Safety and Efficacy of AT-GAA (ATB200/AT2221) in ERT-Switch Non-ambulatory Patients With Pompe Disease: Preliminary Results From the ATB200-02 Trial

Clemens PR,[1] Mozaffar T,[2] Schoser B,[3] Bratkovic D,[4] Byrne BJ,[5] Goker-Alpan O,[6] Roberts M,[7] Schwenkreis P,[8] Sivakumar K,[9] van der Ploeg AT,[10] Wright J,[11] Sitaraman S,[11] Barth JA,[11] Lagast H,[11] Kishnani P,[12] Ming X[13]

[1]University of Pittsburgh and Department of Veterans Affairs Medical Center, Pittsburgh, PA, USA; [2]University of California, Irvine, CA, USA; [3]Friedrich-Baur-Institut, Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany; [4]PARC Research Clinic, Royal Adelaide Hospital, Adelaide, SA, Australia; [5]University of Florida, Gainesville, FL, USA; [6]O&O Alpan LLC, Fairfax, VA, USA; [7]Salford Royal NHS Foundation Trust, Salford, UK; [8]Neurologische Klinik und Poliklinik des Berufsgenossenschaftlichen, Universitätklinikum Bergmannsheil, Bochum, Germany; [9]Neuromuscular Research Center, Phoenix, AZ, USA; [10]Erasmus Medical Center, Rotterdam, The Netherlands; [11]Amicus Therapeutics, Inc., Cranbury, NJ, USA; [12]Duke University Medical Center, Durham, NC, USA; [13]Rutgers New Jersey Medical School, Newark, NJ, USA

INTRODUCTION

- Pompe disease is an inherited, autosomal recessive lysosomal disease caused by mutations in the *GAA* gene that encodes acid α-glucosidase (GAA), leading to accumulation of glycogen in various tissues[1,2]
- Patients with late-onset Pompe disease (LOPD) develop clinical manifestations and experience progressive muscle weakness after infancy, ultimately leading to wheelchair use and/or assisted ventilation[1,3]
  - Wheelchair use in non-ambulatory patients with LOPD is associated with decreased quality of life, greater functional disability, and greater caregiver burden[3]
- 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 rather attenuates, disease progression, and that significant unmet medical needs remain[4]
- AT-GAA (ATB200/AT2221) is a novel dual-mechanism therapy under development that combines 2 investigational agents with complementary mechanisms of action[5,6]
  - 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

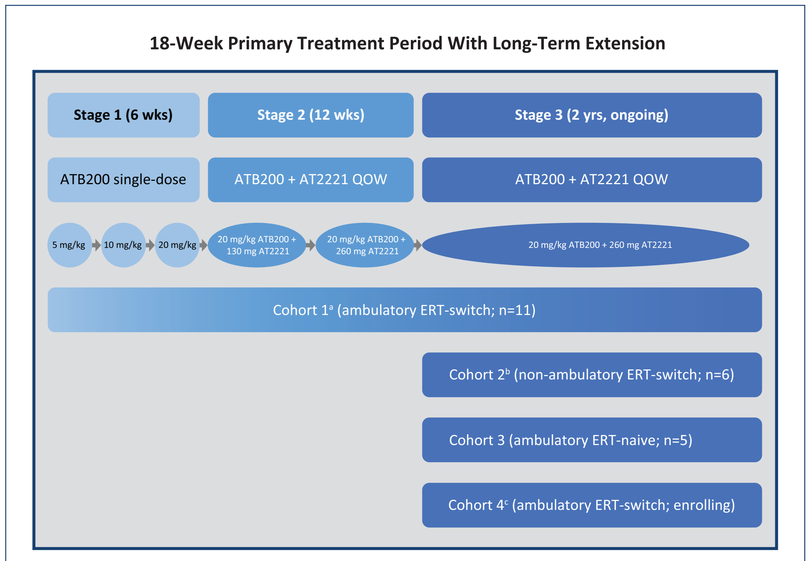
- To report interim safety and efficacy data of AT-GAA in non-ambulatory patients with Pompe disease (Cohort 2) who switched from alglucosidase alfa to AT-GAA in the ATB200-02 trial

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

- 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 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
- Wheelchair-bound and unable to walk unassisted

Assessments

- Muscle strength tests of the upper limbs were performed with medical research criteria (MRC) and a hand-held dynamometer
- Patient-reported outcomes (PROs) include:
  - Rasch-built Pompe-specific Activity (R-PAct) Scale
  - Rotterdam Handicap Scale
  - Fatigue Severity Scale
  - Subject Global Impression of Change (SGIC)
- Plasma levels of creatine kinase (CK) and urine hexose tetrasaccharide (Hex4) were assessed as exploratory biomarkers of Pompe disease
- Data are from interim analysis 7 and include all 21-month data that were available as of the data cutoff
- Safety analyses include all data up to 27 months (the longest duration of treatment)

RESULTS

Patients

- Six non-ambulatory patients who, on average, had received ~10 years of ERT with alglucosidase alfa were enrolled in the ATB200-02 trial (**Table 1**)

Table 1. Baseline Characteristics of Non-ambulatory ERT-Switch Patients

	N=6
Age, years, mean (min, max)	41.5 (18, 57)
Age at Pompe diagnosis, years, median (min, max)	26.9 (0.15, 51.6)
Sex, M:F	4:2
Time on alglucosidase alfa, years, median (min, max)	10.0 (5.4, 15.6)

Per inclusion criteria, all patients in cohorts 2 were wheelchair-bound and unable to walk unassisted.

Muscle Function

- Consistent and substantial increases were observed in upper extremity strength at months 6, 12, and 21 in both manual and quantitative muscle testing (**Table 2**)

Table 2. Manual and Quantitative Muscle Strength Testing in Non-ambulatory ERT-Switch Patients

	Baseline		Change From Baseline					
			Month 6		Month 12		Month 21	
Muscle Testing, upper body	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n
Manual Max score 40	13.5 (10.0)	4[a,b]	+4.5 (0.7)	2[a,c,d]	+2.7 (2.3)	3[a,c]	+1.3 (4.6)	3[a,c]
Quantitative Dynamometer, pounds force	5.7 (6.4)	5[b]	+1.6 (4.9)	4[c]	+3.3 (4.0)	4[c]	+3.5 (3.9)	4[c]

MMT=manual muscle testing; QMT=quantitative muscle testing.
[a]Baseline values missing for 1 patient.
[b]One patient had not reached Month 6 at the time of this interim analysis; baseline data are not shown for this patient.
[c]One patient discontinued prior to Month 6 assessment.
[d]One patient did not complete Month 6 assessment.
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.
Scores reflect testing of 4 movements in the upper limbs (shoulder abduction, shoulder adduction, elbow flexion, elbow extension). MMT scoring combines the total of each of the 4 movements for left and right sides. QMT results are the average pounds of force for each of the 4 movements for left and right sides combined.

Patient-Reported Outcomes

- Improvements in PROs as measured by R-PAct, Rotterdam Handicap Scale, and Fatigue Severity Scale were reported as early as month 6 and continued through month 21 (**Table 3**)
- Improvements in overall physical well-being (per SGIC) with AT-GAA were reported by all patients at months 6, 12, and 21 (**Table 3**)

Table 3. Patient-Reported Outcomes in Non-ambulatory ERT-Switch Patients

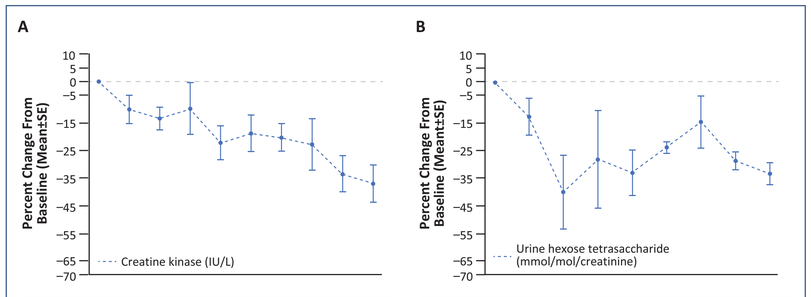
	Baseline[a]		Change From Baseline					
			Month 6[b]		Month 12[b]		Month 21[b]	
Cohort 2	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n
R-PAct Max score 36 (Higher scores = fewer limitations)	1.0 (1.2)	5	+1.5 (2.4)	4	+1.0 (2.0)	4	+1.5 (3.0)	4
Rotterdam Handicap Scale Max score 36 (Higher scores = better functioning)	20.0 (5.7)	5	+1.5 (5.1)	4	+0.5 (3.9)	3[c]	+5.6 (7.0)	3
Fatigue Severity Scale Max score 63 (Lower scores = less fatigue)	44.4 (13.5)	5	+2.3 (8.7)	4	–12.5 (10.0)	4	–15.0 (8.4)	4
			Improvement From Baseline					
SGIC: Overall Physical Well-being, n (%)	—	—	4 (100)	4	4 (100)	4	4 (100)	4

R-PAct= Rasch-built Pompe-specific Activity; SGIC=Subject Global Impression of Change.
[a]One patient had not reached Month 6 at the time of this interim analysis; baseline data are not shown for this patient.
[b]One patient discontinued prior to Month 6 assessment.
[c]One patient did not complete Month 12 assessment.
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.[7]
The 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.[8]
FSS is a 9-item questionnaire to measure the severity of fatigue; each question is scored on a scale from 1 (completely disagree) to 7 (completely agree); total scores range from 9 to 63.[9]
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). The number of patients reporting an improvement in the overall well-being component of the SGIC questionnaire are shown.

Pompe Disease Biomarkers

- Non-ambulatory ERT-switch patients demonstrated persistent improvement in biomarkers of muscle damage (CK) and disease substrate (Hex4) for up to 21 months **(Figure 2)**

Figure 2. Mean Percentage Change From Baseline in Markers of Muscle Damage (A) Creatine Kinase and Disease Substrate (B) Hex4 in Non-ambulatory ERT-Switch Patients



n	BL	W2	W4	M3	M6	M9	M12	M15	M18	M21
Cohort 2	5	5	5	3	4	4	4	4	4	4

n	BL	W2	M4	M3	M6	M9	M12	M15	M18
Cohort 2	6	5	5	5	4	4	4	4	4

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

Safety

- AT-GAA was generally well tolerated
- All 6 patients reported AEs
- Two patients experienced serious AEs
  - One patient experienced infusion-associated reactions (IARs) that led to discontinuation
  - One patient experienced hospitalization due to pneumonia that was deemed unrelated to study drug
- Two patients experienced IARs
  - The patient who discontinued treatment experienced 4 IARs, generally urticarial rash, with nasopharyngeal edema on 1 occasion
  - The second patient experienced 1 episode of skin discoloration that was managed by pre-medication
- Longest duration of treatment was 27 months

CONCLUSIONS

- These data demonstrate the clinical benefit of AT-GAA (ATB200/AT2221) in ERT-switch non-ambulatory patients who have been on ERT for an average of ~10 years
  - Consistent and substantial increases in upper extremity strength in quantitative and manual muscle testing
  - Persistent reductions in markers of muscle damage (CK) and disease substrate (urine Hex4)
  - Improvements in all patient-reported outcome measures (R-PAct, Rotterdam Handicap Scale, Fatigue Severity Scale, SGIC)
  - Generally well tolerated for up to 27 months
- AT-GAA has potential as an important treatment option for non-ambulatory patients with Pompe disease

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DISCLOSURE

Conflicts of Interest

PRC has served on advisory boards for and received research funding from Sanofi Genzyme. TM has served on advisory boards for Amicus Therapeutics and as a speaker for Sanofi Genzyme. 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. 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. JW, SS, JAB, and HL are employees of and own stock in Amicus Therapeutics. 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. DB, MR, and XM have nothing to disclose.

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