First-in-Human Study of ATB200/AT2221 in Patients With Pompe Disease: 24-Month Functional Assessment Results From the ATB200-02 Trial

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Disclosure Statement of Financial Interest

- **Advisory Board:** Audentes Therapeutics, Sanofi-Genzyme, Lupin therapeutics, Nexien Biopharm, Amicus Therapeutics
- **Speaker's Bureau:** Sanofi Genzyme, Kedrion
- **Research Grant**: Sanofi Genzyme, Greenovation biopharm, Amicus Therapeutics

Overview of Pompe Disease

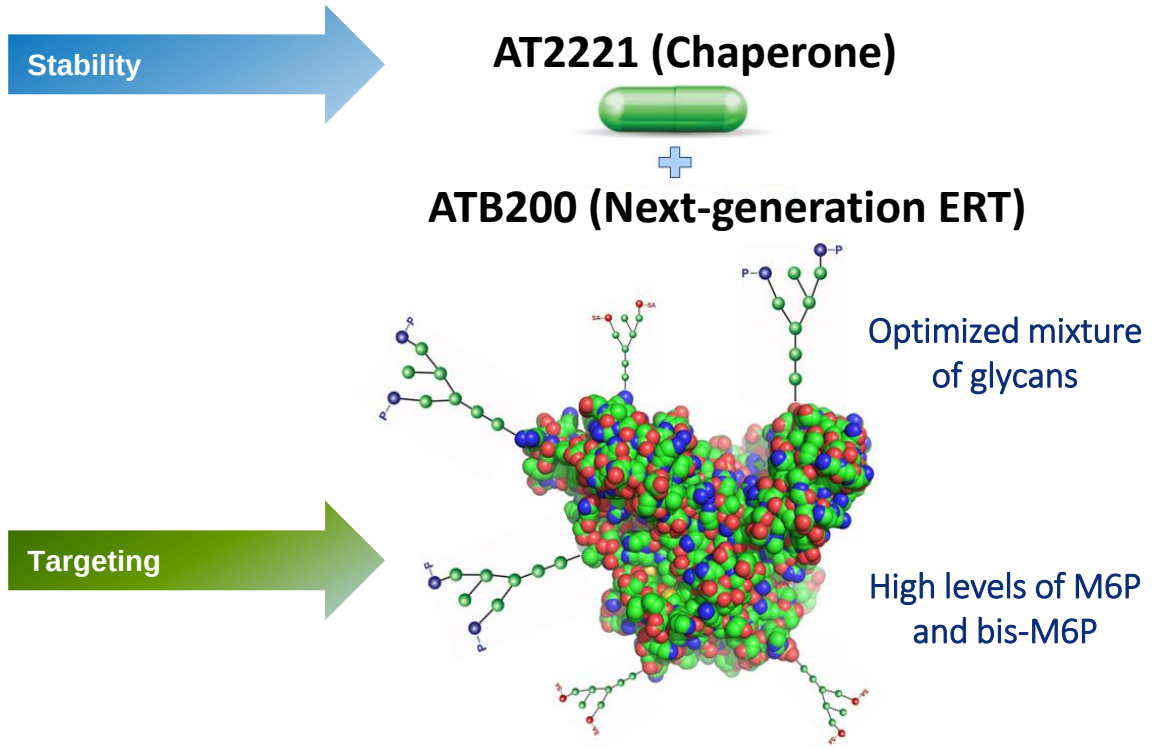
- An inherited lysosomal disorder caused by GAA deficiency[1,2]
- Characterized by progressive accumulation of lysosomal glycogen, primarily in striated muscle[1,2]
- A spectrum of disease severity, including organ failure and/or death[1]
- Can develop at various life stages, from infancy to adulthood[1]
- Skeletal muscle weakness and progressive respiratory involvement are predominant manifestations[1,2]
- Significant unmet medical needs remain despite the enzyme replacement therapy currently available[3]

GAA=acid α-glucosidase; QoL=quality of life.

1. Kishnani PS et al. *Genet Med.* 2006;8(5):267-288. 2. Bijvoet AG et al. *Hum Mol Gen*. 1998;7(1):53-62. 3. Schoser B et al. *BMC Neurology*. 2017;17:202.

ATB200/AT2221: A Novel Therapy for Pompe Disease

- Novel investigational approach: coadministration of 2 distinct agents
  - ATB200: investigational next-generation ERT
    - Designed with optimized glycosylation and high levels of mannose 6-phosphate residues for better uptake to disease-relevant tissues
  - AT2221: orally administered investigational chaperone given prior to infusion of ATB200
    - Shown to stabilize ERT in blood and maintain catalytic activity to enhance delivery of active enzyme to lysosomes



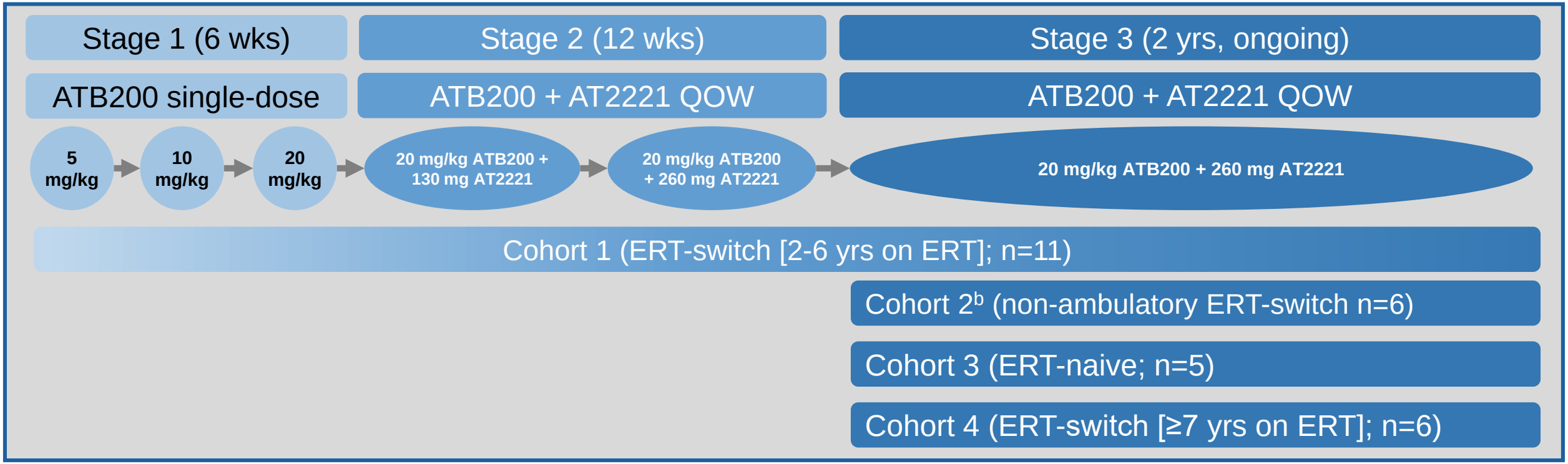
ERT=enzyme replacement therapy; M6P=mannose-6-phosphate.

Xu S, et al. JCI Insight. 2019;4(5):e125358. https://doi.org/10.1172/jci.insight.125358.

ATB200-02 Study Design (NCT02675465)

- Phase 1/2 study to evaluate safety, tolerability, PK, PD, and efficacy of ATB200/AT2221 in adults with Pompe disease[a]

18-Week Primary Treatment Period With Long-Term Extension



- **Assessments:** Safety/tolerability, plasma PK, infusion-associated reactions, antibody levels, PD, efficacy, PRO

ERT=enzyme replacement therapy; PD=pharmacodynamics; PK=pharmacokinetics; PRO=patient-reported outcomes; wks=weeks; yrs=years.
[a]Study conducted in 16 centers across 5 countries. [b]≥2 years on ERT.

Baseline Characteristics

Patients (N=28) enrolled across cohorts 1, 2, 3 and 4 were representative of the Pompe disease population, with significant impairment at baseline

	Cohort 1 ERT-Switch (2-6 yrs on ERT) n=11	Cohort 2 ERT-Switch[a] Non-ambulatory n=6	Cohort 3 ERT-Naïve n=5	Cohort 4 ERT-Switch (≥7 yrs on ERT) n=6
Age, years, mean (min, max)	**49.4** (28, 66)	**41.5** (18, 57)	**49.4** (24, 65)	**40.8** (20, 65)
Sex, M:F	**9:2**	**4:2**	**1:4**	**2:4**
Time on alglucosidase alfa, years, mean (SD)	**4.8** (1.4)	**10.1** (4.8)	NA	**10.0** (1.6)
6MWT, meters, mean (SD)	**392.0** (93.4)	NA	**399.5** (83.5)	**387.3 (161.3)**
Upright FVC, % predicted, mean (SD)	**52.3** (13.2)	42.3 (28.2)[b]	**53.3** (20.4)	**65.3 (21.1)**

6MWT=6-minute walk test; ERT=enzyme replacement therapy; FVC=forced vital capacity; NA=not applicable; SD=standard deviation.
[a]Cohort 2 patients were required to have been on alglucosidase alfa for ≥2 years at baseline. [b]n=3.
Data from interim analysis 8.

6-Minute Walk Test
Cohorts 1 and 3

6MWT improved for both ERT-switch ambulatory and ERT-naive patients at Month 6 with continued benefit observed out to Month 24

Cohort		Baseline (meters)		Change From Baseline (meters)					
				Month 6		Month 12		Month 24	
		mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n
1	ERT-Switch (2-6 yrs on ERT)	**397.2** (96.8)	10[a]	**+23.9** (52.2)	10[a]	**+42.2** (46.5)	10[a]	**+36.4** (61.7)	9[ab]
3	ERT-Naive	**399.5** (83.5)	5	**+41.8** (29.4)	5	**+63.1** (29.1)	5	**+60.7** (36.5)	5

- 6MWT increased in 7/10, 9/10, and 8/9 ERT-switch patients at Months 6, 12, and 24, respectively
- 6MWT increased in 5/5, 5/5, and 5/5 ERT-naive patients at Months 6, 12, and 24, respectively

6MWT=6-Minute Walk Test; ERT=enzyme replacement therapy; SD=standard deviation.
[a]One patient in Cohort 1 discontinued after 18 weeks due to burden of travel; baseline value is not shown for this patient. [b]One patient in Cohort 1 discontinued from study before Month 24.
Data from interim analysis 8.

Sitting Forced Vital Capacity (FVC, % Predicted)

On average, FVC remained stable in ERT-switch patients and increased in ERT-naive patients

Cohort		Baseline		Change From Baseline					
				Month 6		Month 12		Month 24	
		mean (SD)	n	mean (SD)	N	mean (SD)	n	mean (SD)	n
1	ERT-Switch (2-6 yrs on ERT)	**52.6** (14.7)	9[a]	**–1.2** (4.0)	9[a]	**–3.0** (6.0)	9[a]	**+0.9** (4.9)	8[a,b]
3	ERT-Naive	**53.2** (20.1)	5	**+4.4** (5.6)	5	**+4.6** (8.8)	5	**+6.8** (6.8)	5

- FVC was stable or increased in 5/8 ERT-switch patients at Month 24 (2-6 yrs on ERT); MIP was stable and MEP increased
- FVC was stable or increased in 5/5 ERT-naive patients at Month 24; MIP and MEP both increased

ERT=enzyme replacement therapy; SD=standard deviation.
[a]Baseline FVC not available for 1 patient in Cohort 1. [b]One patient in Cohort 1 discontinued from study before Month 24.
Data from interim analysis 8.

Manual Muscle Test Score

Increases were observed in manual muscle strength[a] in Cohorts 1–3 at Month 6 and Month 12, and in Cohorts 1 and 2 at Month 24

Cohort		Body Area	Baseline		Change From Baseline					
					Month 6		Month 12		Month 24	
			mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n
1	ERT switch (2-6 yrs on ERT)	**Total Body** Max score 80	**66.4** (8.1)	10[b]	**+2.5** (3.2)	9[b,c]	**+3.3** (3.4)	9[b,c]	**+ 3.0** (4.8)	8[b,c,d]
2	ERT-switch Non-ambulatory	**Upper Body** Max score 40	**18.4** (14.0)	4[e,f]	**+ 2.7** (3.2)	3[e,f,g]	**+ 2.7** (2.3)	3[e,f,h]	**+ 3.0** (5.9)	3[e,f,h]
3	ERT-Naive	**Total Body** Max score 80	**66.9** (3.7)	5	**+0.3** (2.8)	5	**+1.1** (3.1)	5	**-1.1** (4.3)	5

- Quantitative muscle strength testing[i] results were generally consistent with manual muscle test results

ERT=enzyme replacement therapy; SD=standard deviation. [a]MMT measured via the Medical Research Criteria (MRC) scale.
[b]One patient in Cohort 1 discontinued after 18 weeks due to burden of travel; [c]One patient missing MMT data at Month 6 and Month 12. [d]One patient in Cohort 1 discontinued prior to Month 24. [e]Baseline value missing for 1 patient. [f]One patient discontinued prior to Month 6 assessments; baseline data are not shown for this patient. [g]Manual muscle testing not completed for one patient. [h]One patient yet to complete Month 12 and 24 [i]Measured via hand-held dynamometer.
Data from interim analysis 8.

Timed Motor Function Tests

Timed motor function test results improved for both ERT-switch ambulatory and ERT-naive patients at Month 6 with continued benefit observed out to Month 24

Cohort		Assessment	Baseline, mean (SD)	Change From Baseline, mean (SD)		
				Month 6	Month 12	Month 24
1	ERT-Switch (2-6 yrs on ERT)		n=10[a]	n=10[a]	n=10[a]	n=9[a,b]
		Timed Up and Go, sec	**10.5** (6.6)	**−1.8** (3.5)	**−1.5** (2.8)	**-0.7** (2.5)
		GSGC Score	**12.6** (4.8)	**+0.1** (3.9)	**−0.3** (4.1)	**-0.1** (5.2)
3	ERT-Naive		n=5	n=5	n=5	n=5
		Timed Up and Go, sec	**9.4** (2.3)	**−1.0** (1.1)	**−0.3** (1.9)	**-0.7** (2.0)
		GSGC Score	**12.2** (3.6)	**−1.8** (3.8)	**−0.8** (2.5)	**-1.8** (2.3)

ERT=enzyme replacement therapy; GSGC=Gait, Stairs, Gowers, Chair; SD=standard deviation.
[a]One patient in Cohort 1 discontinued after 18 weeks due to burden of travel; baseline value is not shown for this patient. [b]One patient in Cohort 1 discontinued from study before Month 24.
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.
Data from interim analysis 8.

Fatigue Severity Scale
Patient-Reported Outcome (PRO) Instrument

All cohorts were significantly impacted by fatigue at baseline and demonstrated improvements in fatigue over time

Cohort Max score=63		Baseline		Change From Baseline					
				Month 6		Month 12		Month 24	
		mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n
1	ERT-Switch (2-6 yrs on ERT)	**53.5** (7.7)	10[a]	**-8.0** (10.7)	10[a]	**-8.0** (6.5)	10[a]	**-4.1** (8.6)	9[a,b]
2	ERT-Switch Non-ambulatory	**45.6** (14.7)	5[c]	+ 2.0 (7.5)	5[c]	**-12.5** (10.0)	4[c,d]	**-13.8** (10.9)	4[c,d]
3	ERT-Naive	**39.2** (12.7)	5	**-5.2** (11.7)	5	**-7.2** (7.5)	5	**-7.2** (11.9)	5

ERT=enzyme replacement therapy; SD=standard deviation.

1. Grace J et al. *Parkinsonism Relat Disord*. 2007;13(7):442-445.

[a]One patient in Cohort 1 discontinued after 18 weeks due to burden of travel; baseline value is not shown for this patient. [b]One patient in Cohort 1 discontinued from study before Month 24. [c]One patient discontinued prior to Month 6; baseline value was not shown for this patient. [d]one patient did not complete FSS at Months 12 and 24.

FSS 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. Lower scores equals less fatigue. The normative value in the healthy population is ~27.[1]

Data from interim analysis 8.

Clinical Assessments Summary for Cohort 4
ERT-Switch (≥7 yrs on ERT)

Improvements seen in majority of the patients both on motor function and strength as well as pulmonary function as assessed by FVC after 3-15 months of treatment

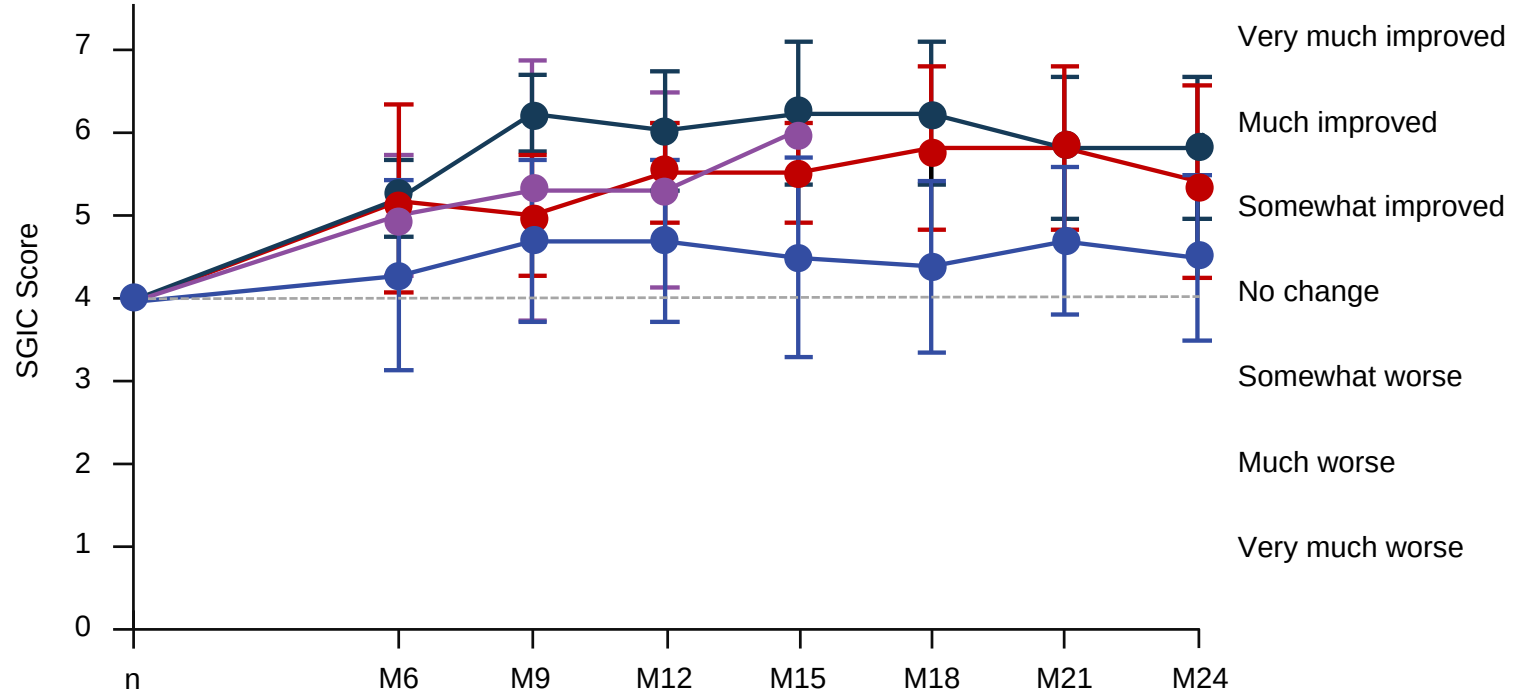
Cohort 4	Baseline		CFBL to 6M		CFBL to LOCF	
	mean (SD)	n	mean (SD)	n[a]	mean (SD)	n
6MWT, meters	**387.3** (161.3)	6	**+24.3** (60.5)	5	**+19.3** (53.3)	6
% predicted sitting FVC	**65.3** (21.1)	6	**+6.6** (4.2)	5	**+ 5.2** (6.0)	6
MMT (max 80)	**59.7** (6.0)	6	**+ 4.0** (2.0)	5	**+ 3.8** (3.8)	6
Timed up and go, sec	**9.1** (4.2)	5[b]	0.3 (1.6)	5	**+ 0.6** (1.4)	5[b]
GSGC	**17.2** (5.0)	6	**-2.8** (4.0)	5	**-2.2** (3.9)	6
FSS (max 63)	**42.8** (14.0)	5[b]	**-3.3** (4.6)	5	**-3.0** (7.2)	5[b]

- 6MWT increased in 2/5 patients at M6 and 4/6 patients at LOCF after 3-15 months of treatment
- FVC increased in 5/5 patients at M6 and 5/6 at LOCF after 3-15 months of treatment; MIP and MEP both increased
- LOCF includes 1 subjects at Month 3, 2 subjects at Month 6, 2 subjects at Month 12 and 1 subject at Month 15

6MWT=6-Minute Walk Test; CFBL=change from baseline; FSS=Fatigue Severity Scale; FVC=forced vital capacity; GSGC=Gait, Stairs, Gowers, Chair; LOCF=last observation carried forward; MMT=manual muscle test. [a]Only 5 patients had completed month 6 assessment at time of IA8. [b]One patient missing data for Timed up and go and one patient missing data for FSS. Data from interim analysis 8.

Subject Global Impression of Change: Overall Physical Well-being

Improvements in overall physical well-being in all four cohorts



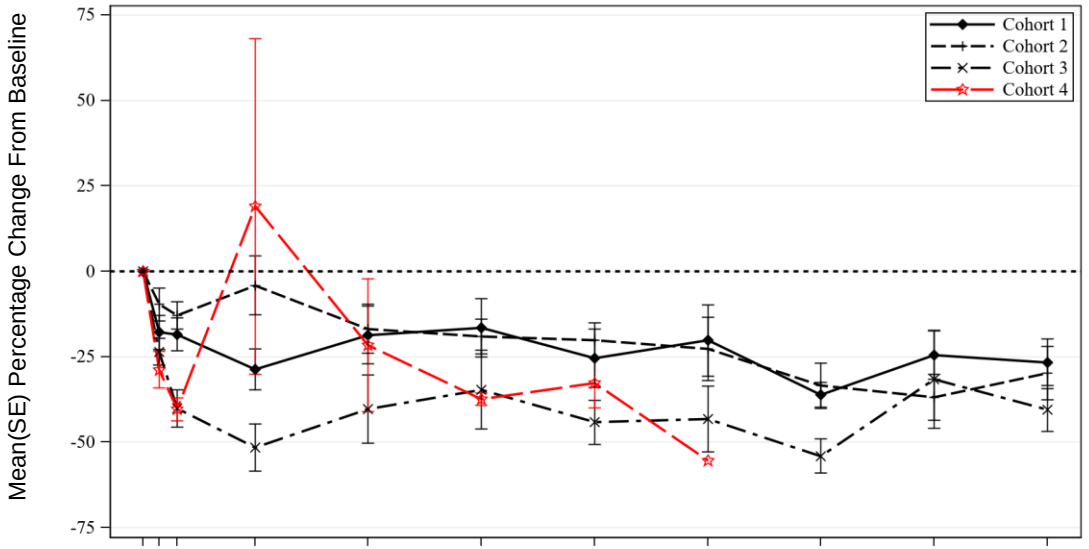
	n	M6	M9	M12	M15	M18	M21	M24
Cohort 1		9	10	10	10	9	9	9
Cohort 2		5	5	4	4	4	4	5
Cohort 3		5	5	5	5	5	5	5
Cohort 4		5	3	3	1			

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 (standard deviation) scores from overall physical well-being component of the SGIC questionnaire are shown. Data from interim analysis 8.

Muscle damage and disease substrate biomarkers

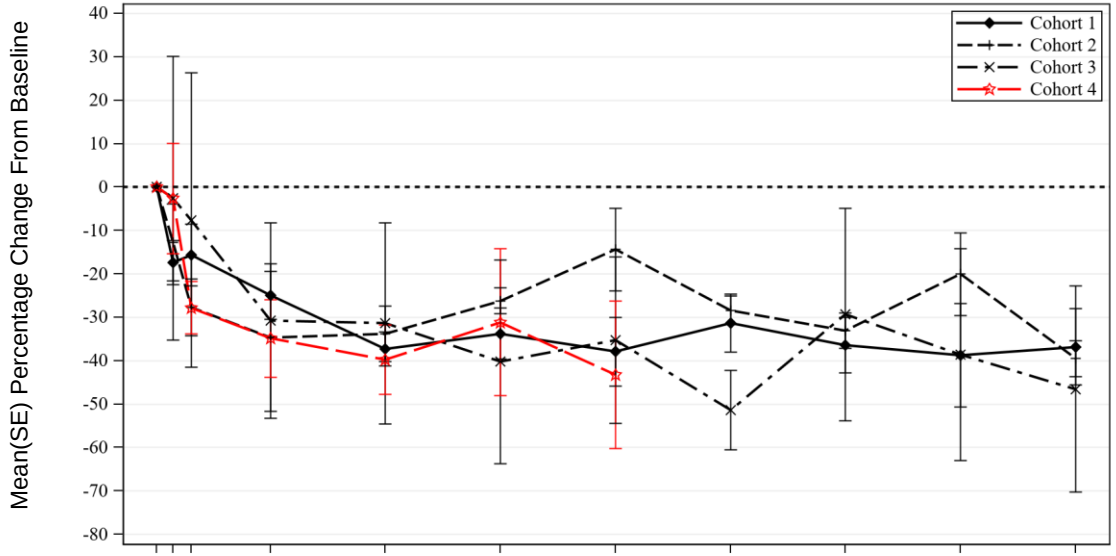
Persistent improvement in biomarkers of muscle damage (CK) and disease substrate (Hex4) in all cohorts

Percentage Change From Baseline for CK



Visit	BL	M3	M6	M9	M12	M15	M18	M21	M24
C1	11	11	10	10	10	9	9	8	9
C2	5	4	5	5	4	4	4	4	4
C3	6	5	5	5	5	3	5	5	5
C4	6	6	6	3	3	1	-	-	-

Percentage Change From Baseline for Hex4



Visit	BL	M3	M6	M9	M12	M15	M18	M21	M24
C1	11	11	10	10	10	10	10	9	9
C2	5	5	5	5	4	4	4	3	4
C3	6	5	5	5	5	3	5	5	5
C4	6	6	5	3	3	-	-	-	-

CK=creatine kinase; Hex4=urine hexose tetrasaccharide; SE=standard error.

Safety Summary

Safety data (N=28) for ATB200/AT2221 show that AEs have been generally mild and transient with very low rates of IARs (1.8%) after 1500+ total infusions across all cohorts

- As of August 28, 2019, the longest treatment duration was 40 months
- Most treatment-emergent AEs were transient and generally mild or moderate in severity
- 11 serious AEs[a] (3 severe, 8 moderate) occurred in 7 patients
  - 6 events, all IARs (in 3 patients) were considered probably related to treatment
- 1 patient discontinued because of a treatment-emergent AE (IAR); a second patient discontinued due to withdrawal of consent
- 28 incidents of IARs (51 events) in 8 patients in 1500+ infusions (1.8% of infusions)
  - 36 IAR events in 7 ERT-switch patients and 15 IAR events in 1 ERT-naive patient (ongoing, 32 months treatment)
- Sero-conversion with evidence of clinically non-relevant anti-GAA antibodies was observed in the majority of Cohort 1 and Cohort 3 patients up to 24 months

AE=adverse events; ERT=enzyme replacement therapy; IAR, infusion-associated reaction.
[a]Serious adverse events (n events) were: IARs entailing bronchospasm (2), urticaria (1), pharyngeal edema (1), IAR (1); pneumonia (1), lower respiratory tract infection (1), lymphoma (1), syncope (1), diverticulitis (1).

Conclusions

- Data from this interim analysis show functional benefit of ATB200/AT2221 in patients with Pompe disease out to 24 months for cohorts 1,2 and 3
  - 6MWT and pulmonary function improved with continued benefit observed to Months 24
  - Patients reported decreased fatigue and felt improved as measured using PROs
- Improvements seen in majority of the cohort 4 patients in motor function, muscle strength, and pulmonary function
- Biomarker CK and Hex4 levels decreased in all cohorts
- ATB200/AT2221 was generally well tolerated over 40+ months of treatment
- No impact of sero-conversion with evidence of clinically non-relevant anti-GAA antibodies on safety, efficacy and exposure or clearance of ATB200
- Phase 3 trial PROPEL (NCT03729362) comparing ATB200/AT2221 with alglucosidase alfa in LOPD is currently underway

6MWT=6-Minute Walk Test; CK=creatine kinase; ERT=enzyme replacement therapy; FVC=forced vital capacity; Hex4=urine hexose tetrasaccharide; LOPD=late-onset Pompe disease; PRO=Patient-Reported Outcome.

Acknowledgments

- The authors thank the patients, their families, and Pompe disease patient organizations, as well as the study investigators
- ATB200-02 investigators: Paula R. Clemens, Drago Bratkovic, Barry J. Byrne, Ozlem Goker-Alpan, Mark Roberts, Peter Schwenkreis, Kumaraswamy Sivakumar, Ans T. van der Ploeg, Priya Kishnani, Xue Ming, Tahseen Mozaffar
- Amicus Therapeutics, Inc.: Vipul Jain, Jacquelyn Wright, Sheela Sitaraman Das, Jay A. Barth, Hjalmar Lagast
- Third-party medical editing assistance was provided by ApotheCom (Yardley, PA)