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First-in-Human Study of ATB200/AT2221 in Patients With Pompe Disease: Interim Results From the ATB200-02 Trial

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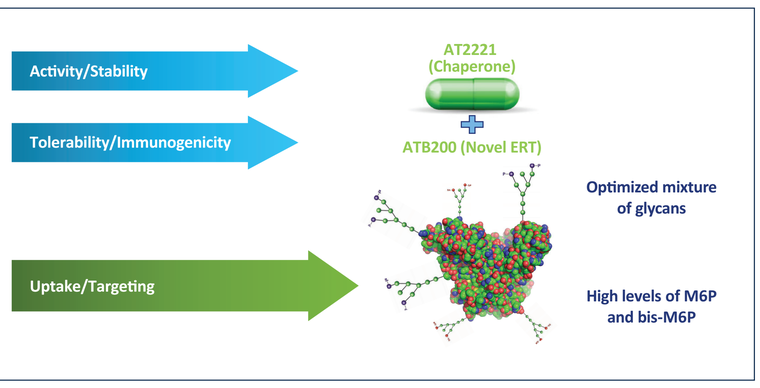
INTRODUCTION

- 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. Skeletal muscle weakness and progressive respiratory involvement are predominant manifestations of late-onset Pompe disease (LOPD)[1,2]
- Enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA) is the definitive therapy for LOPD[1]
- ATB200 is a next-generation rhGAA ERT designed with optimized glycosylation and high levels of mannose 6-phosphate residues for better uptake in target muscle tissues (**Figure 1**). The pharmacological chaperone AT2221 is co-administered with ATB200 to minimize denaturation of the enzyme in blood and maintain catalytic activity to deliver active ERT to lysosomes[3,4]
- Preclinical studies were conducted in *Gaa* knockout mice to evaluate the pharmacokinetics (PK) and efficiency of glycogen reduction at varying ATB200 ERT and AT2221 chaperone doses. These data were used to estimate the comparable AT2221 chaperone doses in humans[5]
- Study ATB200-02 (NCT02675465) was designed to evaluate the safety, tolerability, PK, pharmacodynamics (PD), and efficacy of ATB200 co-administered with AT2221

Figure 1. Representative Schematic of ATB200/AT2221



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

OBJECTIVE

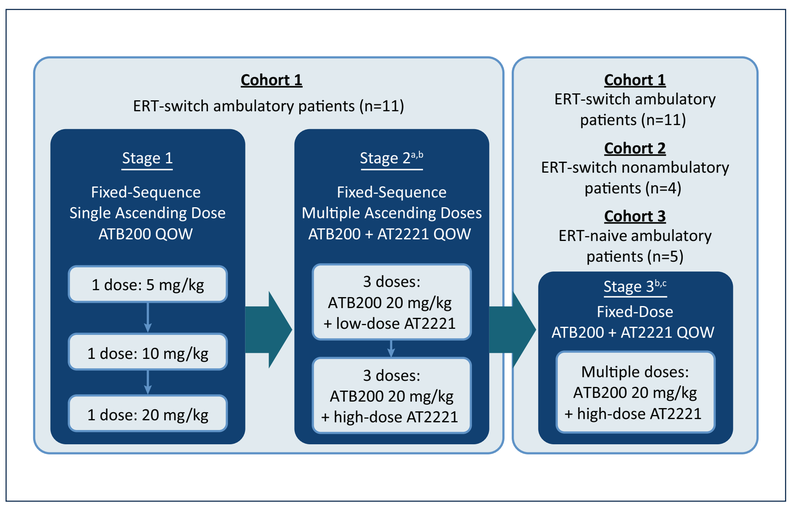
- To evaluate the preliminary safety, PK, PD, and efficacy of ATB200/AT2221 in patients with Pompe disease enrolled in the phase 1/2 ATB200-02 study

METHODS

Study Design

- ATB200-02 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 LOPD (**Figure 2**)

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 having 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 (6MWT) (Cohorts 1 and 3)
- Upright forced vital capacity (FVC) must be 30-80% of predicted normal value (Cohorts 1 and 3)
- Must be wheelchair-bound and unable to walk unassisted (Cohort 2)

Analyses

- Data are from interim analysis 4 (**Figure 3**)

Figure 3. Summary of Analyses and Available Data

Cohort 1 (ERT-Switch Ambulatory, N=11)	Cohort 2 (ERT-Switch Nonambulatory, N=4)	Cohort 3 (ERT-Naive, N=5)
• Safety and tolerability (n=11) • Biomarkers (n=11) • Functional assessments at – Month 6 (n=9)[a] – Month 9 (n=8) • Functional assessments: – 6MWT – Other motor function tests (time tests and GSGC) – Pulmonary function (FVC, MIP/MEP)	• Safety and tolerability (n=4) • Biomarkers (n=4) • Functional assessments at Month 6 (n=4) • Functional assessments: – Muscle Strength Tests	• Safety and tolerability (n=5) • Biomarkers (n=5) • Functional assessments at – Month 6 (n=5) – Month 9 (n=2) • Functional assessments: – 6MWT – Other motor function tests (time tests and GSGC) – Pulmonary function (FVC, MIP/MEP)

6MWT=6-minute walk test; FVC=forced vital capacity; GSGC=Gait, Stair, Gower, Chair; MEP=maximal expiratory pressure; MIP=maximal inspiratory pressure.
[a]One patient discontinued after completing stage 1 (week 18) due to travel burden and family considerations, and 1 patient's month 6 data are pending.

RESULTS

- Sixteen clinical sites in 5 countries participated in the ATB200-02 clinical study
- Patients were representative of the overall LOPD population (**Table 1**)

Table 1. Baseline Characteristics (N=20)

	Cohort 1 ERT-Switch Ambulatory (n=11)	Cohort 2 ERT-Switch Nonambulatory (n=4)	Cohort 3 ERT-Naive (n=5)
Age, years, mean (range)	49.4 (28-66)	36.0 (18-56)	49.4 (24-65)
Sex, M:F	9:2	3:1	1:4
Time on alglucosidase alfa, years, mean (SD)	4.77 (1.42)[a]	8.9 (3.8)	NA
6MWT, meters, mean (SD)	392.0 (93.4)	NA	399.5 (83.5)
FVC upright, % predicted, mean (SD)	52.3 (13.2)	NA	53.4 (20.3)

NA=not applicable; SD=standard deviation.
[a]Cohort 1 patients were required to have been on alglucosidase alfa for 2-6 years at baseline.

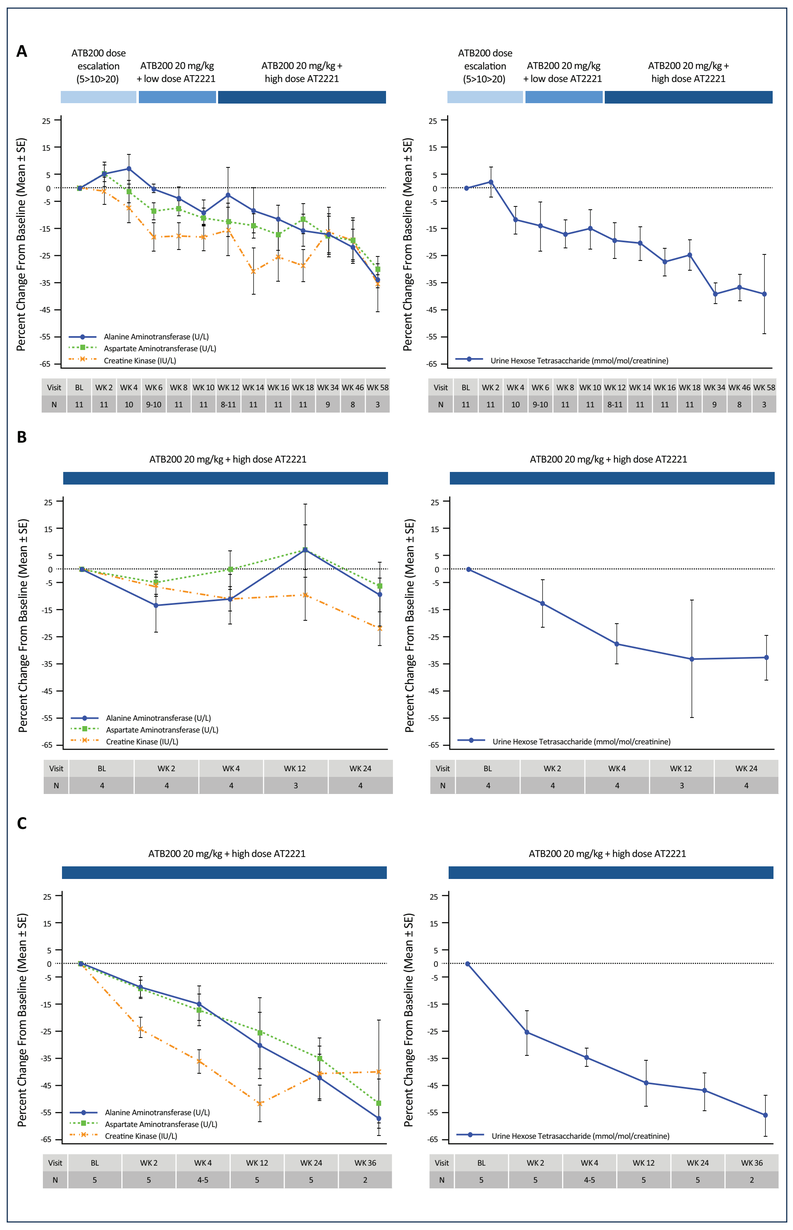
Safety

- AEs were generally mild and transient
  - Most common AEs reported as treatment related were nausea (3/20), tremor (3/20), headache (3/20), fatigue (3/20), diarrhea (2/20), muscle spasm (2/20), and joint swelling (2/20)
- One serious AE was reported, which was unrelated to the study drug (hospitalization for lower respiratory tract infection)
- No patients discontinued the study due to an AE
- There were 3 incidents of infusion-associated reactions (IARs) in 400+ infusions, which were controlled by standard premedication
  - One IAR event in a nonambulatory ERT-switch patient (skin discoloration)
  - Two IAR events in an ERT-naive patient (localized pruritus, erythema and burning sensation)
- Longest duration of treatment was 72 weeks

Markers of Muscle Injury

- Muscle damage markers (creatine kinase enzyme, alanine aminotransferase, and aspartate aminotransferase): Mean reductions from baseline were approximately 30-35%, 5-20%, and 40-55% for ambulatory ERT-switch (n=9), nonambulatory ERT-switch (n=4), and ERT-naive (n=5) patients, respectively (**Figure 4**)
- Glycogen accumulation marker (urine hexose tetrasaccharide [Hex4]): Mean reductions from baseline were approximately 39%, 32%, and 55% for ambulatory ERT-switch (n=9), nonambulatory ERT-switch (n=4), and ERT-naive (n=5) patients, respectively (**Figure 4**)

Figure 4. Mean Percentage Change From Baseline in Markers of Muscle Injury and Disease Substrate in (A) Ambulatory ERT-Switch Patients; (B) Nonambulatory ERT-Switch Patients; and (C) ERT-Naive Patients



Data are reported through an interim data analysis (maximum 58 weeks, 24 weeks, and 36 weeks for cohorts 1, 2, and 3, respectively). Missing values were either unable to be analyzed or not yet analyzed.
BL=baseline; SE=standard error; WK=week.

Efficacy

- 6MWT improved for both ambulatory ERT-switch and ERT-naive patients at month 6, with continued benefit to month 9 (**Table 2**)
  - 6MWT distance increased in 7/9 and 8/8 ERT-switch patients at months 6 and 9, respectively
    - Two patients were stable at month 6; 1 of them reached month 9 and had increased 6MWT
  - 6MWT distance increased in 5/5 and 2/2 ERT-naive patients at months 6 and 9, respectively

Table 2. 6-Minute Walk Test

	Baseline, Mean (SD)	Change From Baseline to Month 6, Mean (SD)	Change From Baseline to Month 9, Mean (SD)
Cohort 1 ERT-Switch	**n=10**	**n=9**	**n=8**
	397.2 (96.8)	**+35.3** (40.1)	**+37.2** (33.8)
Cohort 3 ERT-Naive	**n=5**	**n=5**	**n=2**
	399.5 (83.5)	**+41.8** (29.4)	**+74.9** (4.0)

Results are given in meters.

- Improvement in motor function tests, along with 6MWT, were consistent with an overall improvement in muscle function for both ambulatory ERT-switch and ERT-naive patients (**Table 3**)

Table 3. Other Motor Function Tests

	Assessment, sec	Baseline, Mean (SD)	Change From Baseline to Month 6, Mean (SD)	Change From Baseline to Month 9, Mean (SD)
Cohort 1 ERT-Switch		**n=10**	**n=9**	**n=8**
	Timed Up and Go	**10.5** (6.6)	**−2.2** (3.4)	**−0.6** (2.5)
	4 Stair Climb	**4.1** (2.7)	**−1.0** (1.2)	**−0.9** (1.3)
	10M Walk	**7.4** (3.0)	**−0.3** (1.6)	**0.1** (1.3)
	Gowers[a]	**7.9** (2.8)	**−2.2** (2.0)	**−2.1** (1.3)
	GSGC Score	**12.6** (4.8)	**−0.8** (3.0)	**−0.9** (3.5)
Cohort 3 ERT-Naive		**n=5**	**n=5**	**n=2**
	Timed Up and Go	**9.4** (2.9)	**−1.0** (1.1)	**−1.6** (1.0)
	4 Stair Climb	**4.2** (1.5)	**−0.6** (0.3)	**−0.8** (0.3)
	10M Walk	**7.9** (3.0)	**−0.7** (1.1)	**−1.0** (0.1)
	Gowers	**13.9** (11.0)	**7.9**[b] (21)	**−1.3** (0.0)
	GSGC Score	**12.2** (3.6)	**−1.8** (3.8)	**−4.0** (1.4)

[a]N=9; one patient refused to perform test.
[b]Median change from baseline was −0.8, and 4/5 patients had a decrease.

- Consistent and substantial increases were observed in upper extremity strength in all nonambulatory ERT-switch patients at month 6 (**Table 4**)

Table 4. Muscle Strength Testing in Nonambulatory ERT-Switch Patients (cohort 2)

Assessment	Muscle Group Tested	Baseline, Mean (SD)		Change From Baseline to Month 6, Mean (SD)	
		Right	Left	Right	Left
Quantitative Muscle Testing—Dynamometer, pounds force	Shoulder Adduction[a]	**1.5** (1.9)	**4.2** (6.8)	**+5.8** (8.4)	**+2.3** (4.4)
	Shoulder Abduction	**6.9** (7.6)	**9.8** (10.9)	**+0.8** (1.5)	**+0.3** (5.1)
	Elbow Flex	**4.9** (5.1)	**7.8** (8.7)	**+2.4** (6.1)	**−0.1** (10.0)
	Elbow Extension	**5.0** (5.9)	**7.3** (8.1)	**+4.1** (2.1)	**+1.5** (3.4)
Manual Muscle Testing, manual score[b]	Shoulder Adduction[a]	**1.0** (1.0)	**1.3** (1.2)	**+0.7** (1.2)	**+0.7** (1.2)
	Shoulder Abduction[c]	**1.3** (1.2)	**1.3** (1.2)	**0.0** (0.0)	**+0.5** (0.7)
	Elbow Flex	**2.0** (2.0)	**2.3** (2.5)	**+1.0** (1.0)	**+0.7** (0.6)
	Elbow Extension	**2.0** (2.0)	**2.0** (2.0)	**+1.0** (1.0)	**+0.7** (0.6)

[a]n=3 due to assessment not being performed at some visits for some patients.
[b]Scoring: (1) Visible muscle movement, but no movement at the joint; (2) Movement at the joint, but not against gravity; (3) Movement against gravity, but not against added resistance; (4) Movement against resistance, but less than normal; (5) Normal strength.
[c]n=2 due to assessment not being performed at some visits for some patients.

- FVC was generally stable in ambulatory ERT-switch patients and increased in ERT-naive patients (**Table 5**)
  - FVC was stable or increased in 5/8 and 5/7 ERT-switch patients at months 6 and 9, respectively
  - FVC increased in 4/5 and 2/2 ERT-naive patients at months 6 and 9, respectively
- Maximal inspiratory pressure (MIP) was stable and maximal expiratory pressure (MEP) increased in ambulatory ERT-switch patients; MIP increased and MEP was stable in ERT-naive patients (**Table 5**)

Table 5. Forced Vital Capacity and Other Pulmonary Function Tests

	Assessment	Baseline, Mean (SD)	Change From Baseline to Month 6, Mean (SD)	Change From Baseline to Month 9, Mean (SD)
Cohort 1 ERT-Switch		**n=10**	**n=9**	**n=8**
	FVC, % predicted[a]	**52.6** (14.7)	**−1.0** (4.2)	**−2.0** (3.6)
	MIP	**35.7** (11.0)	**+0.9** (4.5)	**−1.4** (2.7)
	MEP	**72.6** (32.6)	**+20.3** (42.4)	**+31.1** (39.3)
Cohort 3 ERT-naive		**n=5**	**n=5**	**n=2**
	FVC, % predicted	**53.4** (20.3)	**+4.2** (5.6)	**+5.0** (1.4)
	MIP	**32.6** (18.5)	**+11.0** (5.0)	**+1.5** (0.7)
	MEP	**60.6** (8.3)	**−0.4** (12.4)	**−1.0** (19.8)

[a]FVC not available for 1 patient.

SUMMARY AND CONCLUSIONS

- There is concordance in the data showing a parallel improvement in markers of muscle injury and substrate accumulation, motor function (endurance, timed tests, and muscle strength), and stabilization and/or improvement in respiratory function tests across the different cohorts
- Muscle function improved in 16/18 and 10/10 patients at months 6 and 9, respectively
- Increases in 6MWT distance were consistent and durable out to month 9 as were the improvements in other motor function tests in ambulatory ERT-switch and ERT-naive patients
- Qualitative and quantitative measures showed increases in upper extremity strength in nonambulatory ERT-switch patients at month 6
- FVC was generally stable in ambulatory ERT-switch patients and increased in ERT-naive patients
- The multi-dimensional impact of the therapy is suggestive that the combination regimen of ATB200/AT2221 has the potential to be an important treatment option for patients with Pompe disease. Further study of this regimen is ongoing

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DISCLOSURES

Conflicts of Interest

M. Roberts has no conflicts of interest to disclose. S. Sitaraman, J.A. Barth, and S. Sathe are employees of and own stock in Amicus Therapeutics.

For questions, please contact Mark Roberts at markrob@doctors.org.uk.

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