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Updated Results From ATB200-02: A First-in-Human, Open-Label, Phase 1/2 Study of ATB200 Coadministered With AT2221 in Adults 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. Skeletal muscle weakness and progressive respiratory involvement are predominant manifestations of late-onset Pompe disease (LOPD)[1,2]
- ATB200 is a next-generation recombinant human GAA (rhGAA) enzyme replacement therapy (ERT) designed with optimized glycosylation and high levels of mannose 6-phosphate residues for better uptake in target muscle tissues. The pharmacological chaperone AT2221 is coadministered with ATB200 to minimize denaturation of the enzyme in blood and maintain catalytic activity to deliver active ERT to lysosomes[3,4]

OBJECTIVE

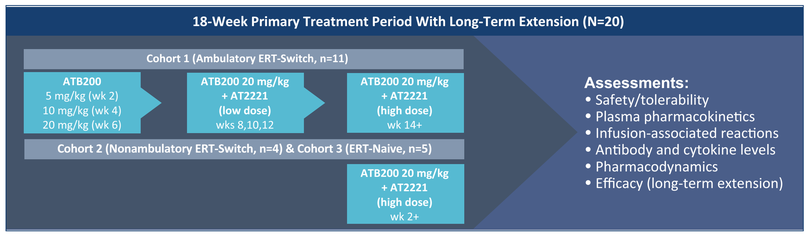
- To assess the safety, pharmacodynamics, and efficacy of ATB200 coadministered with AT2221 in patients with Pompe disease enrolled in the phase 1/2 ATB200-02 study (NCT02675465)

METHODS

Study Design

- Data are from interim analysis 5 and include all 12-month data that were available as of the data cutoff (n=8/11 for Cohort 1; n=1/4 for Cohort 2; n=2/5 for Cohort 3)
- Safety analyses include all data up to 20 months

Figure 1. ATB200-02 Study Design



ERT=enzyme replacement therapy.

Key Inclusion Criteria

- Males and females aged 18-65 years diagnosed with Pompe disease per documented deficiency of GAA enzyme activity or *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)
- Able to walk between 200 and 500 meters on the 6-Minute Walk Test (6MWT) (Cohorts 1 and 3)
- Upright forced vital capacity (FVC) 30-80% of predicted normal value (Cohorts 1 and 3)
- Wheelchair-bound and unable to walk unassisted (Cohort 2)

RESULTS

- Sixteen clinical sites in 5 countries participated in the ATB200-02 trial
- Patients were representative of the overall LOPD population, with significant impairment at baseline (**Table 1**)

Table 1. Baseline Characteristics

	Cohort 1 Ambulatory ERT-Switch N=11	Cohort 2 Nonambulatory ERT-Switch N=4	Cohort 3 ERT-Naive N=5
Age, years, mean (min, max)	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)	4.8 (1.4)[a]	8.9 (3.8)	NA
6MWT, meters, mean (SD)	392.0 (93.4)	NA	399.5 (83.5)
Upright FVC, % predicted, mean (SD)	52.3 (13.2)	NA	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.

Efficacy

- 6MWT improved for ambulatory ERT-switch patients and ERT-naive patients at Month 6 with continued benefit observed to Month 12 (**Table 2**)
  - 6MWT increased in 7/10, 8/10, and 8/8 ERT-switch patients at Months 6, 9, and 12, respectively
  - 6MWT increased in 5/5, 5/5, and 2/2 ERT-naive patients at Months 6, 9, and 12, respectively

Table 2. 6-Minute Walk Test, meters

Patient	Baseline	Change From Baseline		
		Month 6	Month 9	Month 12
Cohort 1 ERT-Switch				
1	544	+51	+56	+112
2	379	+125	+110	+103
3	339	+21	+45	+73
4	332	+8	+26	+45
5	456	−5	+8	+41
6	500	+55	+20	+33
7	220	+29	+21	+30
8	410	+38	+11	+22
9	464	−4	−9	—[a]
10	328	−78	−43	—[a]
Mean (SD)	397.2 (96.8)	+23.9 (52.2)	+24.5 (40.8)	+57.4 (34.4)
Cohort 3 ERT-Naive				
1	480	+41	+72	+95
2	384	+62	+78	+79
3	460	+79	+89	—[a]
4	406	+14	+44	—[a]
5	267	+13	+35	—[a]
Mean (SD)	399.5 (83.5)	+41.8 (29.4)	+63.5 (23.1)	+86.8 (11.1)

[a]12-month data not yet available.

- Improvements in 6MWT and other motor function tests were consistent with an overall improvement in motor performance for ambulatory ERT-switch patients and ERT-naive patients over 12 months (**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)	Change From Baseline to Month 12, Mean (SD)
Cohort 1 ERT-Switch		n=10	n=10	n=10	n=8
	Timed Up and Go	10.5 (6.6)	−1.8 (3.5)	−1.2 (3.3)	−1.0 (2.2)
	4-Stair Climb	4.1 (2.7)	−0.6 (1.6)	−0.4 (1.6)	−1.0 (1.5)
	10M Walk	7.4 (3.0)	+0.1 (1.9)	−0.1 (1.6)	−0.5 (1.7)
	Gowers[a]	7.9 (2.9)	−1.1 (3.8)	+4.5[b] (13.4)	−2.6 (1.9)
	GSGC Score	12.6 (4.8)	+0.1 (3.9)	+0.5 (4.6)	−1.9 (2.2)
Cohort 3 ERT-Naive		n=5	n=5	n=5	n=2
	Timed Up and Go	9.4 (2.9)	−1.0 (1.1)	−0.6 (1.4)	−1.8 (0.5)
	4-Stair Climb	4.2 (1.5)	−0.6 (0.3)	0.0 (1.5)	−0.4 (0.4)
	10M Walk	7.9 (3.0)	−0.7 (1.1)	−1.3 (1.0)	−0.6 (0.0)
	Gowers	13.9 (11.0)	+7.9[c] (20.9)	−1.6 (3.9)	−2.1 (1.3)
	GSGC Score	12.2 (3.6)	−1.8 (3.8)	−2.4 (3.4)	0.0 (1.4)

GSGC=Gait, Stairs, Gowers, Chair.
GSGC is an observer-rated combined score of 4 motor function assessments: Gait (10m walk), 4-Stair Climb, Gowers (stand from floor), and Rising From Chair. Each test is scored from 1 (normal) to 7 (cannot perform; max score of 6 for Rising From Chair). Total scores range from 4 to 27.
[a]N=9, missing values not obtained due to patient refusal to perform test.
[b]Median change from baseline was −1.5, and 7/9 patients had a decrease.
[c]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 nonambulatory ERT-switch patients at Month 6 and Month 9 (**Table 4**)
  - Three out of 4 patients showed improvements in upper extremity strength from baseline to Month 9 as measured by quantitative muscle testing (QMT) and manual muscle testing (MMT)

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

	Muscle Group Tested	Baseline, Mean (SD) n=4	Change From Baseline to Month 6, Mean (SD) n=4	Change from Baseline to Month 9, Mean (SD) n=4
Quantitative Muscle Testing—Dynamometer, pounds force	Shoulder Adduction[a]	5.7 (8.8)	+8.1 (12.8)	+9.6 (12.3)
	Shoulder Abduction	16.7 (18.1)	+1.0 (6.6)	+0.5 (9.3)
	Elbow Flexion	12.7 (13.7)	+2.4 (15.9)	+6.0 (19.3)
	Elbow Extension	12.3 (13.9)	+5.5 (4.7)	+7.5 (8.2)
Manual Muscle Testing, manual score[b]	Shoulder Adduction	2.3 (2.1)	+1.3 (2.3)	0.0 (4.0)
	Shoulder Abduction	2.7 (2.3)	+0.5 (0.7)	−1.0 (2.7)
	Elbow Flexion	4.3 (4.5)	+1.7 (1.5)	+1.7 (1.5)
	Elbow Extension	4.0 (4.0)	+1.7 (1.5)	+1.7 (1.5)

QMT results are pounds of force for right and left sides combined. MMT scores are for right and left sides combined. MMT 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. Total MMT scores are out of 10 (right and left combined). Data shown to Month 9 because only 1 patient in Cohort 2 had Month 12 QMT and MMT data available at the time of the analysis.
[a]Shoulder adduction not available for 1 patient.
[b]n=3 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 5/9, 6/9, and 3/7 ERT-switch patients at Months 6, 9, and 12, respectively
  - FVC was stable or increased in 5/5, 5/5, and 2/2 ERT-naive patients at Months 6, 9, and 12, 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)	Change From Baseline to Month 12, Mean (SD)
Cohort 1 ERT-Switch		n=10	n=10	n=10	n=8
	FVC, % predicted[a]	52.6 (14.7)	−1.3 (4.1)	−1.7 (3.9)	−3.1 (4.8)
	MIP	35.7 (11.0)	+0.3 (4.6)	−0.6 (3.0)	+0.3 (3.6)
	MEP	72.6 (32.6)	+16.1 (42.1)	+23.7 (38.1)	+36.8 (45.7)
Cohort 3 ERT-Naive		n=5	n=5	n=5	n=2
	FVC, % predicted	53.4 (20.3)	+4.2 (5.6)	+6.2 (5.3)	+6.0 (7.1)
	MIP	32.6 (18.5)	+11.0 (5.0)	+12.0 (10.3)	−0.5 (9.2)
	MEP	60.6 (8.3)	−0.4 (12.4)	+7.2 (15.3)	−2.0 (9.9)

MEP=maximal expiratory pressure; MIP=maximal inspiratory pressure.
[a]FVC not available for 1 patient.
MIP and MEP were measured in centimeters of water.

Patient-Reported Outcomes

- All cohorts were significantly impacted by fatigue at baseline, and demonstrated a mean improvement in their Fatigue Severity Scale (FSS) after receiving ATB200/AT2221 (**Table 6**)

Table 6. Fatigue Severity Scale

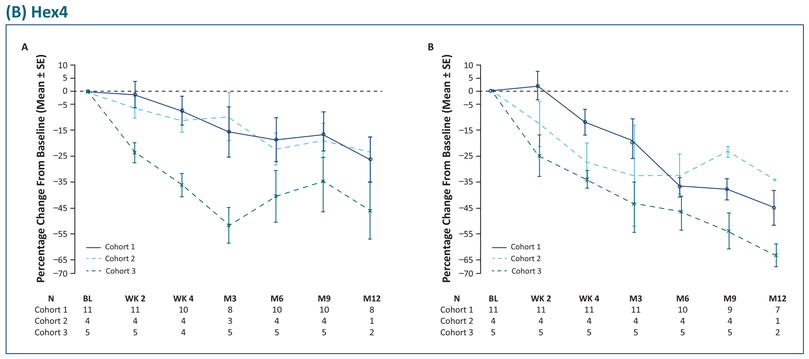
	Baseline, Mean (SD)	Change From Baseline to Month 6, Mean (SD)	Change From Baseline to Month 9, Mean (SD)	Change From Baseline to Month 12, Mean (SD)
Cohort 1 Ambulatory ERT-Switch	n=10	n=10	n=10	n=8
	53.5 (7.7)	−8.0 (10.7)	−6.8 (6.8)	−7.8 (6.0)
Cohort 2 Nonambulatory ERT-Switch	n=4	n=2	n=2	—
	54.0 (8.5)	−3.5 (7.8)	−6.5 (5.0)	—
Cohort 3 ERT-Naive	n=5	n=5	n=5	n=2
	39.2 (12.7)	−5.2 (11.7)	−7.8 (7.5)	−1.5 (2.1)

Fatigue Severity Scale consists of 9 questions, each scored on a scale from 1 to 7. The total score ranges from 9 to 63, with higher values representing higher levels of fatigue due to the disease condition. The normative value in the healthy population is ~21.[5]

Markers of Muscle Injury

- All cohorts demonstrated persistent improvement in biomarkers of muscle damage (creatine kinase; CK) and disease substrate (urine hexose tetrasaccharide; Hex4) for up to 12 months (**Figure 2**)

Figure 2. Mean Percentage Change From Baseline in Markers of Muscle Damage (A) Creatine Kinase and (B) Hex4



Hex4=urine hexose tetrasaccharide; M=month; SE=standard error; WK=week.

Safety

- At the data cutoff, the longest duration on treatment was 20+ months
- AEs were generally mild and transient
- The most common AEs reported as treatment related were upper and lower abdominal pain (8/20), diarrhea (8/20), nasopharyngitis (6/20), nausea (5/20), headache (5/20), and upper respiratory tract infection (5/20)
- There were 3 incidents of infusion-associated reactions (IAR) in 550+ infusions, which were controlled by standard premedication
  - One IAR in a nonambulatory ERT-switch patient (skin discoloration)
  - Two IARs in an ERT-naive patient (localized pruritus, erythema and burning sensation)

CONCLUSIONS

- Muscle function
  - 6MWT distance continued to improve in ambulatory ERT-switch and ERT-naive patients out to Month 12
  - Other motor function tests were consistent with 6MWT results in both ambulatory cohorts
  - There were increases in elbow and shoulder muscle strength in nonambulatory ERT-switch patients at Months 6 and Month 9
- Pulmonary function
  - FVC, MIP, and MEP were generally stable in ambulatory ERT-switch patients
  - FVC, MIP, and MEP generally increased in ERT-naive patients
- Fatigue Severity Scale
  - Improvements in fatigue score were observed in all cohorts
- Biomarkers and safety
  - CK and Hex4 levels decreased in all cohorts
  - ATB200/AT2221 was generally well tolerated

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DISCLOSURES

Conflicts of Interest

T. Mozaffar has served as a consultant for Amicus Therapeutics and Sanofi Genzyme, and is a member of a speaker bureau for Sanofi Genzyme. S. Sitaraman, J.A. Barth, and S. Sathe are employees of and own stock in Amicus Therapeutics.

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