Top Line Results From the PROPEL Phase 3 Study Comparing AT-GAA (cipaglucosidase alfa/miglustat) Versus alglucosidase alfa/placebo In Late Onset Pompe Disease

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Pompe Disease Overview

Pompe disease is a severe and fatal neuromuscular disease and one of the most prevalent lysosomal disorders. Despite the majority of diagnosed Pompe patients in the addressable geographies in the world being treated with currently approved ERT alglucosidase alfa, there remains significant unmet medical need

5,000 – 10,000+ patients diagnosed WW

newborn screening suggests underdiagnosis

Age of onset ranges from infancy to adulthood

Patients on currently approved ERT decline after ~3-5 years

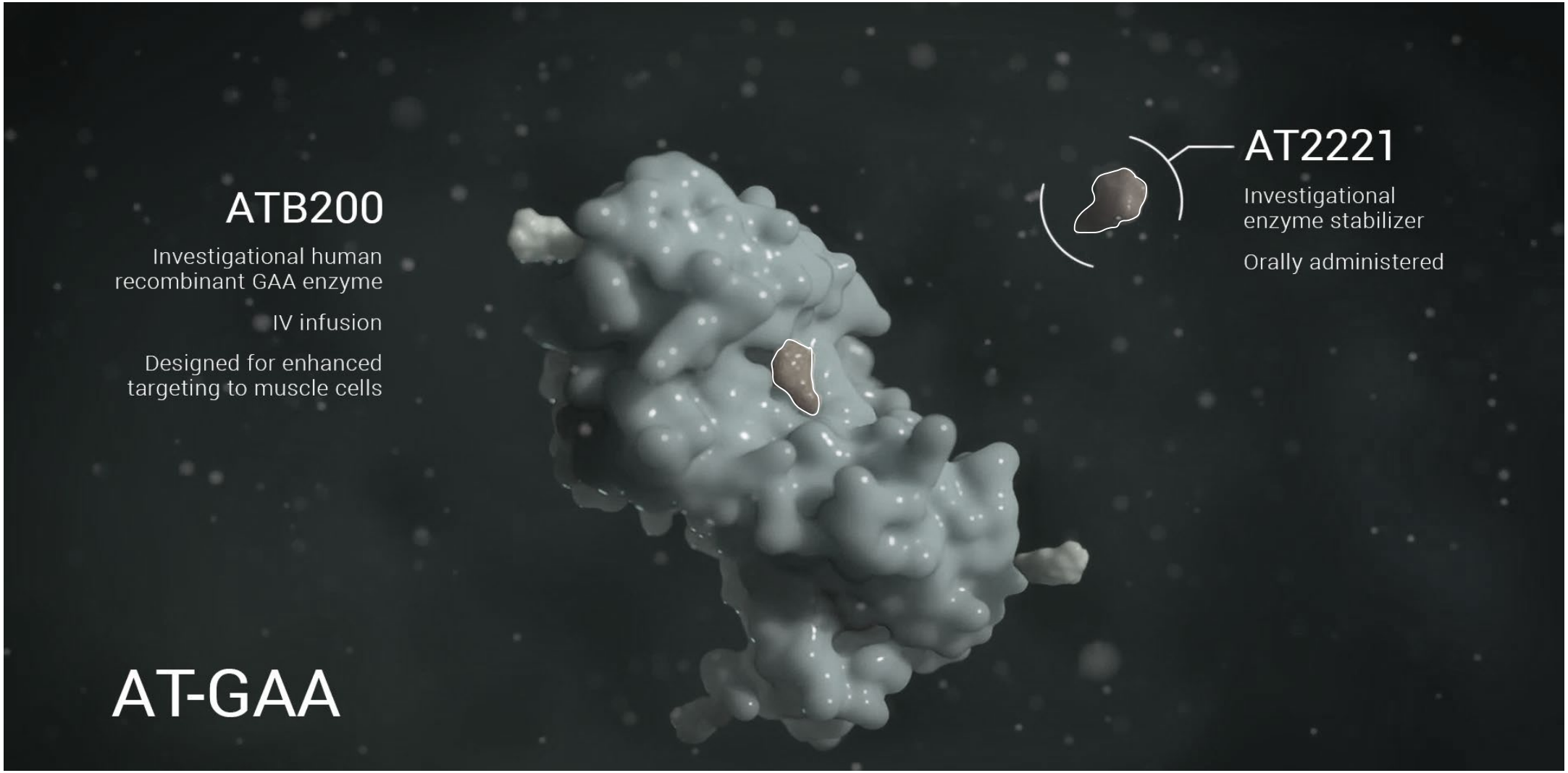
Respiratory failure is leading cause of morbidity and early mortality

Deficiency of GAA leading to glycogen accumulation and cellular dysfunction

Symptoms include muscle weakness, respiratory failure, and cardiomyopathy (in infants)

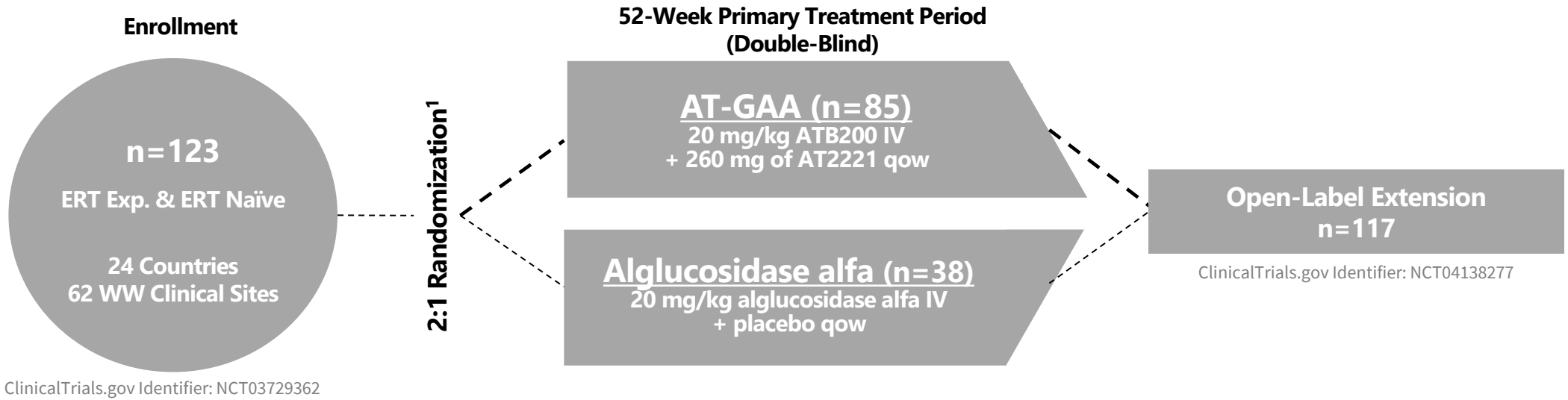
AT-GAA: ATB200 (cipaglucosidase alfa) and AT2221 (miglustat)

ATB200 is a novel rhGAA being developed as a next-generation enzyme replacement therapy (ERT) for the treatment of Pompe disease, used in conjunction with AT2221, an iminosugar that stabilizes and enhances the PK of ATB200



PROPEL (ATB200-03): Study Design

Phase 3 double-blind randomized study to assess the efficacy and safety of AT-GAA in adult subjects with late onset Pompe disease compared with alglucosidase alfa/placebo



Key Enrollment Criteria:

- ≥18 years old, weigh ≥ 40 kg at screening with confirmed diagnosis of LOPD
- Classified as one of the following with respect to ERT status:
  - ERT-experienced, defined as currently receiving standard of care ERT (alglucosidase alfa) for ≥24 months
  - ERT-naïve, defined as never having received ERT
- 6MWD ≥ 75 meters and ≤ 90% of the predicted value for healthy adults at screening
- Sitting FVC ≥ 30% of the predicted value for healthy adults at screening

[1]2:1 randomization with stratification factors on ERT status, baseline 6MWD

Study Endpoints and Statistical Methods

Primary & Key Secondary Endpoint

- Change from baseline to Week 52 in 6 Minute Walk Distance (6MWD)
- Change from baseline to Week 52 in % predicted sitting Forced Vital Capacity (FVC)

Statistical Methods

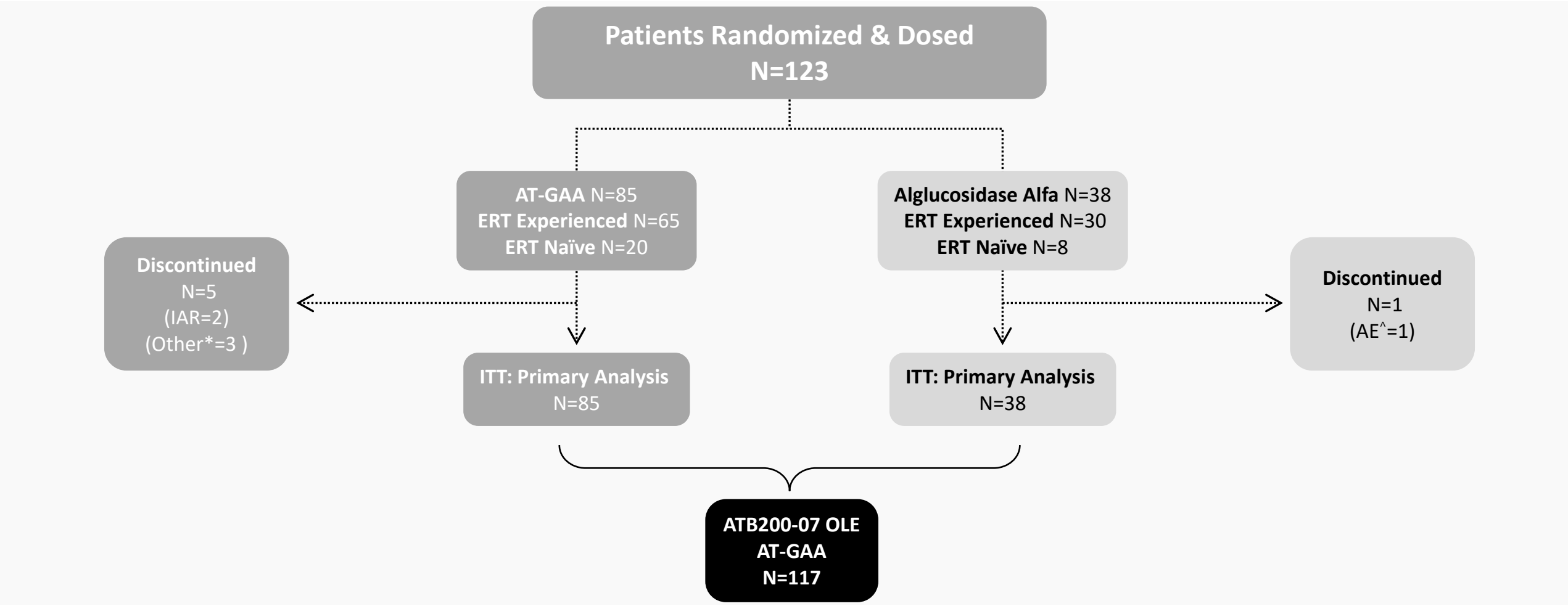
- Primary endpoint of 6MWD analyzed using MMRM on ITT observed cases
- All key secondary endpoints including FVC analyzed by ANCOVA with last observation carried forward (ITT LOCF)

Other Key Secondary Endpoints

- Change from baseline to Week 52 in the manual muscle test (MMT) score for the lower extremities
- Change from baseline to Week 52 in the PROMIS® – Physical Function domain score
- Change from baseline to Week 52 in the PROMIS® – Fatigue domain score
- Change from baseline to Week 52 in the GSGC score (Gait, Stairs, Gowers, Chair)

Patient Disposition

There was a very low drop-out rate and all patients completing the study subsequently enrolled in the AT-GAA extension study



Note: * 1 Covid pneumonia, 2 withdrew no longer wanting to travel to sites for infusion all unrelated to study drug; ^1 stroke, unrelated to study drug

Baseline Demographics

Baseline demographics were representative of the population and generally similar in the two treatment arms

	AT-GAA n=85	Alglucosidase alfa n=38	Total n=123
Age (years)			
Mean (SD)	47.6 (13.3)	45.1 (13.3)	46.8 (13.3)
Median (Min, Max)	48.0 (19, 74)	46.0 (22, 66)	47.0 (19, 74)
Gender, n (%)			
Male	36 (42.4)	20 (52.6)	56 (45.5)
Female	49 (57.6)	18 (47.4)	67 (54.5)
Previous ERT Duration (ERT Exp. only)			
<3 years	4 (6.2)	5 (16.7)	9 (9.5)
3-5 years	16 (24.6)	6 (20.0)	22 (23.2)
>5 years	45 (69.2)	19 (63.3)	64 (67.4)
Race, n (%)			
White	74 (87.1)	30 (78.9)	104 (84.6)
Asian	5 (5.8)	5 (13.2)	10 (8.1)
Other	6 (7.1)	3 (7.9)	9 (7.3)
Regions, n(%)			
North/South America	26 (30.6)	15 (39.5)	41 (33.3)
Europe	43 (50.6)	12 (31.6)	55 (44.7)
Asia Pacific	16 (18.8)	11 (28.9)	27 (22.0)

Baseline Characteristics

Baseline 6MWD and FVC were representative of the population and generally similar in the two treatment arms

	AT-GAA n=85		Alglucosidase alfa n=37	
6MWD, m				
Mean (SD)	357.9 (111.8)		351 (121.3)	
Median (Min, Max)	359.5 (79.0, 575.0)		365.5 (112.5, 623.0)	
	ERT Experienced	**ERT Naive**	**ERT Experienced**	**ERT Naive**
	n=65	n=20	n=30	n=7
Mean (SD)	346.9 (110.2)	393.6 (112.4)	334.6 (114.0)	420.9 (135.7)
Median (Min, Max)	352.5 (79.0, 557.5)	375.2 (154.0, 575.0)	343.5 (112.5, 532.3)	385.5 (201.0, 623.0)

	AT-GAA n=85		Alglucosidase alfa n=37	
FVC % Predicted, Sitting				
Mean (SD)	70.7 (19.6)		69.7 (21.5)	
Median (Min, Max)	70.0 (30.5, 132.5)		71.0 (31.5, 122.0)	
	ERT Experienced	**ERT Naive**	**ERT Experienced**	**ERT Naive**
	n=65	n=20	n=30	n=7
Mean (SD)	67.9 (19.1)	80.2 (18.7)	67.5 (21.0)	79.1 (22.6)
Median (Min, Max)	68 (30.5, 132.5)	82.3 (48.0, 111.0)	69.0 (31.5,122.0)	93.5 (46.5, 98.0)

6MWD=6-minute walk distance; FVC=forced vital capacity

6MWD and FVC Results: Overall Population (n=122)

6MWD showed greater improvement with AT-GAA versus alglucosidase alfa but did not demonstrate statistical superiority; FVC demonstrated clinically significant improvement with AT-GAA over alglucosidase alfa

6MWD (m)

Treatment	Baseline	CFBL at Week 52	Difference	P-Value
AT-GAA (n=85)	357.9 (111.8)	+20.8 (4.6)	+13.6 (8.3)	p=0.072
Alglucosidase alfa (n=37)	351.0 (121.3)	+7.2 (6.6)		

FVC (% predicted)

Treatment	Baseline	CFBL at Week 52	Difference	P-Value
AT-GAA (n=85)	70.7 (19.6)	-0.9 (0.7)	+3.0 (1.2)	**p=0.023**
Alglucosidase alfa (n=37)	69.7 (21.5)	-4.0 (0.8)		

NOTES: Baseline is Mean (STDEV); CFBL is Mean LOCF (SE); P-values are nominal 2-sided; FVC data normally distributed and p–values are from ANCOVA.
Results exclude one clinically implausible patient who used an investigational anabolic steroid ostarine (selective androgen receptor modulator) just prior to study start.
6MWD data not normally distributed and 6MWD p-value is for non-parametric ANCOVA; 6MWD parametric MMRM p-value was p=0.097.

6MWD and FVC Results: ERT Experienced Population (n=95)

In the ERT experienced population (n=95), there was a clinically significant improvement in both 6MWD and FVC with AT-GAA over alglucosidase alfa

6MWD (m)

Treatment	Baseline	CFBL at Week 52	Difference	P-Value
AT-GAA (n=65)	346.9 (110.2)	+16.9 (5.0)	+16.9 (8.8)	**p=0.046**
Alglucosidase alfa (n=30)	334.6 (114.0)	0.0 (7.2)		

FVC (% predicted)

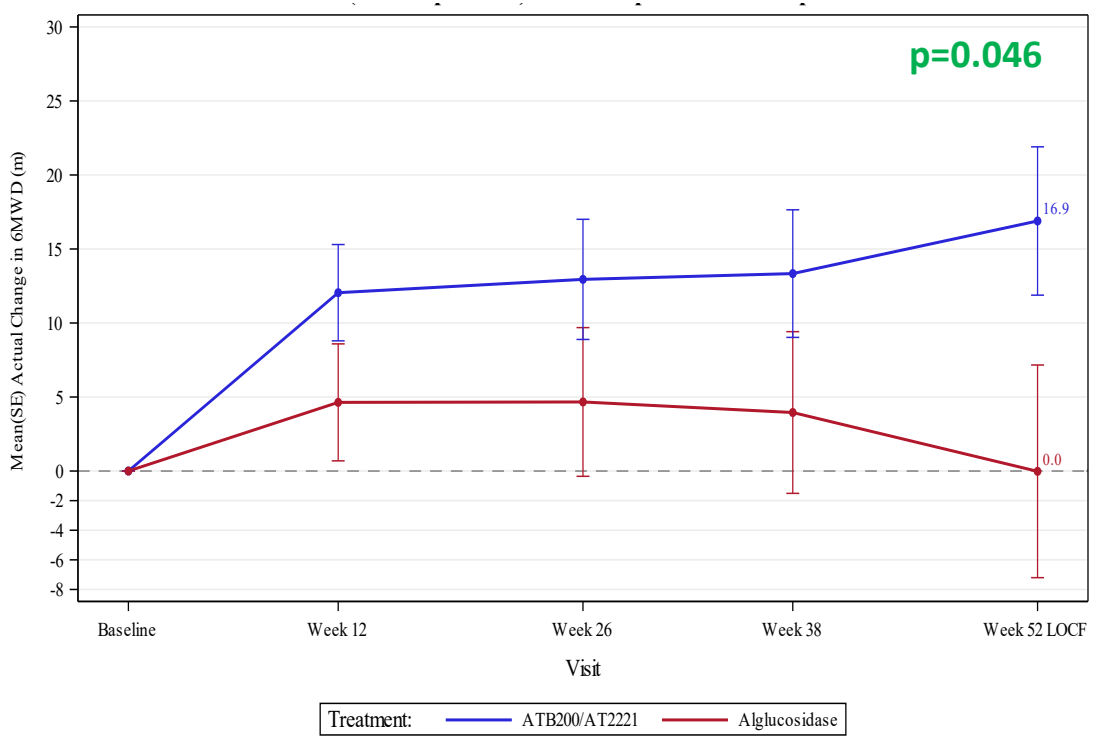
Treatment	Baseline	CFBL at Week 52	Difference	P-Value
AT-GAA (n=65)	67.9 (19.1)	+0.1 (0.7)	+4.1 (1.2)	**p=0.006**
Alglucosidase alfa (n=30)	67.5 (21.0)	-4.0 (0.9)		

NOTE: Baseline is Mean (STDEV); CFBL is Mean LOCF (SE); P-values are nominal 2-sided; FVC data normally distributed and p–values are from ANCOVA
6MWD data not normally distributed and 6MWD p-value is for non-parametric ANCOVA; 6MWD parametric MMRM p-value was p=0.078

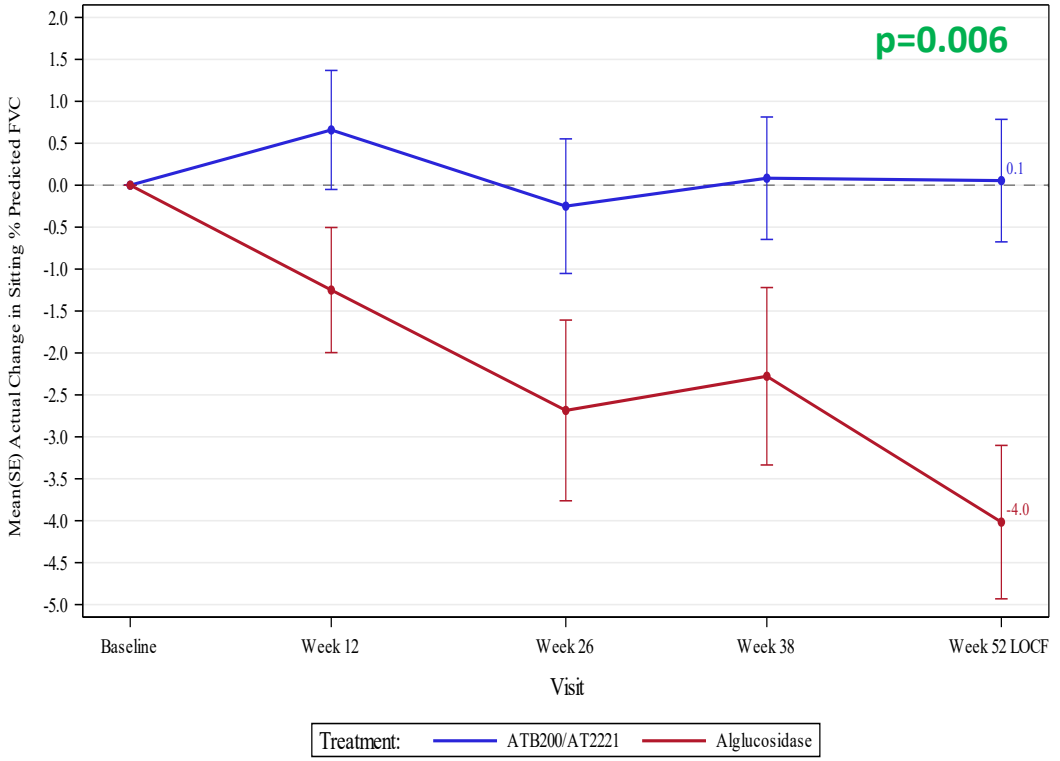
6MWD and FVC Plots: ERT Experienced Population (n=95)

ERT experienced patients treated with AT-GAA demonstrated improvements over time in 6MWD and stabilization over time in FVC versus alglucosidase alfa

6MWD (m): Change from baseline (n=65, n=30)



FVC (% predicted): Change from baseline (n=65, n=30)



NOTE: Baseline is Mean (STDEV); CFBL is Mean (SE); P-values are nominal 2-sided; FVC data normally distributed and p–values are from ANCOVA
6MWD data not normally distributed and 6MWD p-value is for non-parametric ANCOVA; 6MWD parametric MMRM p-value was p=0.078

6MWD and FVC Results: ERT Naive Population (n=27)

In the smaller ERT naive population (n=27), variability was greater and 6MWD and FVC both numerically favored alglucosidase alfa

6MWD (m)

Treatment	Baseline	CFBL at Week 52	Difference	P-Value
AT-GAA (n=20)	393.6 (112.4)	+33.4 (10.9)	-4.9 (19.7)	p=0.60
Alglucosidase alfa (n=7)	420.9 (135.7)	+38.3 (11.1)		

FVC (% predicted)

Treatment	Baseline	CFBL at Week 52	Difference	P-Value
AT-GAA (n=20)	80.2 (18.7)	-4.1 (1.5)	-0.5 (2.7)	p=0.57
Alglucosidase alfa (n=7)	79.1 (22.6)	-3.6 (1.8)		

NOTES: Baseline is Mean (STDEV); CFBL is Mean LOCF (SE); P-values are nominal 2-sided; FVC data normally distributed and p–values are from ANCOVA.
Results exclude one clinically implausible patient who used an investigational anabolic steroid ostarine (selective androgen receptor modulator) just prior to study start.
6MWD data not normally distributed and p-value is for Wilcoxon Test; 6MWD parametric MMRM p-value was p=0.75

Primary, Key Secondary and Biomarker Endpoint Heat Map

Overall& ERT Experienced Populations

Endpoints across motor function, pulmonary, function, muscle strength, PROs and biomarkers favored AT-GAA over alglucosidase alfa in both the overall and ERT experienced populations

Overall Population

	Alglucosidase alfa	AT-GAA
Motor Function		6MWD
		GSGC*
Pulmonary Function		FVC*
Muscle Strength		Lower MMT
PROs		PROMIS-Physical
		PROMIS-Fatigue
Biomarker		Hex4*
		CK*

ERT Experienced Population

	Alglucosidase alfa	AT-GAA
Motor Function		6MWD*
		GSGC*
Pulmonary Function		FVC*
Muscle Strength		Lower MMT
PROs		PROMIS-Physical
		PROMIS-Fatigue
Biomarker		Hex4*
		CK*

Note: *Nominal P-value <0.05; Based on LOCF means

Safety Summary

Safety profile was similar for AT-GAA and alglucosidase alfa

	AT-GAA n=85	Alglucosidase Alfa n=38
TEAEs	81 (95.3%)	37 (97.4%)
TEAEs Potentially Related to Treatment	26 (30.6%)	14 (36.8%)
Serious TEAEs	8 (9.4%)	1 (2.6%)
Serious TEAEs Potentially Related to Treatment	1 (1.2%)	0
TEAEs Leading to Study Withdrawal	2 (2.4%)	1 (2.6%)
TEAEs Leading to Death	0	0
IARs	21 (24.7%)	10 (26.3%)

- **TEAEs leading to withdrawal in the AT-GAA arm were two IARs, one of which was a serious AE**
- **TEAEs leading to withdrawal in the alglucosidase arm was due to stroke (unrelated)**
- **Overall safety profile of AT-GAA is similar to alglucosidase alfa**

Conclusions

- Topline data demonstrate clinically meaningful improvements with AT-GAA on both motor and respiratory function in the overall population studied
- In the overall study population, AT-GAA outperformed the currently approved ERT (+21 meters compared to +7 meters) which did not reach statistical significance for superiority on 6MWD
- In the overall study population, AT-GAA showed a nominally statistically significant and clinically meaningful difference for superiority on the first key secondary endpoint of percent-predicted forced vital capacity (FVC)
- ERT experienced patients switching to AT-GAA from alglucosidase alfa walked farther and showed stabilization of FVC compared to patients remaining on alglucosidase alfa who showed no improvement in their walking and declined in FVC
- Improvements in the two important biomarkers of Pompe Disease (Hex-4 and CK) for the overall study population significantly favored AT-GAA compared to the currently approved ERT
- All key secondary and biomarker endpoints favored AT-GAA compared to alglucosidase alfa in the overall and ERT experienced population
- Overall safety profile of AT-GAA is similar to alglucosidase alfa

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