First-in-Human Study of AT-GAA (ATB200/AT2221) in Patients With Pompe Disease: Functional Assessment 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]
- Even as the current enzyme replacement therapy (ERT), alglucosidase alfa, has provided benefits, clinical outcomes vary markedly among patients, with a consensus that the therapy does not reverse but attenuates disease progression, and that significant unmet medical needs remain[3]
- AT-GAA (ATB200/AT2221) is a novel dual-mechanism therapy under development that combines 2 investigational agents with complementary mechanisms of action[4,5]
  - ATB200 is an investigational next-generation recombinant human GAA (rhGAA) intravenous ERT designed with optimized glycosylation and high levels of mannose 6-phosphate residues for better uptake in target tissues
  - AT2221 is an orally administered pharmacologic chaperone given prior to infusion of ATB200 to stabilize this ERT in blood and maintain its catalytic activity to enhance delivery of active enzyme to lysosomes

OBJECTIVE

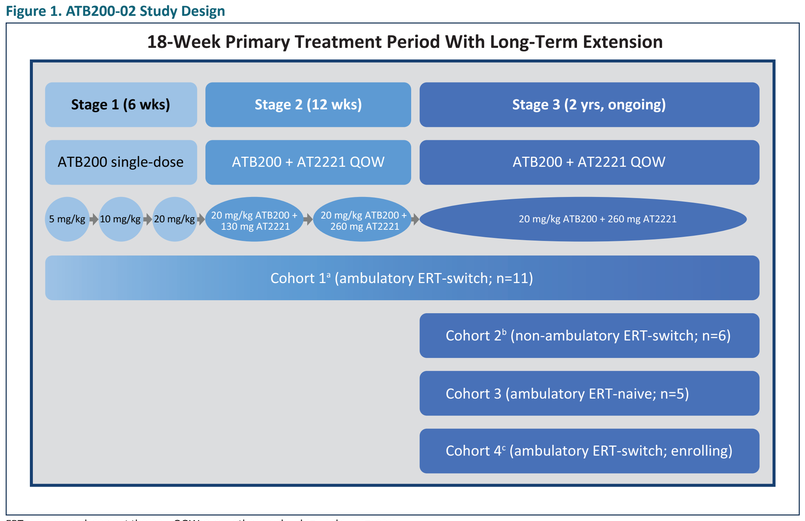
- To assess the safety, efficacy, patient-reported outcomes (PROs), and pharmacodynamics of AT-GAA in patients with Pompe disease enrolled in the phase 1/2 ATB200-02 study (NCT02675465)

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, pharmacokinetics, pharmacodynamics, and efficacy of intravenous infusions of ATB200 co-administered with oral AT2221 in adults with Pompe disease (**Figure 1**)

Figure 1. ATB200-02 Study Design



ERT=enzyme replacement therapy; QOW, every other week; wks=weeks; yrs=years.
[a]2-6 years on ERT; [b]≥2 years on ERT; [c]≥7 years on ERT.

Key Inclusion Criteria

- All cohorts: males and females aged 18-65 years (18-75 years for Cohort 4) diagnosed with Pompe disease per documented deficiency of GAA enzyme activity or *GAA* genotyping
- Cohort 1 (ambulatory ERT-switch)
  - Received ERT with alglucosidase alfa for 2-6 years prior to trial initiation
  - 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
  - Able to walk between 200 and 500 m on the 6-Minute Walk Test (6MWT)
  - Upright forced vital capacity (FVC) 30% to 80% of predicted normal value
- Cohort 2 (non-ambulatory ERT-switch)
  - Received ERT with alglucosidase alfa for ≥2 years for prior to trial initiation
  - Currently receiving alglucosidase alfa at a frequency of every other week and having completed the last 2 infusions without a drug-related AE resulting in dose interruption
  - Wheelchair-bound and unable to walk unassisted
- Cohort 3 (ambulatory ERT-naive)
  - Has not received any ERT at any time, or any investigational therapy for Pompe disease within 30 days or 5 half-lives of the therapy, whichever is longer, before study start
  - Able to walk between 200 and 500 m on the 6MWT
  - Upright FVC 30% to 80% of predicted normal value
- Cohort 4 (ambulatory ERT-switch)
  - Has been on ERT for ≥7 years
  - Currently receiving alglucosidase alfa at a frequency of every other week and having completed the last 2 infusions without a drug-related AE resulting in dose interruption
  - Able to walk between 75 and 600 m on the 6MWT
  - Upright FVC 30% to 85% of predicted normal value

Analyses

- Safety/tolerability, infusion-associated reactions, pharmacodynamics, efficacy, and PROs are reported
- Data are from interim analysis 7; efficacy data for Cohort 4 were not available at the time of this analysis
- Safety analyses include all data for up to 33 months of treatment, including data from 3 patients in Cohort 4

RESULTS

Patients

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

Table 1. Baseline Characteristics

	Cohort 1 ERT-Switch n=11[a]	Cohort 2 ERT-Switch Non-ambulatory n=6[b]	Cohort 3 ERT-Naive n=5
Age, years, mean (min, max)	49.4 (28, 66)	41.5 (18, 57)	49.4 (24, 65)
Sex, M:F	9:2	4:2	1:4
Time on alglucosidase alfa, years, mean (SD)	4.8 (1.4)	10.1 (4.8)	NA
6MWT, m, mean (SD)	392.0 (93.4)	NA	399.5 (83.5)
Upright FVC, % predicted, mean (SD)	52.3 (13.3)	NA	53.3 (20.4)

6MWT=6-Minute Walk Test; FVC=forced vital capacity; NA=not applicable; SD=standard deviation.
Baseline characteristics for Cohort 4 patients are not shown.
[a]One patient in Cohort 1 discontinued after 18 weeks due to burden of travel; another patient in Cohort 1 withdrew consent.
[b]One patient in Cohort 2 discontinued due to an infusion-associated reaction.

Efficacy

- 6MWT improved for ERT-switch (Cohort 1) and ERT-naive (Cohort 3) patients at Month 6 with continued benefit observed to Months 24 and 21, respectively (**Table 2**)
  - Cohort 1 (ERT-Switch): 6MWT increased in 7/10, 9/10, and 8/8 patients at Months 6, 12, and 24, respectively; 1 patient had not reached Month 24 at the time of this interim analysis
  - Cohort 3 (ERT-Naive): 6MWT increased in 5/5, 5/5, and 5/5 patients at Months 6, 12, and 21, respectively

Table 2. 6-Minute Walk Test, m

Baseline, mean (SD)	Change From Baseline, mean (SD)		
	Month 6	Month 12	Month 24[a,b]
Cohort 1 ERT-Switch			
n=10	n=10	n=10	n=8
397.2 (96.8)	+23.9 (52.2)	+42.2 (46.5)	+53.6 (36.4)
Baseline	**Month 6**	**Month 12**	**Month 21**
Cohort 3 ERT-Naive			
n=5	n=5	n=5	n=5
399.5 (83.5)	+41.8 (29.4)	+63.1 (29.1)	+54.8 (34.7)

[a]One patient in Cohort 1 discontinued from study before Month 24. [b]At the time of this interim analysis, 1 patient in Cohort 1 had not reached Month 24.

- Improvements in 6MWT and other motor function tests were generally consistent with an overall improvement in motor performance for ERT-switch patients and ERT-naive patients over 24 and 21 months, respectively (**Table 3**)

Table 3. Other Motor Function Tests

Assessment, sec	Baseline, mean (SD)	Change From Baseline, mean (SD)		
		Month 6	Month 12	Month 24
Cohort 1 ERT-Switch				
	n=10	n=10	n=10	n=8[a,b]
Timed Up and Go	10.5 (6.6)	−1.8 (3.5)	−1.5 (2.8)	−1.2 (2.1)
GSGC Score	12.6 (4.8)	+0.1 (3.9)	−0.3 (4.1)	−1.6 (2.7)
	Baseline	**Month 6**	**Month 12**	**Month 21**
Cohort 3 ERT-Naive				
	n=5	n=5	n=5	n=5
Timed Up and Go	9.4 (2.3)	−1.0 (1.1)	−0.3 (1.9)	−0.7 (2.4)
GSGC Score	12.2 (3.6)	−1.8 (3.8)	−0.8 (2.5)	−1.8 (2.6)

GSGC=Gait, Stairs, Gowers, Chair.
GSGC is an observer-rated combined score of 4 motor function assessments: Gait (10-m 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]At the time of this interim analysis, 1 patient in Cohort 1 had not reached Month 24. [b]One patient discontinued from study before Month 24.

- Consistent and substantial increases were observed in manual muscle strength in all cohorts at Months 6, 12, and 21 (Cohorts 2 and 3) or 24 (Cohort 1) (**Table 4**)
- Quantitative muscle strength testing results were generally consistent with manual muscle test results (data not shown)

Table 4. Manual Muscle Strength Testing

		Baseline		Change From Baseline					
				Month 6		Month 12		Month 21 or Month 24[a]	
		Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n
Cohort 1 ERT-Switch	Total Body Max score 80	66.4 (8.1)	10	+2.5 (3.2)	9[b]	+3.3 (3.4)	9[b]	+2.6 (5.0)	7[c,d]
Cohort 2 ERT-Switch Non-ambulatory[h]	Upper Body Max score 40	13.5 (10.0)	4[e]	+4.5 (0.7)	2[e,f,g]	+2.7 (2.3)	3[e,f]	+1.3 (4.6)	3[e,f]
Cohort 3 ERT-Naive	Total Body Max score 80	66.9 (3.7)	5	+0.3 (2.8)	5	+1.1 (3.1)	5	+0.2 (4.4)	5

MMT=manual muscle testing.
[a]Month 24 data shown for Cohort 1; Month 21 data shown for Cohort 2 and Cohort 3. [b]One patient missing MMT data at Month 6 and Month 12. [c]At the time of this interim analysis, 1 patient in Cohort 1 had not reached Month 24. [d]One patient discontinued prior to Month 24. [e]Baseline values missing for 1 patient. [f]One patient discontinued prior to Month 6 assessments. [g]One patient did not complete Month 6 assessment. [h]One patient had not reached Month 6 at the time of this interim analysis; baseline data are not shown for this patient.
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.
MMT scoring combines the total for left and right sides.

- On average, FVC remained stable in ERT-switch patients and increased in ERT-naive patients (**Table 5**)
  - FVC was stable or increased in 5/9, 6/9, and 6/7 ERT-switch patients at Months 6, 12, and 24, respectively
  - FVC was stable or increased in 5/5, 4/5, and 5/5 ERT-naive patients at Months 6, 12, and 21, respectively
- Maximal inspiratory pressure (MIP) was stable and maximal expiratory pressure (MEP) increased in ambulatory ERT-switch patients; both MIP and MEP increased in ERT-naive patients (**Table 5**)

Table 5. Forced Vital Capacity and Other Pulmonary Function Tests

Assessment	Baseline, Mean (SD)	Change From Baseline, mean (SD)		
		Month 6	Month 12	Month 24
Cohort 1 ERT-Switch				
	n=10	n=10	n=10	n=8[a,b]
FVC, % predicted	52.5 (14.8)[c]	−1.2 (3.9)[c]	−3.0 (6.0)[c]	−0.6 (2.8)[d]
MIP	35.7 (11.0)	+0.3 (4.6)	0.0 (3.2)	−1.0 (5.3)
MEP	82.7 (26.5)	+6.0 (24.9)	+18.5 (33.6)	+26.5 (32.5)
	Baseline	**Month 6**	**Month 12**	**Month 21**
Cohort 3 ERT-Naive				
	n=5	n=5	n=5	n=5
FVC, % predicted	53.3 (20.4)	+4.2 (5.6)	+4.5 (8.4)	+6.1 (9.7)
MIP	32.6 (18.5)	+11.0 (5.0)	+5.2 (12.2)	+7.2 (10.7)
MEP	60.6 (8.3)	−0.4 (12.4)	+8.6 (16.3)	+12.4 (20.8)

MEP=maximal expiratory pressure; MIP=maximal inspiratory pressure.
[a]At the time of this interim analysis, 1 patient in Cohort 1 had not reached Month 24. [b]One patient discontinued prior to Month 24. [c]Baseline FVC missing for 1 patient in Cohort 1 (n=9). [d]n=7.
MIP and MEP were measured in cm water.

Patient-Reported Outcomes

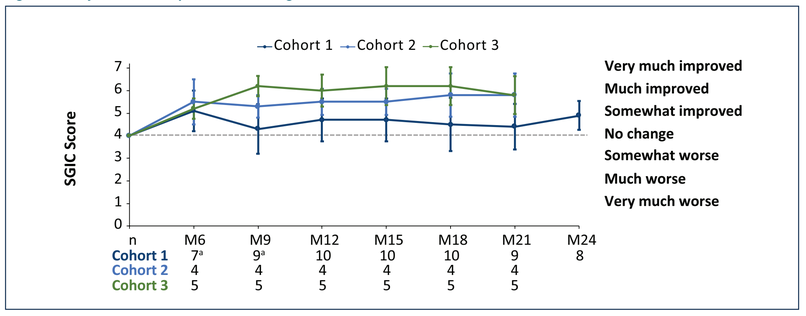
- Patients reported improvements in activities of daily living and patient well-being (**Table 6; Figure 2**)

Table 6. Patient-Reported Outcomes

	Baseline		Change From Baseline					
			Month 6		Month 12		Month 21 or Month 24[a]	
	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n
R-PAct (max score=36)								
Cohort 1 ERT-Switch[b]	20.3 (3.6)	10	+1.5 (3.0)	10	+1.7 (3.7)	10	+1.4 (2.5)	8[c]
Cohort 2 ERT-Switch Non-ambulatory[d]	1.0 (1.2)	5	+1.5 (2.4)	4	+1.0 (2.0)	4	+1.5 (3.0)	4
Cohort 3 ERT-Naive	23.6 (4.3)	5	−0.2 (0.8)	5	+2.6 (3.5)	5	+1.8 (2.5)	5
Rotterdam Handicap Scale (max score=36)								
Cohort 1 ERT-Switch[b]	29.7 (4.6)	10	−1.1 (1.9)	10	−0.7 (3.2)	10	−1.6 (2.5)	8[c]
Cohort 2 ERT-Switch Non-ambulatory[d]	20.0 (5.7)	5	+1.5 (5.1)	4	+0.5 (3.9)	3[e]	+5.6 (7.0)	3[e]
Cohort 3 ERT-Naive	32.3 (1.8)	5	−0.5 (1.8)	5	+0.4 (1.2)	5	+0.1 (1.2)	5
Fatigue Severity Scale (max score=63)								
Cohort 1 ERT-Switch[b]	53.5 (7.7)	10	−8.0 (10.7)	10	−8.0 (6.5)	10	−4.4 (9.2)	8[c]
Cohort 2 ERT-Switch Non-ambulatory[d]	44.4 (13.5)	5	+2.3 (8.7)	4	−12.5 (10.0)	4	−15.0 (8.4)	4
Cohort 3 ERT-Naive	39.2 (12.7)	5	−5.2 (11.7)	5	−7.2 (7.5)	5	−4.6 (8.4)	5

R-PAct= Rasch-built Pompe-specific Activity.
[a]Month 24 data shown for Cohort 1; Month 21 data shown for Cohort 2 and Cohort 3. [b]One patient in Cohort 1 discontinued after 18 weeks due to burden of travel; another patient in Cohort 1 withdrew consent. [c]At the time of this interim data cut, 1 patient in Cohort 1 had not reached Month 24. [d]One patient in Cohort 2 discontinued due to an infusion-associated reaction. [e]One data point missing for Cohort 2 at Months 12 and 21.
R-PAct is an 18-item questionnaire to measure limitations in activities and social participation in patients with Pompe disease; each activity is ranked from 0 (no) to 2 (yes, without difficulty); total scores range from 0 to 36, with lower scores representing more limitations.[6]
Rotterdam Handicap Scale is a 9-item questionnaire to measure functional ability and level of handicap; each item is ranked from 1 (unable to perform task) to 4 (able to perform task independently); total scores range from 9 to 36; lower scores represent worse functioning.[7]
Fatigue Severity Scale consists of 9 questions, each scored on a scale from 1 to 7. Total scores range 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 ~27.[8]

Figure 2. Subject Global Impression of Change

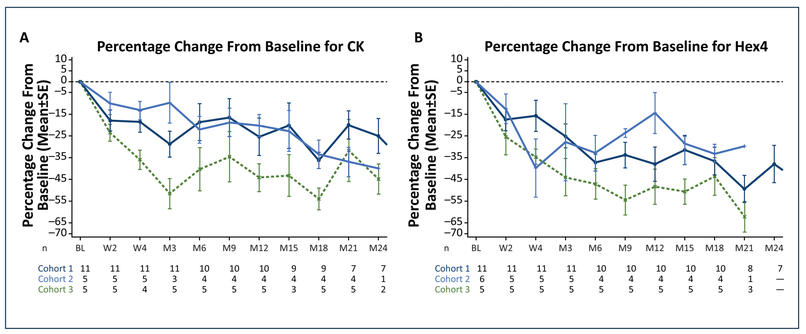


SGIC= Subject Global Impression of Change.
[a]Missing due to change in questionnaire mid-study.
SGIC is a questionnaire to assess the effects of a drug on 8 areas of a patient's life; each question is scored on a scale from 1 (very much worse) to 7 (very much improved).
Mean (SD) scores from overall well-being component of the SGIC questionnaire are shown.

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 24 months (**Figure 3**)

Figure 3. Mean Percentage Change From Baseline in Markers of Muscle Damage: (A) Creatine Kinase and (B) Hex4



BL=baseline; CK=creatine kinase; Hex4=urine hexose tetrasaccharide; M=month; SE=standard error; W=week.

Safety

- At the data cutoff, the longest treatment duration was 33 months
- Most treatment-emergent AEs were mild or moderate in severity
  - Most common treatment-emergent AEs (N=25): nasopharyngitis (13), fall (10), abdominal pain (9; includes upper and lower abdominal pain), diarrhea (8), headache (8), upper respiratory tract infection (7), arthralgia (7), nausea (7), back pain (6), fatigue (6), pain in extremities (6), myalgia (6), tremor (5), oropharyngeal pain (5), and muscle spasms (5)
- For serious AEs, 9 events occurred in 5 patients (severity: 2 severe, 5 moderate, 2 mild); 3 events (in 1 patient) were considered probably related to treatment
- One patient discontinued because of a treatment-emergent AE (infusion-associated reaction [IAR]); a second patient discontinued due to withdrawal of consent
- Sixteen incidents of IARs in 6 patients in 1110+ infusions
  - Eight IAR events in 5 ERT-switch patients and 8 IAR events in 1 ERT-naive patient

CONCLUSIONS

- Data from this interim analysis show continued functional benefit of AT-GAA (ATB200/AT2221) in patients with Pompe disease out to 24 months
  - 6MWT improved for ERT-switch and ERT-naive patients at Month 6 with continued benefit observed to Months 24 and 21, respectively
  - Other motor function tests were generally consistent with 6MWT results in both ambulatory cohorts
  - Muscle strength (manual muscle testing and quantitative muscle testing) improved in all cohorts
- Pulmonary function
  - FVC, MIP, and MEP increased in ERT-naive patients
  - FVC and MIP were generally stable and MEP increased in ERT-switch patients
- Patients reported improvements in activities of daily living as measured using PROs
- Biomarkers and safety
  - CK and Hex4 levels decreased in all cohorts
  - ATB200/AT2221 was generally well tolerated
- Data from this interim analysis suggest that AT-GAA has the potential to be an effective and well-tolerated novel treatment regimen for patients with Pompe disease

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DISCLOSURE

Conflicts of Interest

PK has served on advisory boards for Amicus Therapeutics, Baebies, and Sanofi Genzyme and as a consultant for Amicus Therapeutics, Sanofi Genzyme, and Vertex, and has received research funding from Amicus Therapeutics, Sanofi Genzyme, and Valerion. BS has served on advisory boards for Audentes and as a speaker for Sanofi Genzyme, CSL Behring, Recordati, and Biomarin, and has received research funding from Sanofi Genzyme. BJB has ownership interest of Genetic Technologies Corporation. PRC has served on advisory boards for and received research funding from Sanofi Genzyme. OGA has received research funding and honoria from Sanofi Genzyme, Pfizer, and Shire. PS has served on advisory boards for Novartis Pharma GmbH and as a speaker for Bayer Vital GmbH and Merck Serono GmbH. KS holds ownership interest in Biogen. ATP has received consulting fees and research funding from Amicus Therapeutics, Sanofi Genzyme, and Biomarin, and has received consulting fees from Shire. VJ, SS, JAB, and HL are employees of and own stock in Amicus Therapeutics. TM has served on advisory boards for Amicus Therapeutics and as a speaker for Sanofi Genzyme. DB, XM, and MR have nothing to disclose.

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