination with AT2221 has been safe and well tolerated, with no infusion-associated reactions to date
- ATB200 alone showed greater-than-dose-proportional increases in exposure, which was further enhanced with AT2221, suggesting a stabilizing effect of chaperone on ATB200
- After switching from standard of care (SOC) to ATB200/AT2221, patients generally showed an improvement in biomarkers of muscle damage, with many patients demonstrating normalization by week 18
- The initial 2 treatment-naive patients treated with ATB200/ATB2221 demonstrated robust reduction in all 3 biomarkers of muscle damage
- Urine Hex4, a biomarker of disease substrate, showed reduction in both SOC-treated and treatment-naive patients on ATB200/AT2221

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DISCLOSURES

Conflicts of Interest

FKJ, NH, JAB, and SS are employees of and own stock in Amicus Therapeutics. DB, PC, TH, PK, XM, TM, MR, PS, KS, and AvdP have no conflicts of interest to disclose. BB is a founder of and holds minor equity in Applied Genetic Technologies Corporation, and is an inventor on patents owned by Johns Hopkins University and the University of Florida. OG-A has received research funding and honoraria from Genzyme/Sanofi, Pfizer, and Shire. BS is a speaker for Amicus Therapeutics, Genzyme/Sanofi, and Biomarin, has received research funding from Genzyme/Sanofi, and is a member of the neuromuscular advisory board of Audentes Therapeutics.

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