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First-in-human Preliminary Pharmacokinetic Data on a Novel Recombinant Acid α-Glucosidase, ATB200, Co-administered With the Pharmacological Chaperone AT2221, in Patients With Late-onset Pompe Disease

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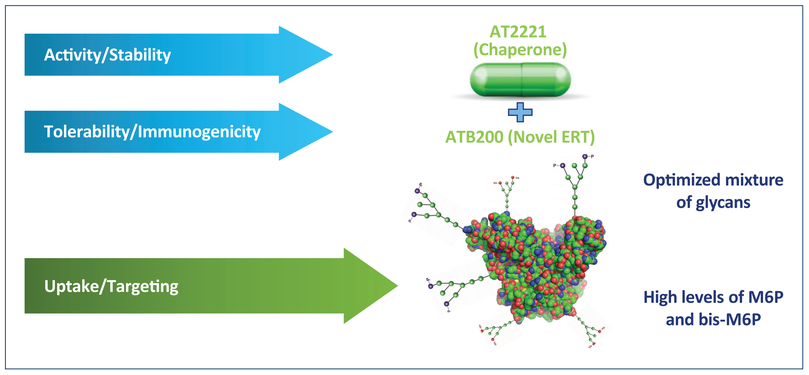
INTRODUCTION

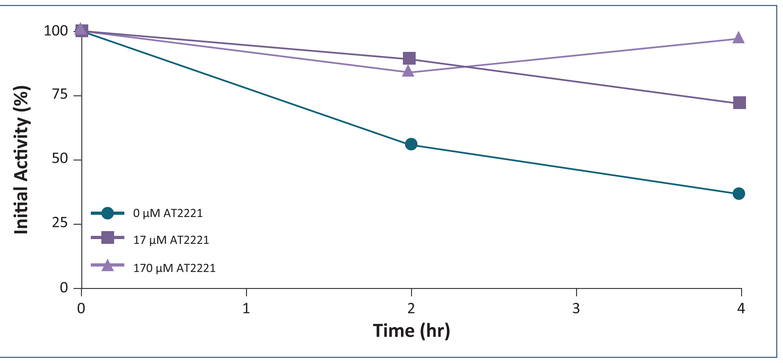
- Pompe disease is an inherited metabolic disease of impaired lysosomal glycogen clearance due to acid α-glucosidase (GAA) deficiency, which leads to accumulation of the substrate most prominently in the heart, skeletal muscle, and smooth muscle[1,2]
- Progressive accumulation of glycogen results in 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 (M6P) 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.

Figure 2. Stabilization of ATB200 by AT2221



OBJECTIVE

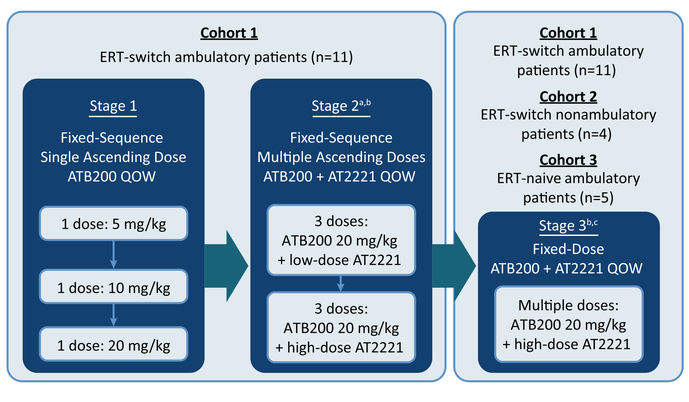
- To evaluate preliminary total GAA protein (ATB200) and AT2221 PK data from patients with LOPD in the phase 1/2 study ATB200-02

METHODS

Study Design

- 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 3**)

Figure 3. 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

- Men and women 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)
- Receiving alglucosidase alfa at a frequency of every other week and completion of the last 2 infusions without a drug-related adverse event resulting in dose interruption (Cohorts 1 and 2)
- Able to walk between 200 and 500 meters on the 6-Minute Walk Test (Cohorts 1 and 3)
- Upright forced vital capacity 30%-80% of predicted normal value (Cohorts 1 and 3)
- Wheelchair-bound and unable to walk unassisted (Cohort 2)

PK Analysis

- Mean total GAA protein (T09) and AT2221 PK analyses were performed for 11 patients in Cohort 1 who completed stages 1 and 2 and 5 patients in Cohort 3 who completed the PK study in stage 3
- Blood samples for plasma total GAA protein concentration were collected
  - Stage 1: prior to start of ATB200 infusion and at 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours after start of infusion
  - Stages 2 and 3: 0 (before start of infusion) and at 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours after start of infusion
- Blood samples for plasma AT2221 concentrations were taken just prior to AT2221 oral administration (time 0) and at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 11, and 25 hours after AT2221 oral administration. Plasma AT2221 was determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay
- Total GAA protein concentrations in plasma for ATB200 5, 10, and 20 mg/kg were determined by validated LC-MS/MS quantification of rhGAA-specific "signature" peptides T09 (primary) and T50 (confirmatory)

RESULTS

- ERT-switch patients are representative of the Pompe disease population, with a mean of 4.8 years on ERT (**Table 1**)

Table 1. Baseline Characteristics

	Cohort 1 Ambulatory ERT-Switch (N=11)	Cohort 3 ERT-Naive (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)[a]	NA
6MWT, meters, mean (SD)	392.0 (93.4)	399.5 (83.5)
Upright FVC, % predicted, mean (SD)	52.3 (13.2)	53.4 (20.3)

6MWT=6-Minute Walk Test; FVC=forced vital capacity; NA=not applicable; SD=standard deviation.
[a]Cohort 1 patients were required to have been on alglucosidase alfa for 2-6 years at baseline.

Total GAA Protein

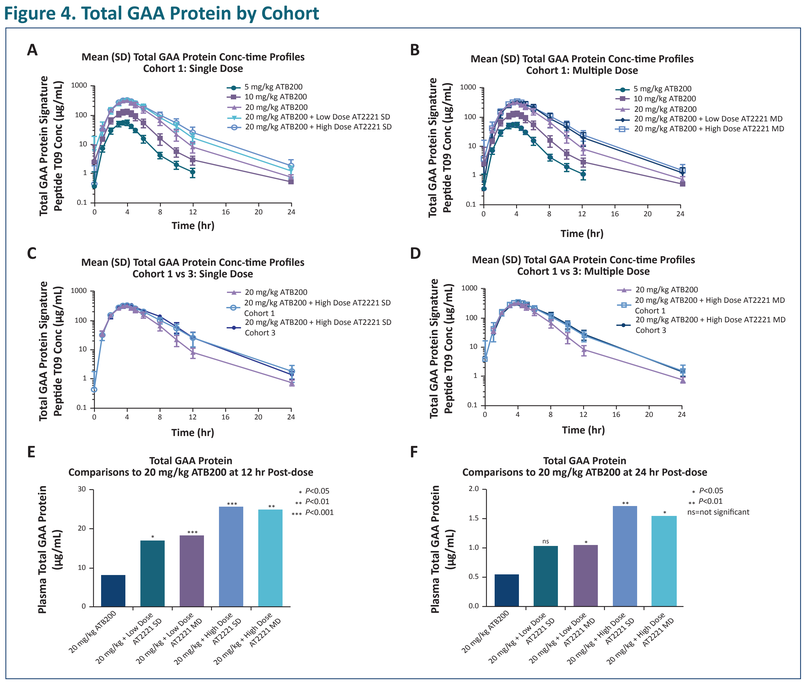
- When given alone, ATB200 increased in a slightly greater-than-dose-proportional manner (**Table 2** and **Figures 4A** and **4B**)
- Co-administration of ATB200 20 mg/kg with the low dose of AT2221 increased total GAA protein exposure area under the curve (AUC) by approximately 17% and by approximately 29% for the high dose of AT2221 relative to ATB200 20 mg/kg alone (**Table 2** and **Figures 4C** and **4D**), confirming the results of the in vitro study (**Figure 2**)
- Increases in distribution half-life and partial AUC_{24h} were observed on the log scale during the terminal elimination phase (**Table 2** and **Figures 4A** and **4B**)
  - The distribution half-life (α-phase) increased by 40%, consistent with high-dose AT2221 stabilizing ATB200 in plasma (**Table 2**)
  - The increase in the distribution half-life was accompanied by an increase in partial AUC from time to maximum plasma concentration to 24 hours post-dose of 42.2% (**Table 2** and **Figure 4B**)
- Further evidence of ATB200 stabilization by AT2221 was observed in 12- and 24-hour post-dose comparisons of low- and high-dose AT2221 vs ATB200 alone (**Figures 4E** and **4F**)
- There was no statistically significant difference in plasma total GAA protein exposure between ERT-naive (Cohort 3) and ERT-switch patients (Cohort 1) (**Table 3**)
- The PK disposition of signature peptide T50 did not differ from that of T09 (AUC ratio: 1.00)

Table 2. Total GAA Protein by Signature Peptide T09

Cohort	Treatment	C_{max} (ng/mL)[a]	t_{max} (hr)[b]	AUC $t_{max\text{-}24h}$ (ng·hr/mL)[a]	$AUC_{0-\infty}$ (ng·hr/mL)[a]	F_{rel} [c]	α $t_{½}$ (hr)[c]	CL_T (L/hr)[c]
1	ATB200 5 mg/kg alone[d]	58.4 (19.1)	4.0 (3.0-4.0)	108 (25.1)	211 (17.2)	—	1.1 (10.2)	2.2 (16.9)
1	ATB200 10 mg/kg alone[d]	135 (18.3)	4.0 (3.5-4.0)	287 (25.6)	538 (24.4)	2.6 (9.4)	1.3 (10.6)	1.7 (22.4)
1	ATB200 20 mg/kg alone[d]	325 (13.5)	4.0 (3.5-4.0)	844 (20.8)	1418 (16.9)	6.9 (7.4)	1.5 (8.5)	1.3 (18.4)
1	ATB200 20 mg/kg + AT2221 low dose MD[d]	335 (15.4)	4.0 (3.5-5.0)	1062 (23.8)	1662 (20.5)	1.17 (7.7)	1.8 (21.8)	1.1 (20.5)
1	ATB200 20 mg/kg + AT2221 high dose MD[d]	345 (18.5)	4.0 (3.5-4.0)	1203 (24.2)	1821 (21.5)	1.28 (9.4)	2.1 (16.1)	1.0 (22.7)
3	ATB200 20 mg/kg + AT2221 high dose MD[e]	322 (14.3)	4.0 (4.0-4.5)	1147 (20.9)	1775 (19.3)	N/A	2.2 (9.9)	0.8 (28.4)

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; F_{rel}=AUC ratio of 20 mg/kg and 10 mg/kg vs 5 mg/kg, and 20 mg/kg + low dose or high dose AT2221 vs 20 mg/kg alone.
[a]Geometric mean (CV%). [b]Median (min-max). [c]Arithmetic mean (CV%). [d]n=11. [e]n=5.

Figure 4. Total GAA Protein by Cohort



conc=concentration; GAA=α-glucosidase; SD=single dose.

Table 3. ANOVA for Total GAA Protein by Signature Peptide T09 AUC (µg·h/mL)

Reference	Test	AUC Ratio % Ref	90% Lower-bound CI	90% Upper-bound CI
Cohort 1 SD	Cohort 1 MD	98.0	94.9	101.2
Cohort 1 SD	Cohort 3 SD	100.1	82.3	121.8
Cohort 1 MD	Cohort 3 MD	97.5	80.2	118.6

ANOVA=analysis of variance; AUC=area under the curve; CI=confidence interval.

AT2221 Pharmacokinetics

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

Table 4. AT2221 PK Summary

Treatment	C_{max} (ng/mL)[a]	t_{max} (h)[b]	AUC_{0-t} (ng·h/mL)[a]	$AUC_{0-\infty}$ (ng·h/mL)[a]	$t_{1/2}$ (h)[c]	CL/F (L/h)[c]	V_z/F (L)[c]
Low-dose MD (N=11)	1504 (23.9)	3.0 (1.5-4.0)	11,968 (24.5)	12,913 (25.6)	6.5 (29.3)	10.3 (21.3)	97.3 (39.8)
High-dose MD (N=16)	3086 (29.4)	3.0 (1.0-4.0)	24,095 (25.9)	25,506 (25.9)	5.9 (18.3)	10.5 (22.9)	90.5 (34.1)

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%).

CONCLUSIONS

- Co-administration of low- and high-dose AT2221 showed dose-related increases in ATB200 exposures and distribution half-life, indicating stabilization of ATB200 in blood by AT2221
  - These increases were significantly or highly significantly different from ATB200 administered alone
- High levels of M6P and bis-M6P along with an optimized mixture of glycans may provide enhanced plasma clearance of ATB200 and improved tissue targeting relative to standard of care
- Exposures from ERT-switch patients were not statistically different from those of ERT-naive patients

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5. Data on file. Amicus Therapeutics, Inc.

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DISCLOSURE

Conflicts of Interest

FKJ, NH, SS, JAB, and SS are employees of and hold stock in Amicus Therapeutics, Inc. 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 Sanofi Genzyme, Pfizer, and Shire. BS is a speaker for Amicus Therapeutics, Sanofi Genzyme, and Biomarin, has received research funding from Sanofi Genzyme, and is a member of the neuromuscular advisory board of Audentes Therapeutics.

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