Preliminary Patient-Reported Outcomes and Safety of AT-GAA (ATB200/AT2221) in Patients With Pompe Disease From the ATB200-02 Trial

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INTRODUCTION

- Pompe disease is an inherited metabolic disease caused by acid α-glucosidase (GAA) deficiency, characterized by progressive accumulation of lysosomal glycogen, primarily in striated muscle[1,2]
- Glycogen accumulation results in a spectrum of disease severity, often leading to organ failure and/or death, that can develop at various life stages, from infancy to adulthood[1,2]
- Late-onset Pompe disease (LOPD) has a substantial impact on patient quality of life (QoL) and daily living, with clinical disease progression strongly associated with decreased QoL[3]
- Treatment with recombinant human GAA (rhGAA) enzyme replacement therapy (ERT), the only currently approved treatment option for patients with LOPD, can improve or stabilize QoL in the short term, but QoL benefits have not persisted long term[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 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

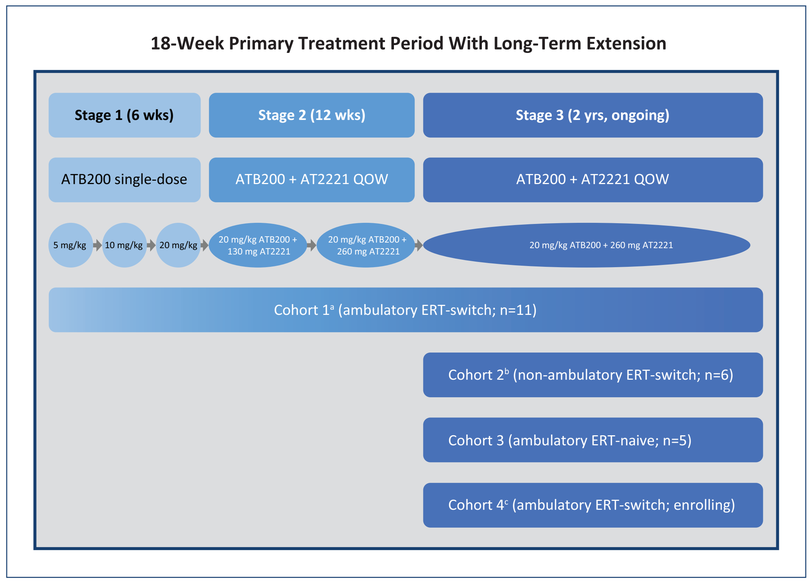
- To report interim patient-reported outcomes (PROs) with AT-GAA in patients with Pompe disease enrolled in the phase 1/2 ATB200-02 study (NCT02675465)

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)
  - Have 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

- PROs were collected every 3 months (**Table 1**)
- Data are from interim analysis 7; PRO data for Cohort 4 were not available at the time of this analysis
- Safety analyses include all data up to 33 months of treatment, including data from 3 patients in Cohort 4

Table 1. Patient-Reported Outcome Instruments Used in ATB2000-02

Assessment	Definition	Total Score Range	Better Functioning/Improvement
Rasch-built Pompe-specific Activity (R-PAct)	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)[6]	0 to 36	↑ Higher scores = Fewer limitations
Rotterdam Handicap Scale	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)[7]	9 to 36	↑ Higher scores = Better functioning
Fatigue Severity Scale (FSS)	9-item questionnaire to measure the severity of fatigue; each question is scored on a scale from 1 (completely disagree) to 7 (completely agree)[8]	9 to 63	↓ Lower scores = Less fatigue
Subject Global Impression of Change (SGIC)	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)	1 to 7 for each question	↑ Higher scores = Improved

RESULTS

Patients

- Sixteen clinical sites in 5 countries participated in the ATB200-02 trial
- Patients in all cohorts reported significant impairment at baseline, with the largest functional limitations observed in non-ambulatory patients (**Table 2**)

Table 2. 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)
R-PAct, mean (SD) Max score=36	20.3[c] (3.6)	1.0[d] (1.2)	23.6 (4.3)
Rotterdam Handicap Scale, mean (SD) Max score=36	29.7[c] (4.6)	20.0[d] (5.7)	32.3 (1.8)
FSS,[e] mean (SD) Max score=63	53.5[c] (7.7)	44.4[d] (13.5)	39.2 (12.7)

6MWT=6-Minute Walk Test; FSS=Fatigue Severity Scale; FVC=forced vital capacity; NA=not applicable; R-PAct=Rasch-built Pompe-specific Activity; SD=standard deviation; SGIC=Subject Global Impression of Change.
[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.
[c]n=10.
[d]n=5.
[e]For FSS, the normative value in the healthy population is ~27.[8]
Baseline characteristics for Cohort 4 patients are not shown.

Patient-Reported Outcomes

- R-PAct scores improved in all cohorts by Month 12 with continued benefit observed out to Month 24 in Cohort 1 and Month 21 in Cohorts 2 and 3 (**Table 3**)

Table 3. Rasch-built Pompe-specific Activity (max score 36)

	Baseline		Change From Baseline					
			Month 6		Month 12		Month 21 or Month 24[d,e]	
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n
Cohort 1[a] ERT-switch	20.3 (3.6)	10	+1.5 (3.0)	10	+1.7 (3.7)	10	+1.4 (2.5)	8
Cohort 2[b,c] ERT-switch non-ambulatory	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

[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.
[c]One patient in Cohort 2 had not reached Month 6 at the time of this interim analysis; baseline data for this patient are not shown.
[d]Month 24 data shown for Cohort 1; Month 21 data shown for Cohort 2 and Cohort 3.
[e]At the time of this interim data cut, 1 patient in Cohort 1 had not reached Month 24.
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]

- At Month 21, improvements in the Rotterdam Handicap Scale were observed in non-ambulatory ERT-switch patients and ERT-naive patients (**Table 4**)

Table 4. Rotterdam Handicap Scale (max score 36)

	Baseline		Change From Baseline					
			Month 6		Month 12[d]		Month 21 or Month 24[d,e,f]	
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n
Cohort 1[a] ERT-switch	29.7 (4.6)	10	–1.1 (1.9)	10	–0.7 (3.2)	10	–1.6 (2.5)	8
Cohort 2[b,c] ERT-switch non-ambulatory	20.0 (5.7)	5	+1.5 (5.1)	4	+0.5 (3.9)	3	+5.6 (7.0)	3
Cohort 3 ERT-naive	32.3 (1.8)	5	–0.5 (1.8)	5	+0.4 (1.2)	5	+0.1 (1.2)	5

[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.
[c]One patient in Cohort 2 had not reached Month 6 at the time of this interim analysis; baseline data for this patient are not shown.
[d]One data point missing for Cohort 2 at Months 12 and 21.
[e]Month 24 data shown for Cohort 1; Month 21 data shown for Cohort 2 and Cohort 3.
[f]At the time of this interim data cut, 1 patient in Cohort 1 had not reached Month 24.
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]

- Patients in all cohorts were significantly impacted by fatigue at baseline and demonstrated improvements in fatigue over time (**Table 5**)

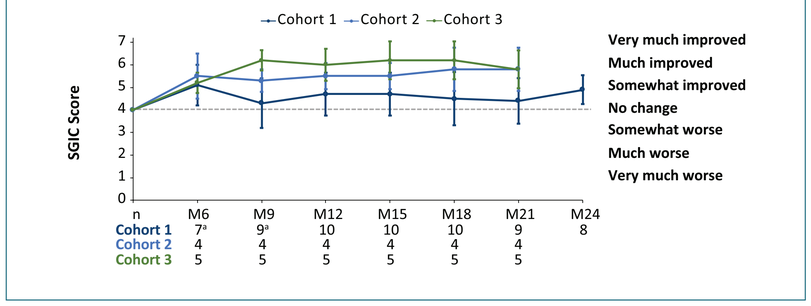
Table 5. Fatigue Severity Scale (max score 63)

	Baseline		Change From Baseline					
			Month 6		Month 12		Month 21 or Month 24[d,e]	
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n
Cohort 1[a] ERT-Switch	53.5 (7.7)	10	–8.0 (10.7)	10	–8.0 (6.5)	10	–4.4 (9.2)	8
Cohort 2[b,c] ERT-Switch Non-ambulatory	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

[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.
[c]One patient in Cohort 2 had not reached Month 6 at the time of this interim analysis; baseline data for this patient are not shown.
[d]Month 24 data shown for Cohort 1; Month 21 data shown for Cohort 2 and Cohort 3.
[e]At the time of this interim data cut, 1 patient in Cohort 1 had not reached Month 24.
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]

- Improvements in overall physical well-being in the Subject Global Impression of Change questionnaire were reported as early as Month 6 and were maintained out to Month 24 (**Figure 2**)

Figure 2. 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.

Safety

- Most treatment-emergent AEs were mild or moderate in severity
  - Most common treatment-emergent AEs out of 25 patients: 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
- 1 patient discontinued because of a treatment-emergent AE (infusion-associated reaction [IAR]); a second patient discontinued due to withdrawal of consent
- 16 incidents of IARs in 6 patients in 1110+ infusions
  - 8 IAR events in 5 ERT-switch patients and 8 IAR events in 1 ERT-naive patient
- Longest duration of treatment is 33 months

CONCLUSIONS

- Data from this interim analysis show benefits in activities of daily living and patient well-being in patients with Pompe disease treated with AT-GAA (ATB200/AT2221)
  - Improvements in daily living (R-PAct) in all cohorts, in functioning (Rotterdam Handicap Scale) in non-ambulatory ERT-switch patients and ERT-naive patients, in fatigue (FSS) in all cohorts, and in overall physical well-being (SGIC) in most patients were shown
- AT-GAA was generally well tolerated over 30+ months of treatment
- These data suggest that AT-GAA has the potential to be a treatment for Pompe disease that reduces the burden of Pompe disease as experienced by the patients

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DISCLOSURE

Conflicts of Interest

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. DB does not have anything to disclose. 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. 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. XM and MR do not have anything to disclose. 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. JW, 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. ATP has received consulting fees and research funding from Amicus Therapeutics, Sanofi Genzyme, and Biomarin and has received consulting fees from Shire.

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