

Structure and Receptor Affinity for High Mannose and
Phosphorylated Oligosaccharides

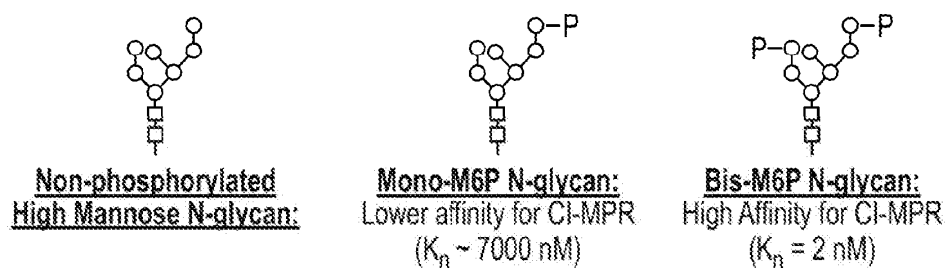


Fig. 1A

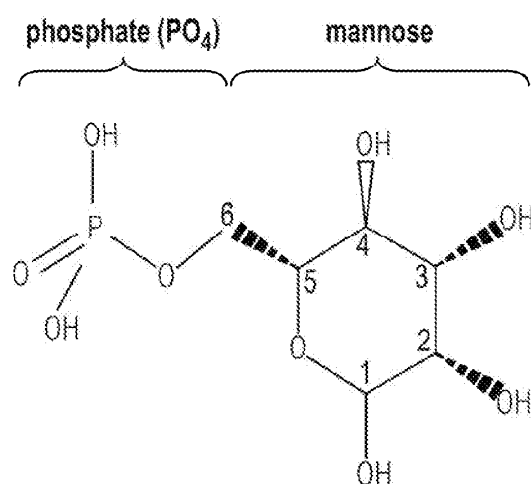


Fig. 1B

Comparison of Productive and Non-Productive Targeting Glycan Specific Receptors

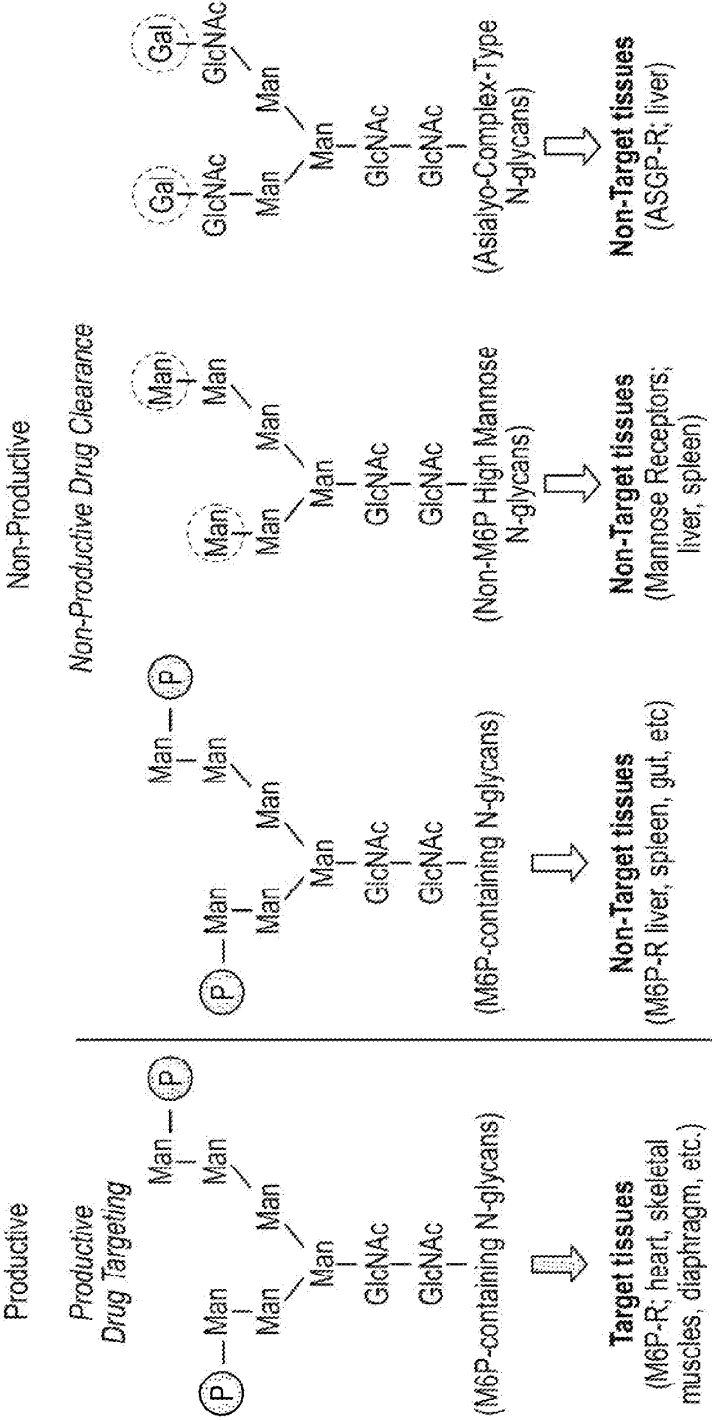


Fig. 2A

Fig. 2B

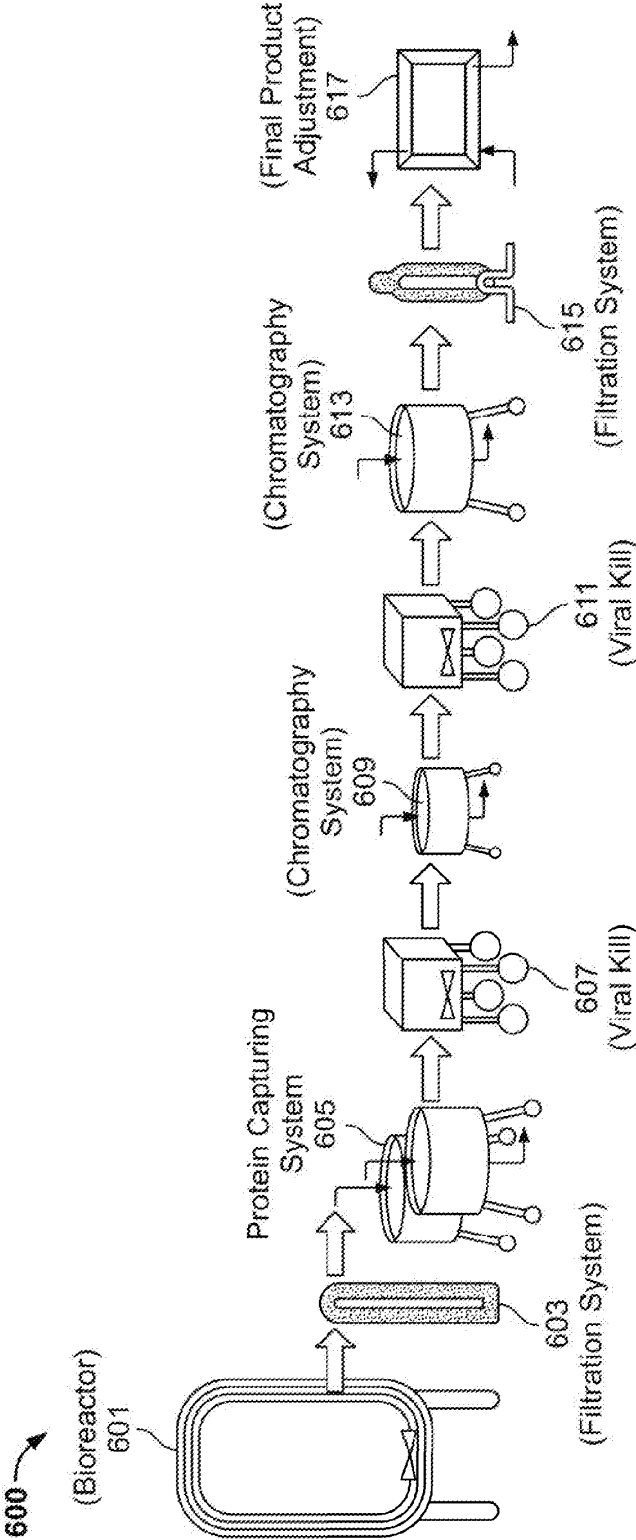
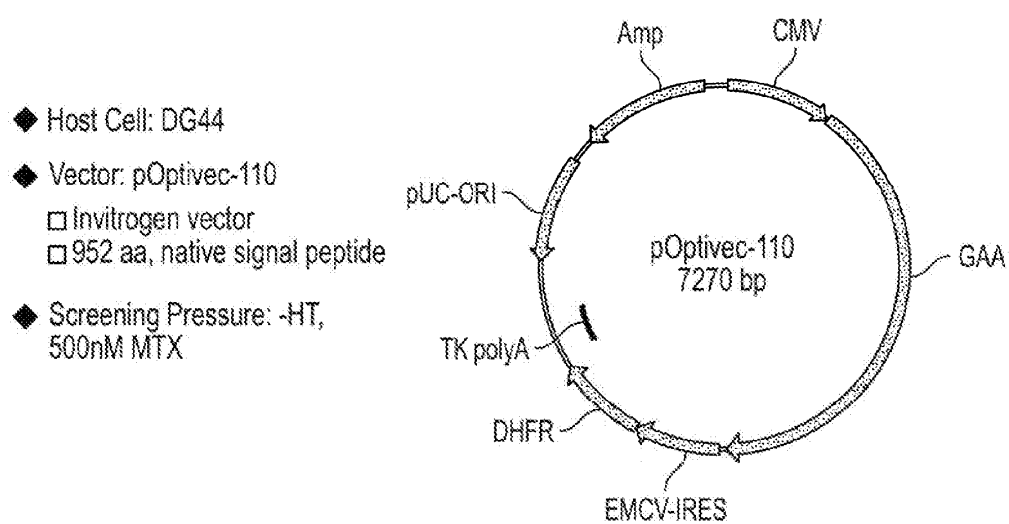
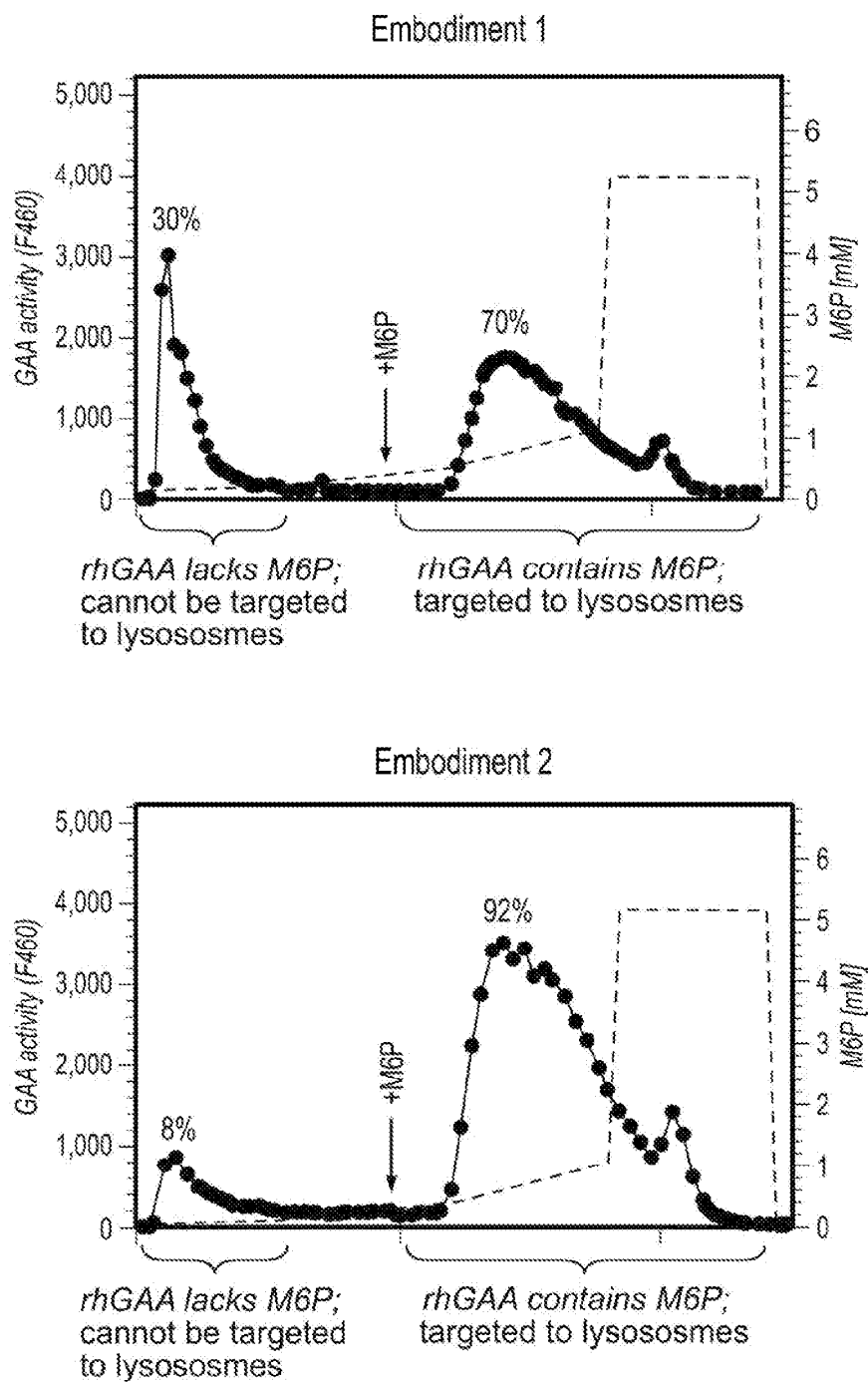


Fig. 3

ATB200 Vector Construction

**Fig. 4**

**Fig. 5**

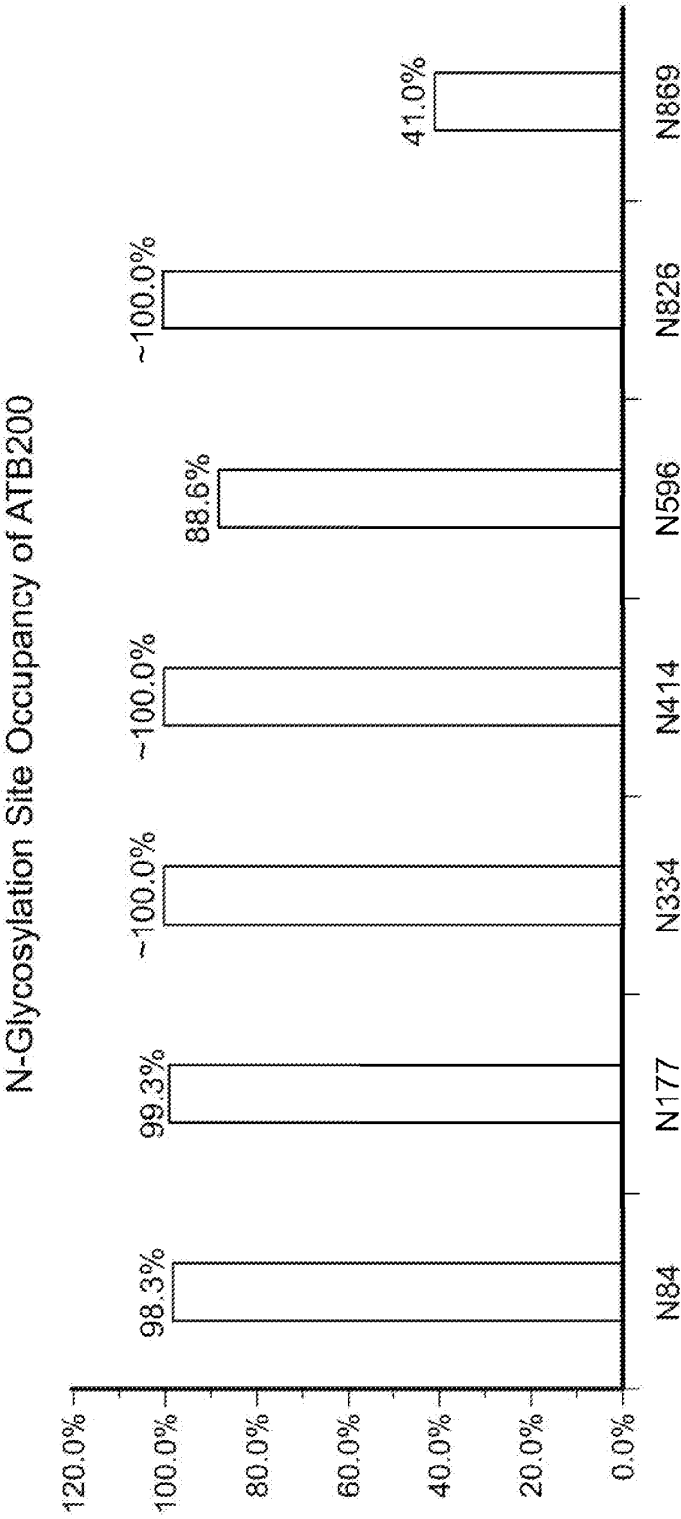


Fig. 6A

N-Glycosylation Profile of N84

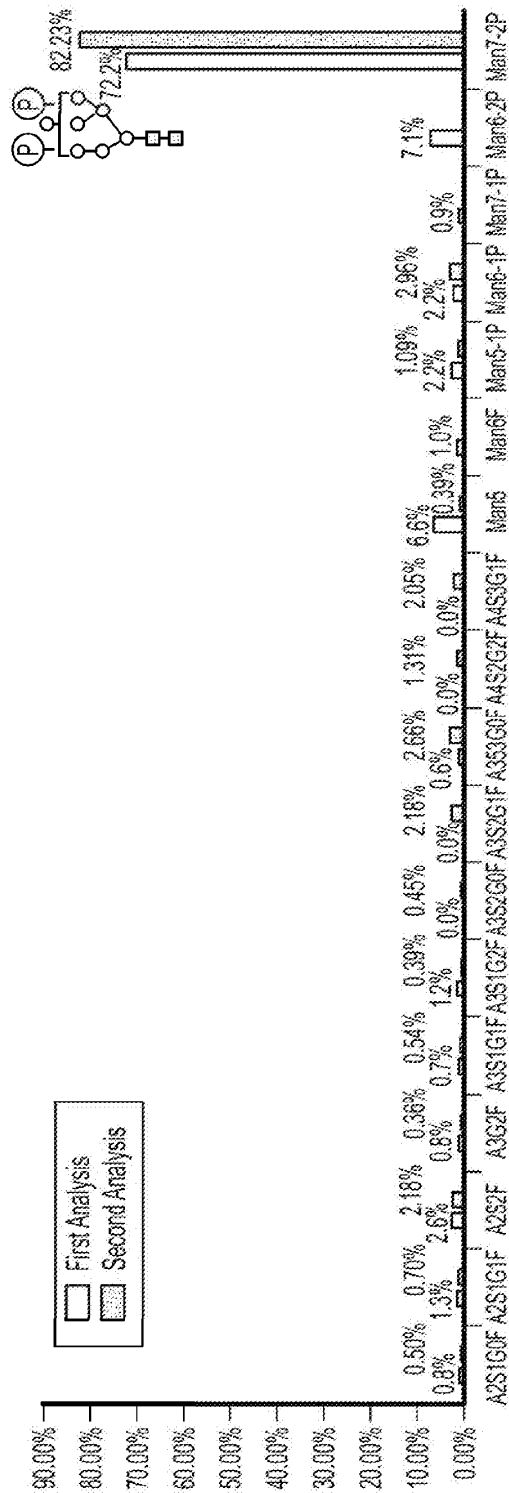


Fig. 6B

N-Glycosylation Profile of N177



Fig. 6C

N-Glycosylation Profile of N414

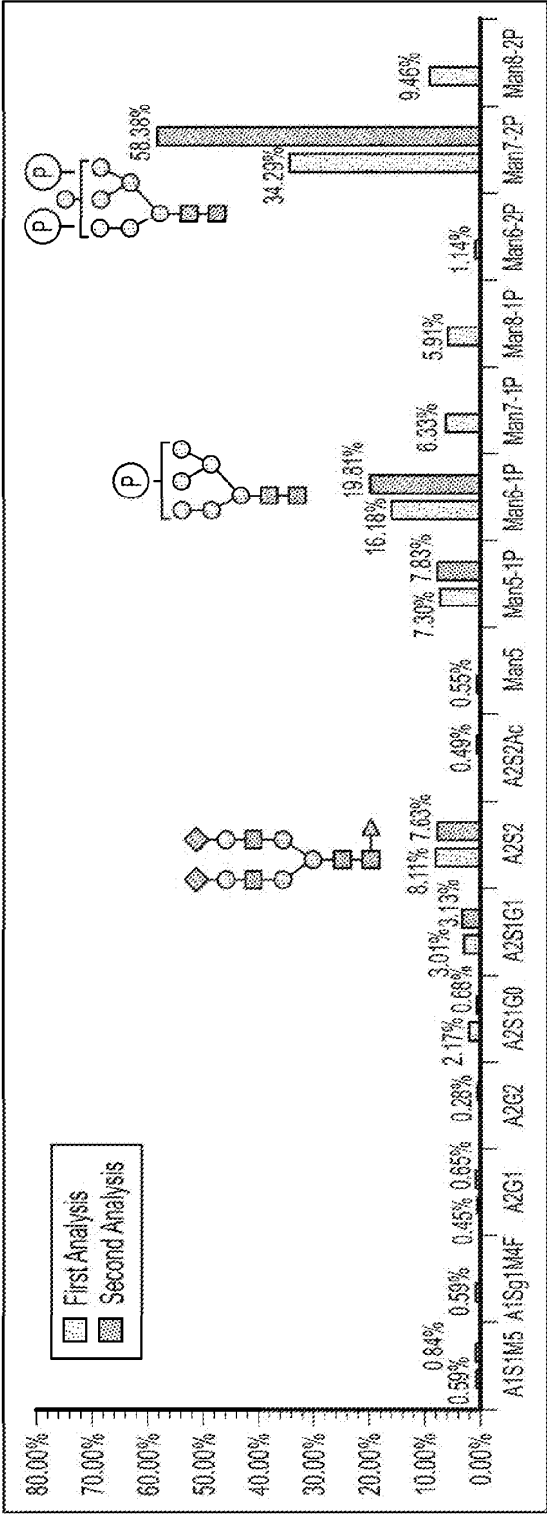


Fig. 6E

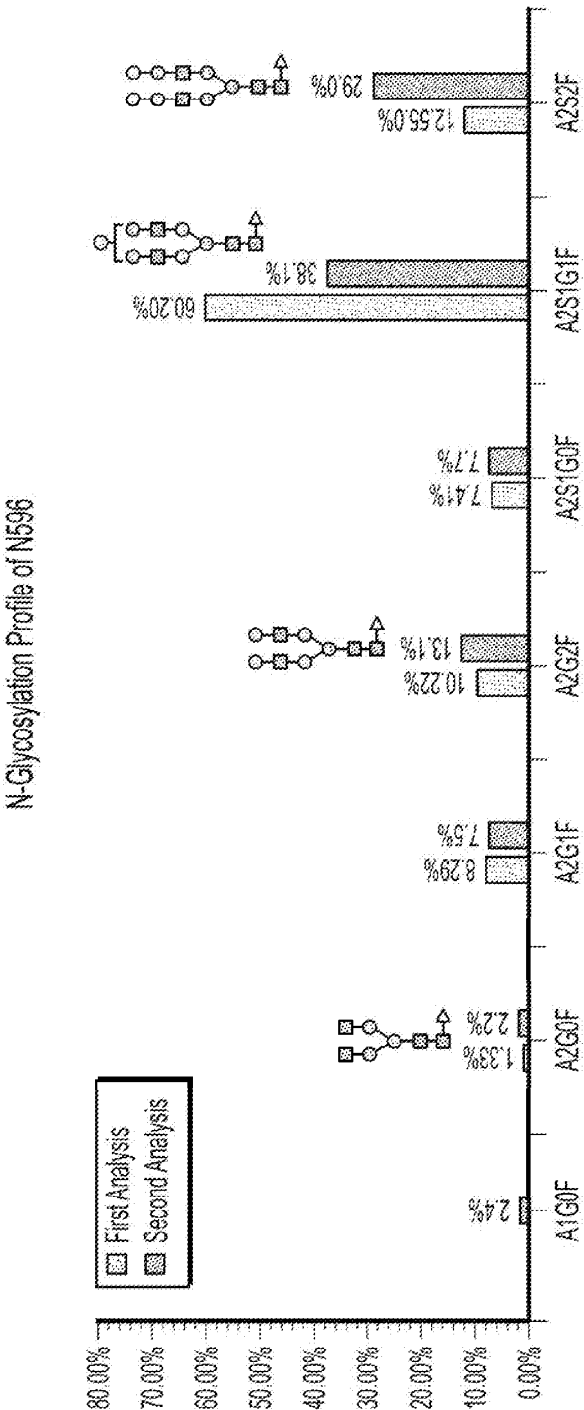


Fig. 6F

N-Glycosylation Profile of N826

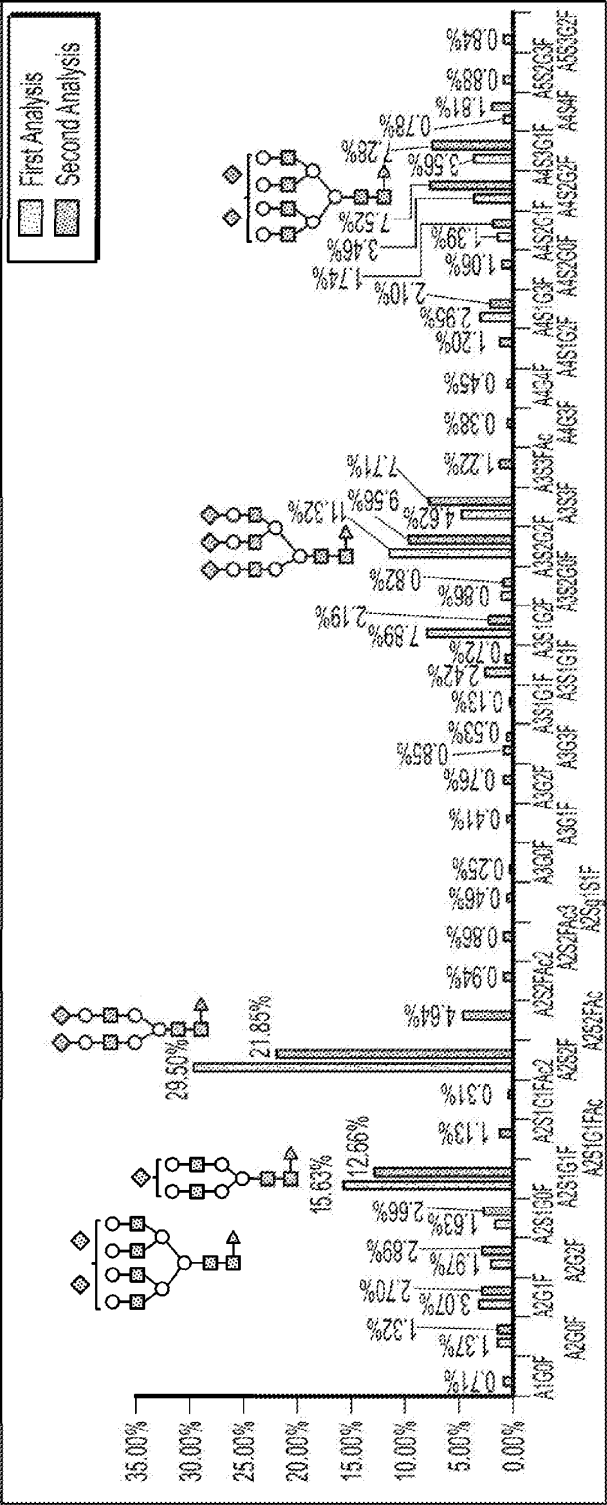


Fig. 6C

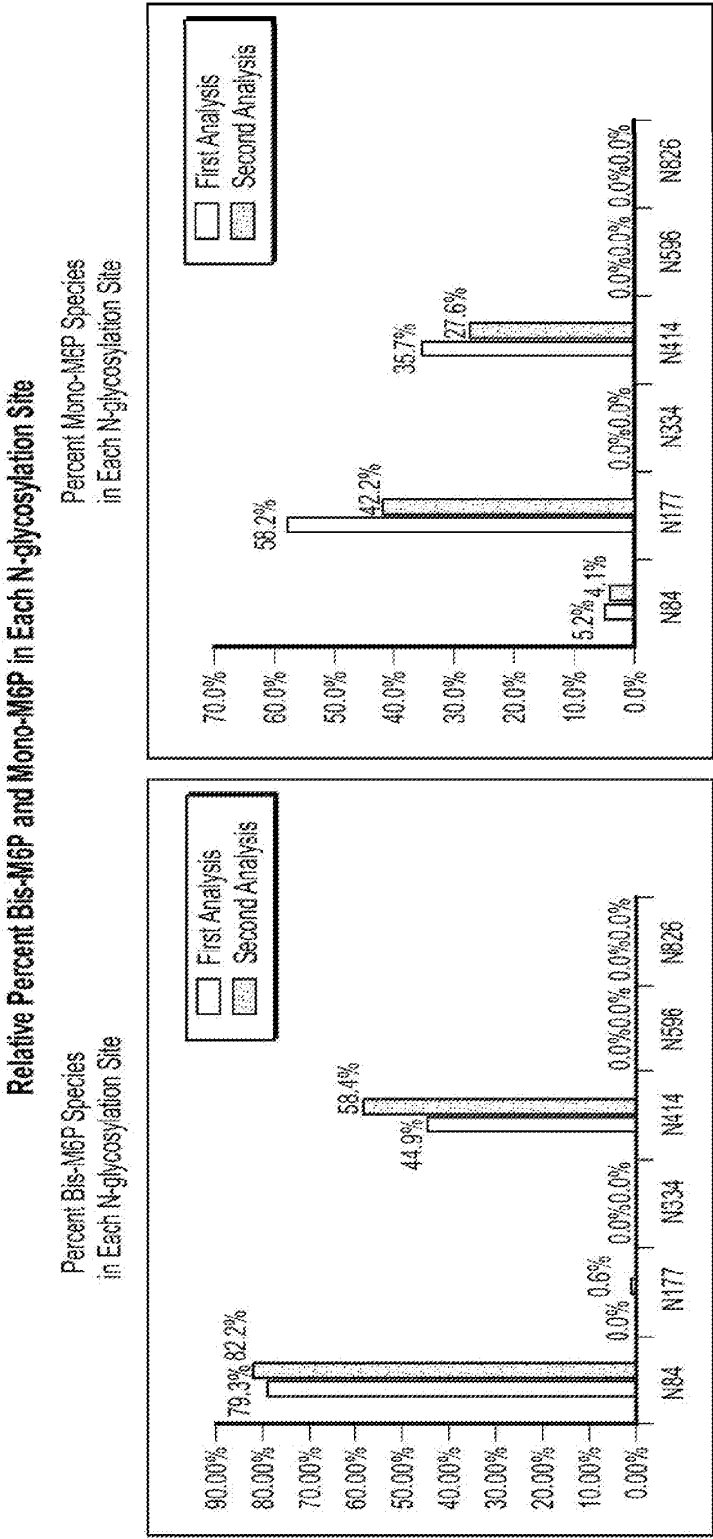
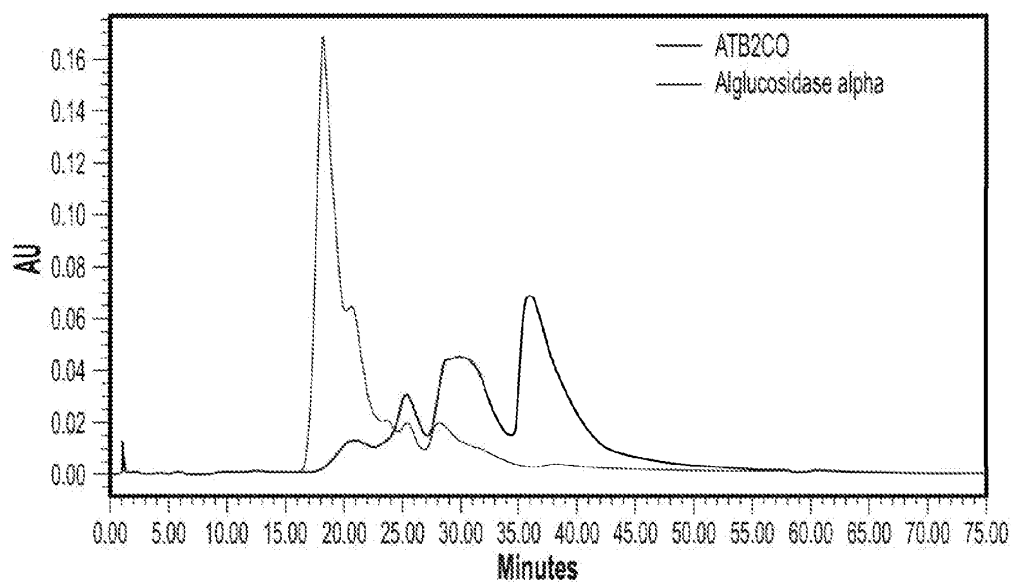


Fig. 6H

**Fig. 7****Distribution of N-Glycans on rhGAA Preparations**

	Lumizyme	BP-rhGAA*	ATB200	
			1	2
Complex Type N-Glycans	70.7%	48.9%	51.0%	47.5%
Hibrid Type N-Glycans	6.7%	9.7%	4.4%	3.7%
High Mannose Type N-Glycans:				
Non-phosphorylated	15.8%	23.7%	14.0%	9.9%
Mono-M6P	5.2%	10.4%	13.4%	14.2%
Bis-M6P	1.6%	6.8%	17.2%	24.7%

Fig. 8

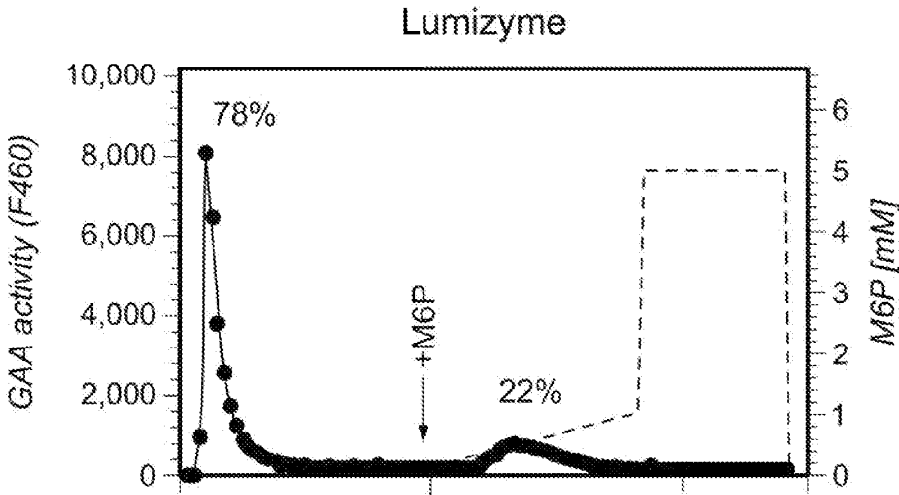


Fig. 9A

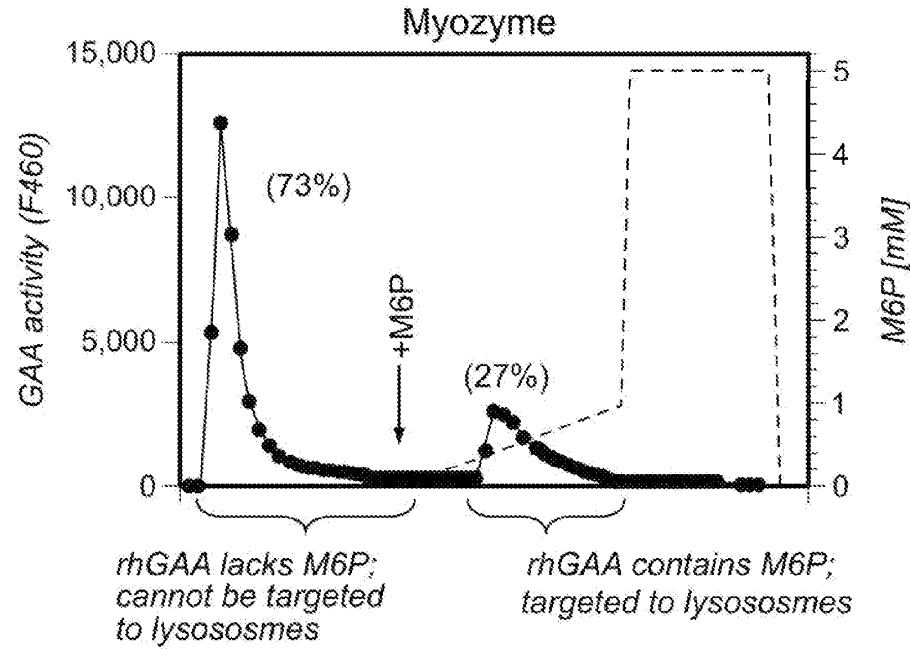


Fig. 9B

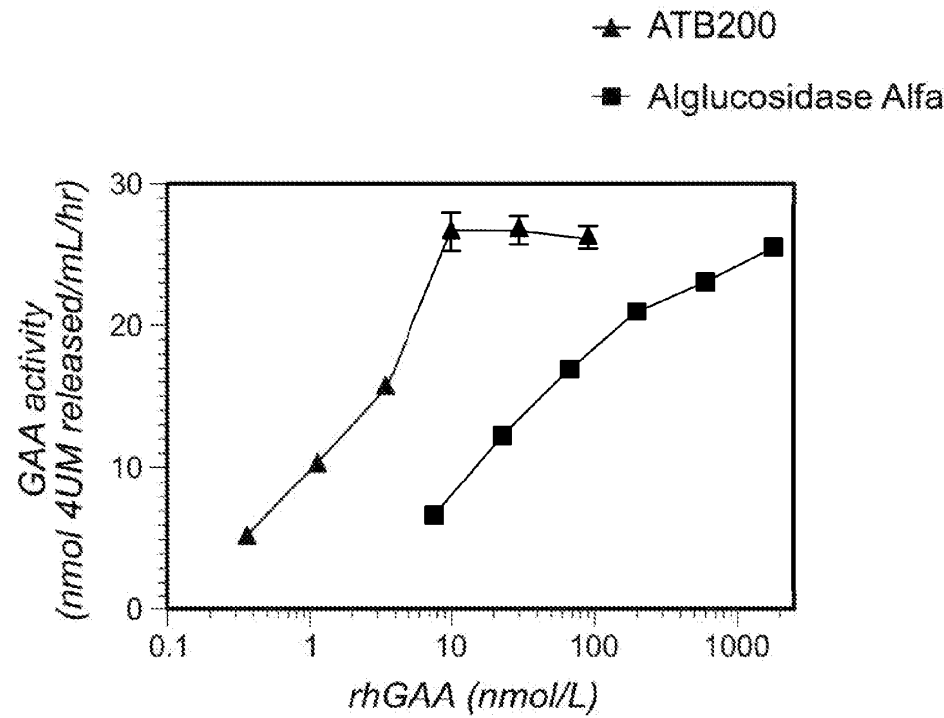


Fig. 10A

Glycan	Alglucosidase Alfa (mol bis-glycan/ mol protein)	ATB200 (mol bis-glycan/ mol protein)
Bis-M6P	0.1	1.3

Fig. 10B

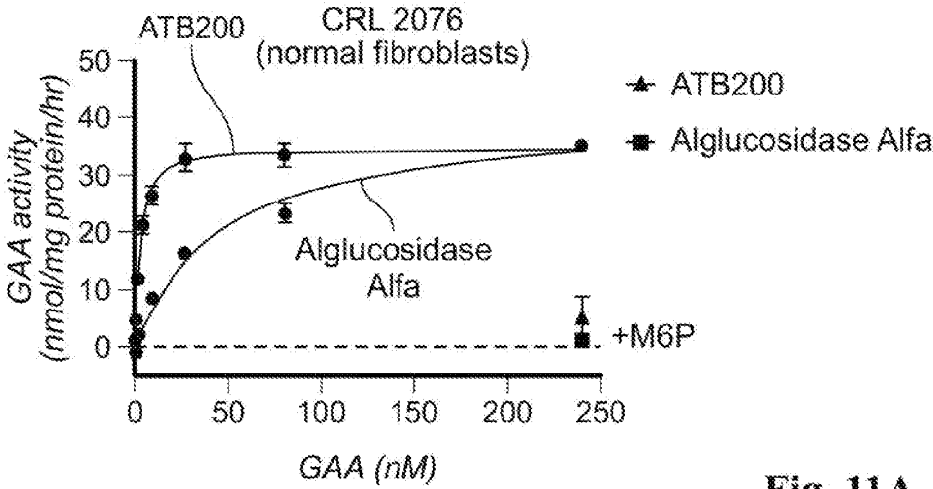


Fig. 11A

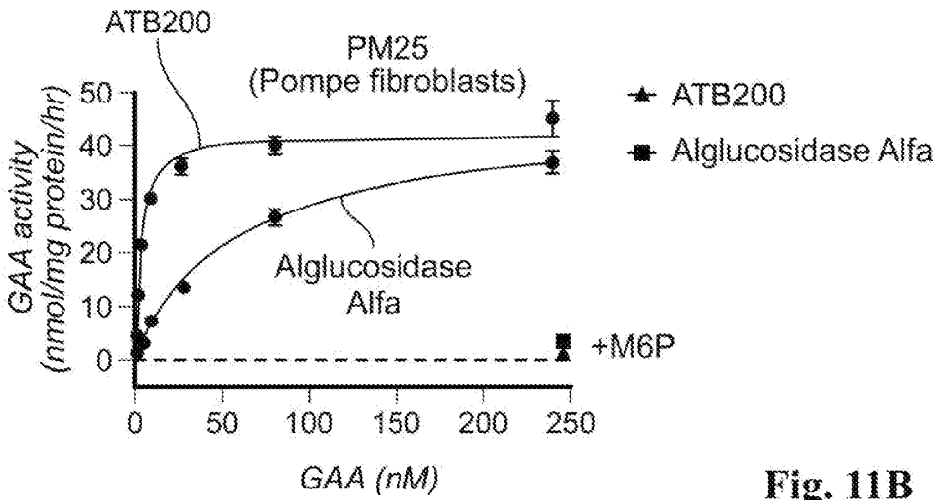


Fig. 11B

Cell Line	K _{uptake} (nM)	
	ATB200	Lumizyme®
normal	2	56
Pompe	3	57

Fig. 11C

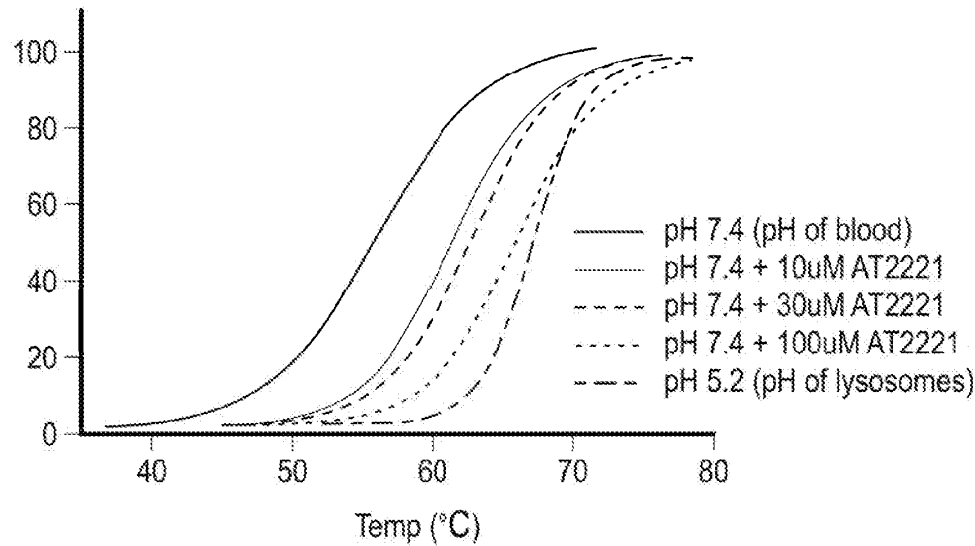


Fig. 12

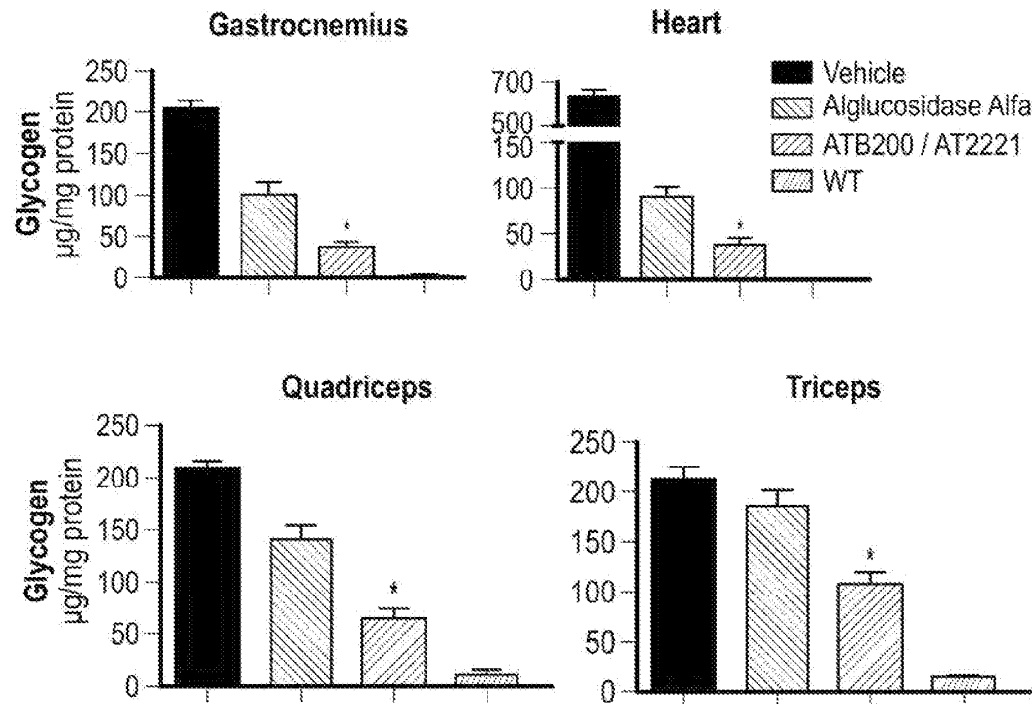


Fig. 13

IHC Examination of LAMP1 in *vastus lateralis* of Quadriceps

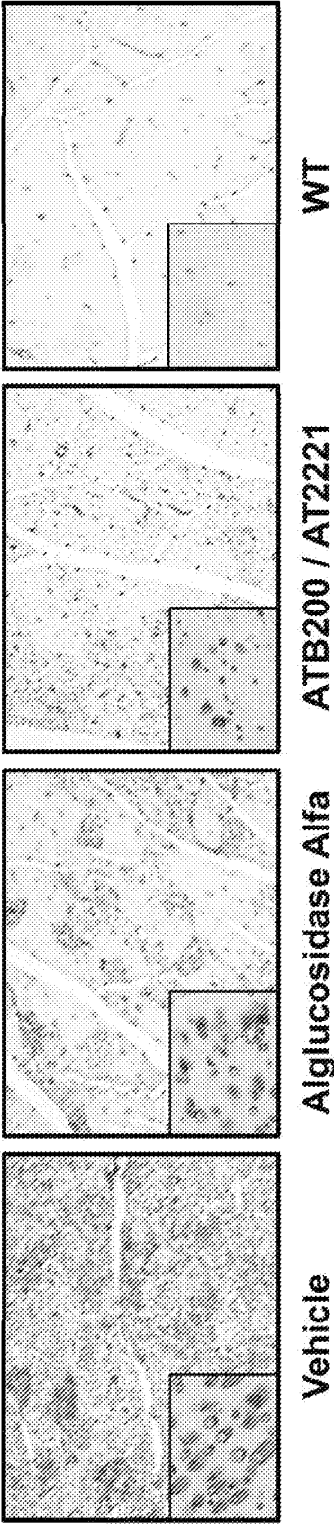


Fig. 14

IHC Examination of LC3 in *vastus lateralis* of Quadriceps

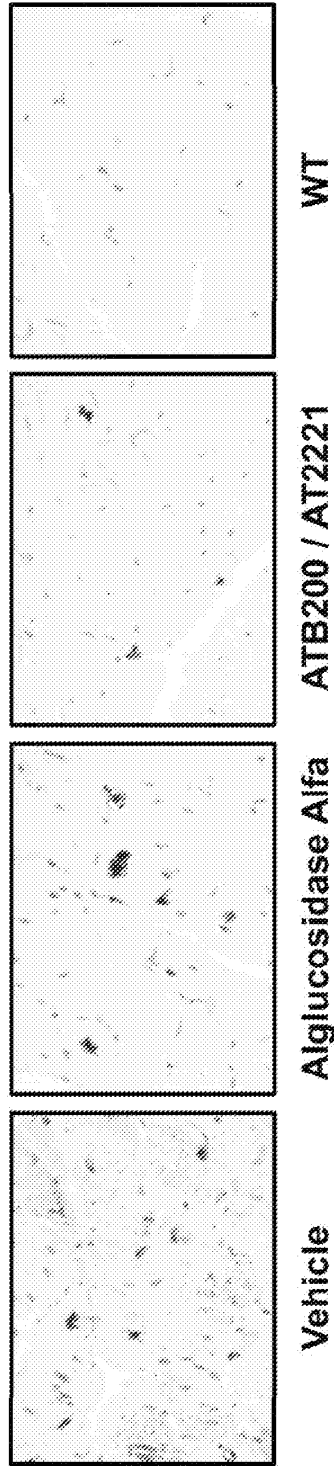


Fig. 15A

WB Examination of LC3 in Quadriceps

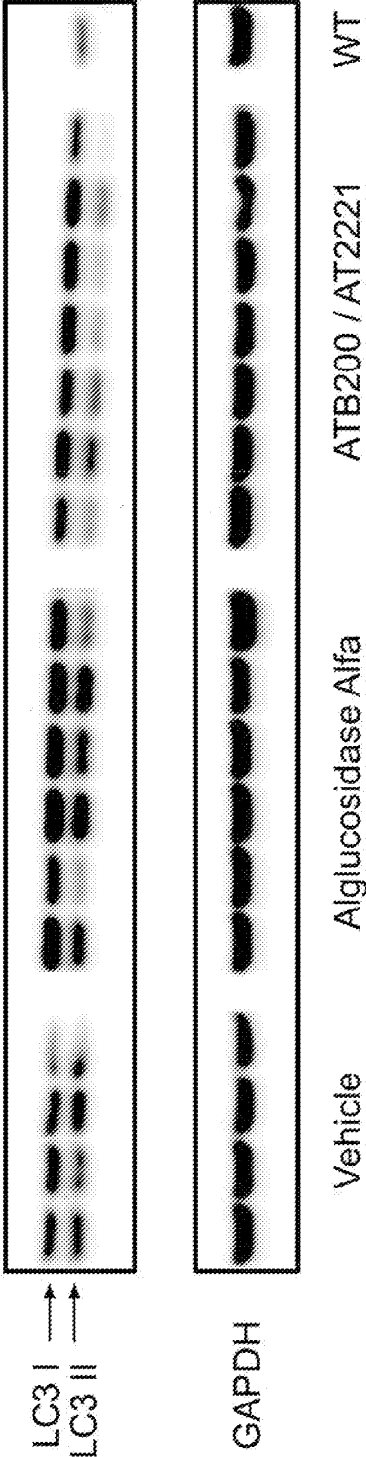


Fig. 15B

IHC Examination of Dysferlin in *vastus lateralis* of Quadriceps

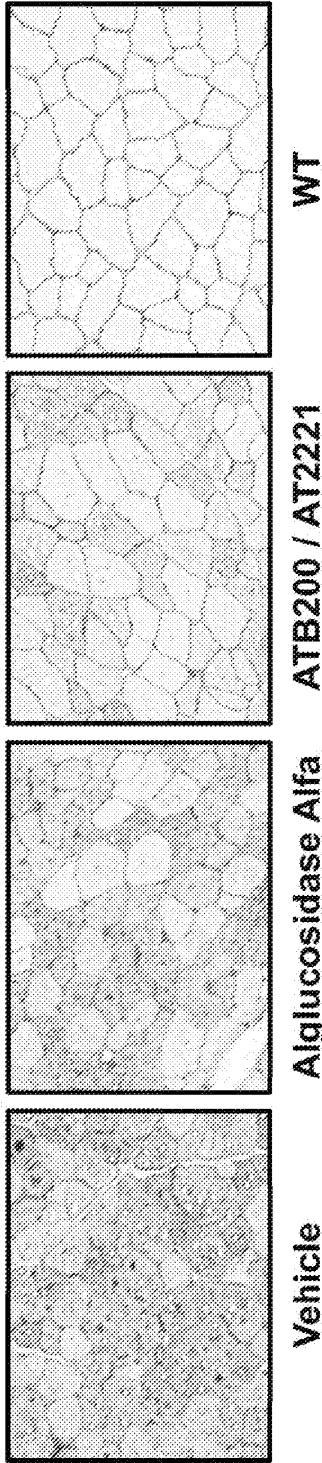


Fig. 16

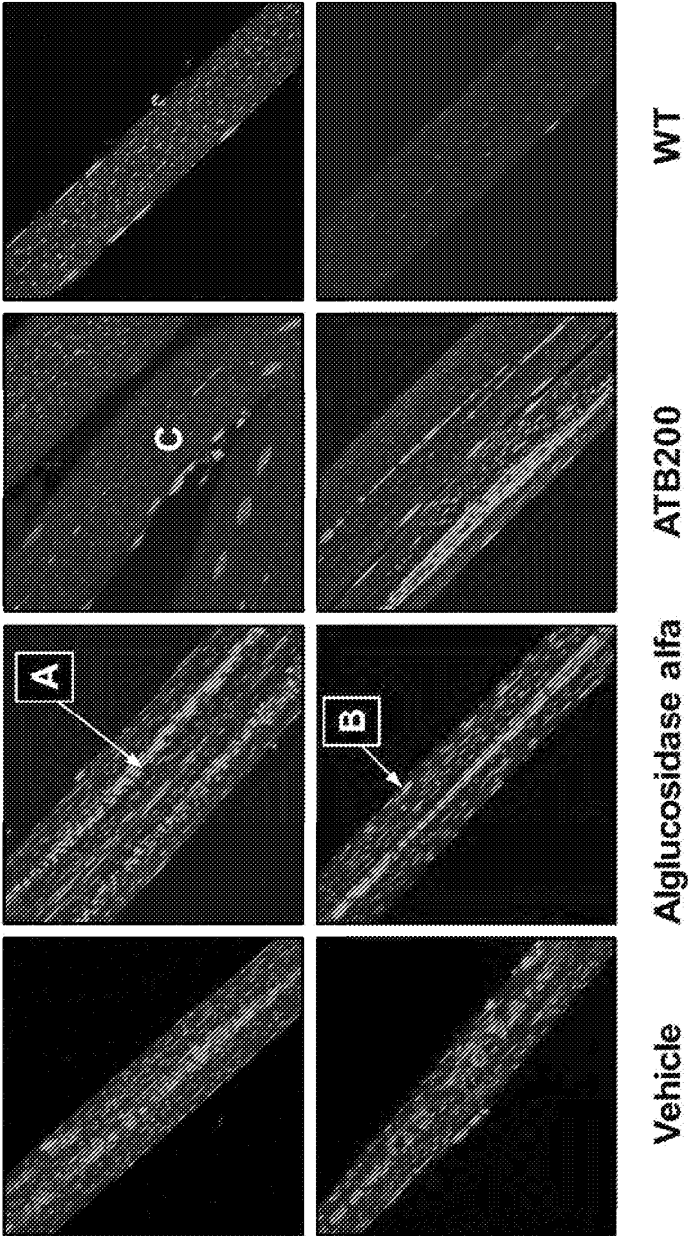
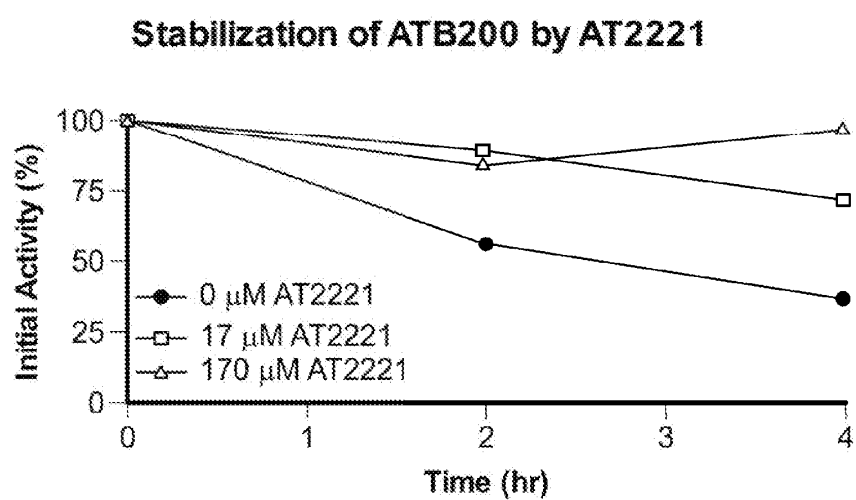


Fig. 17

**Fig. 18**

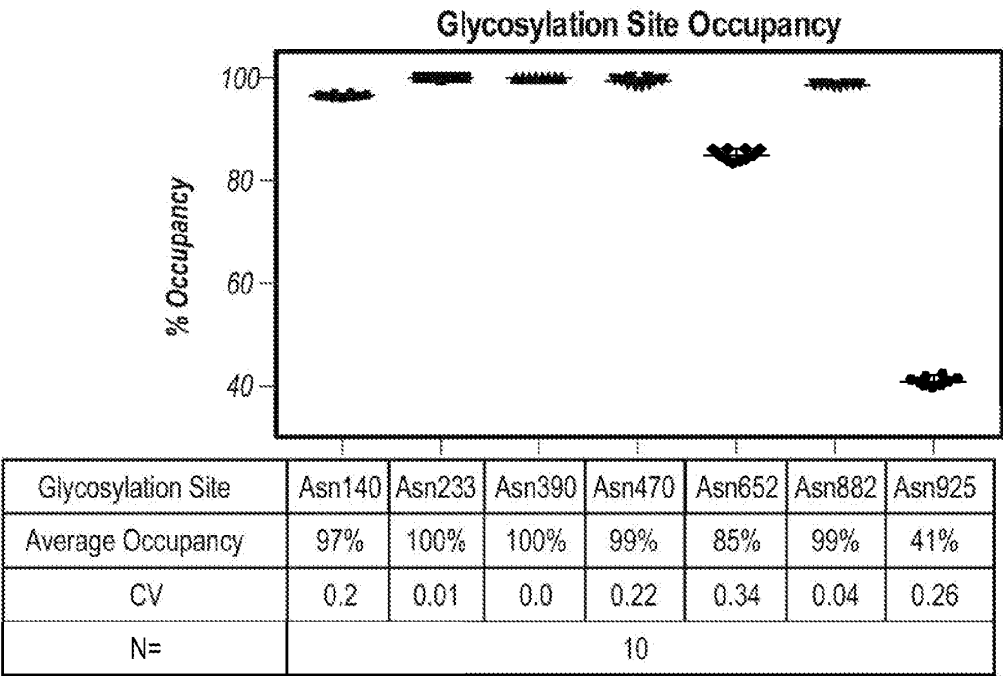


Fig. 19A

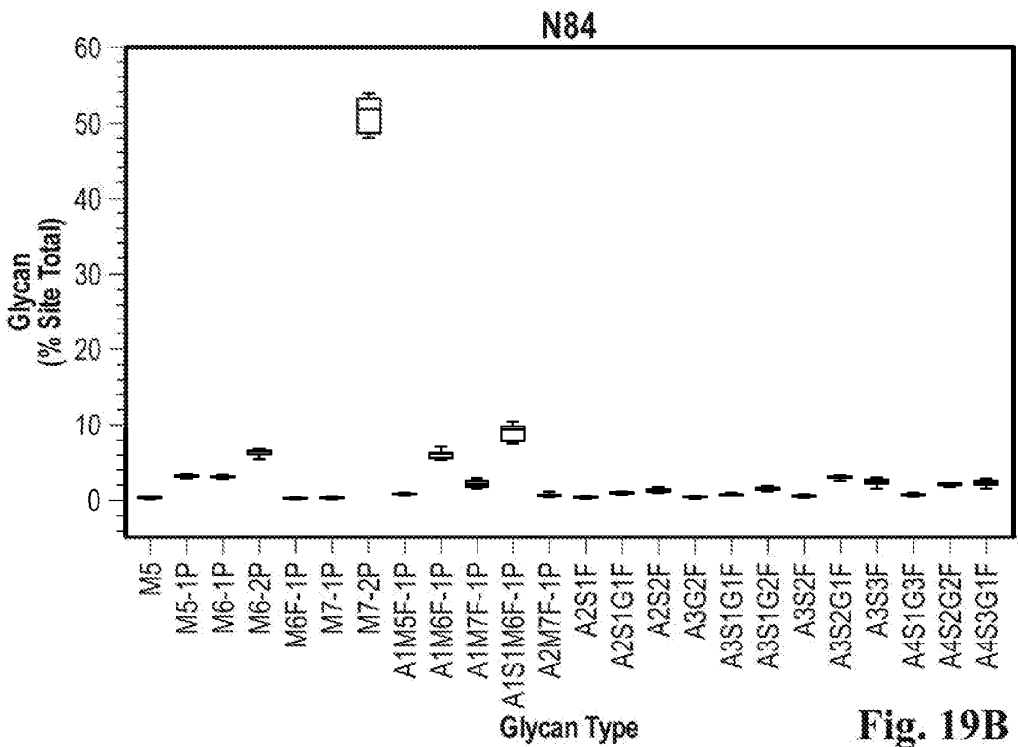


Fig. 19B

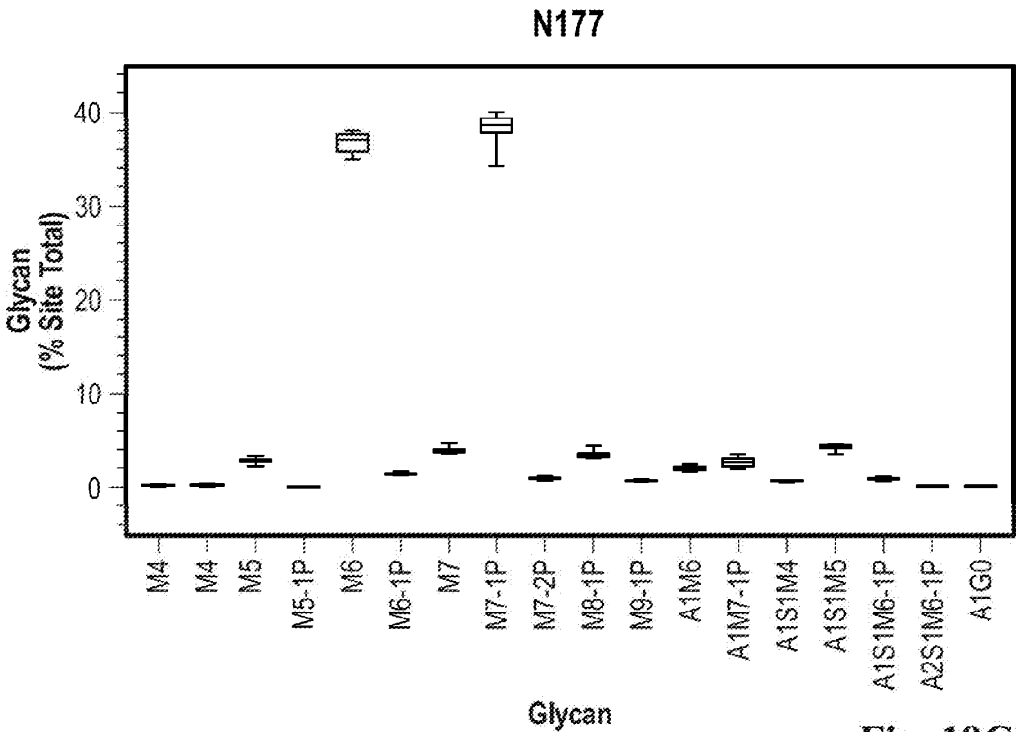


Fig. 19C

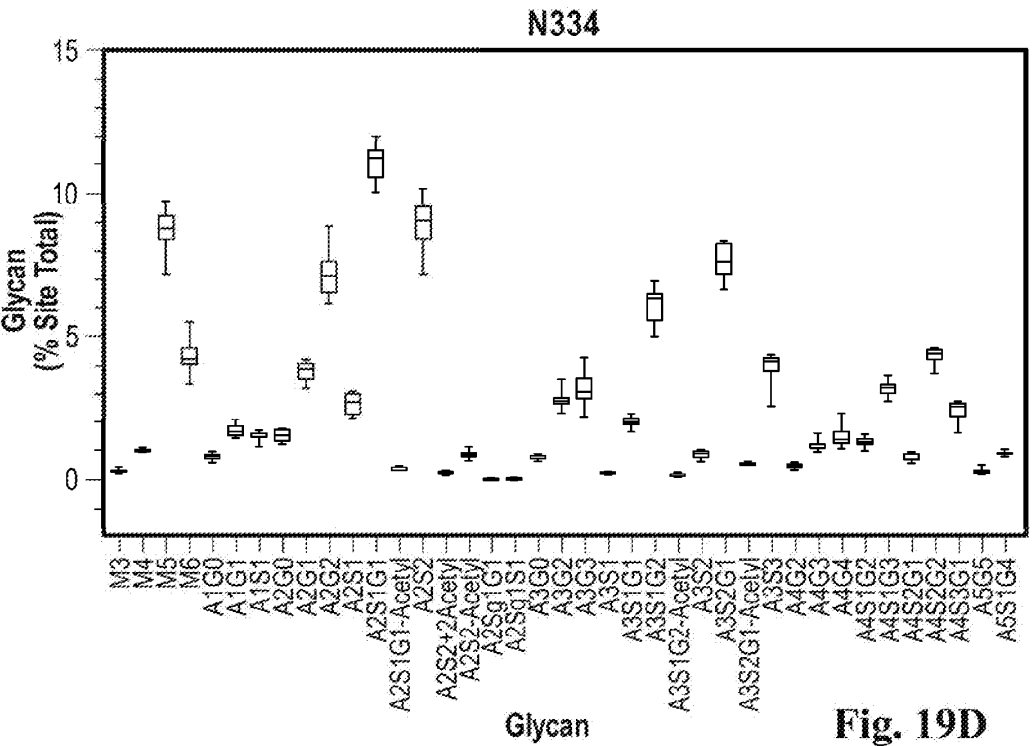


Fig. 19D

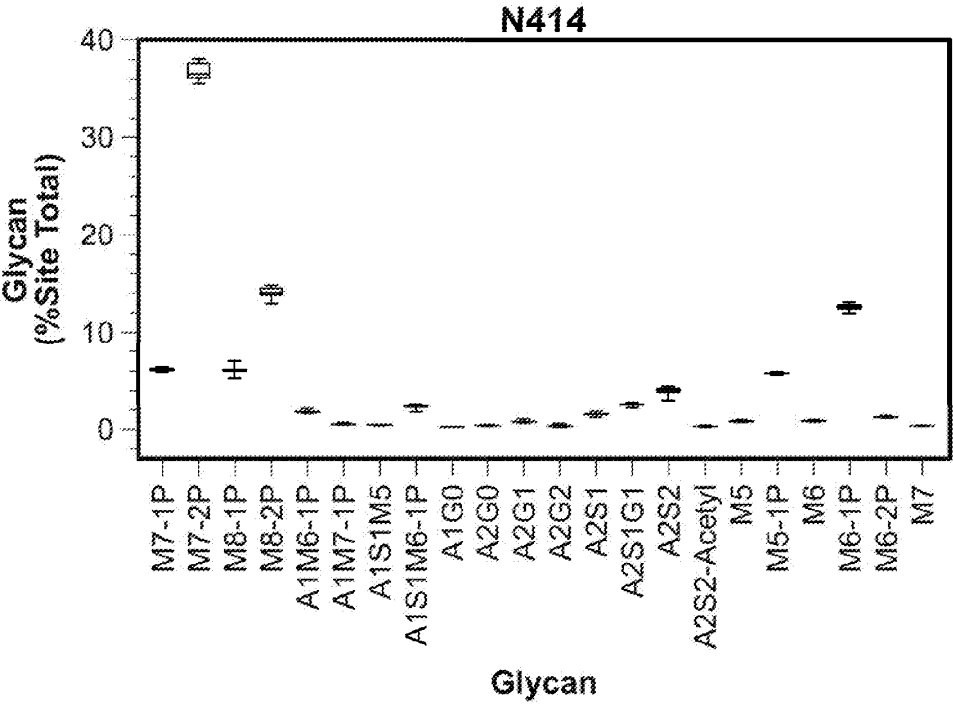


Fig. 19E

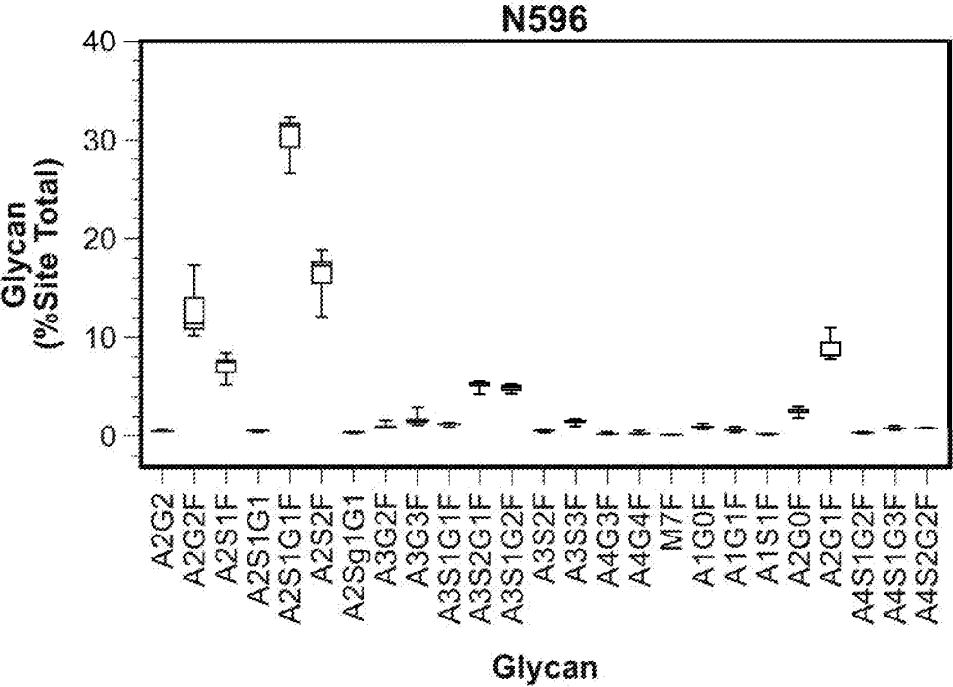
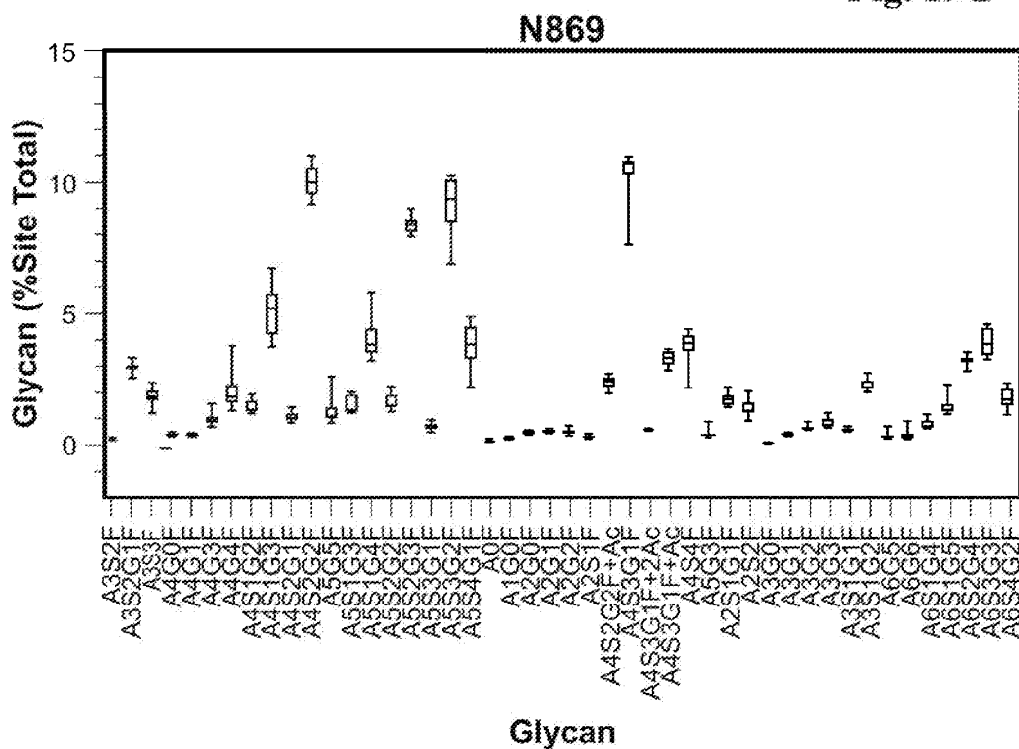
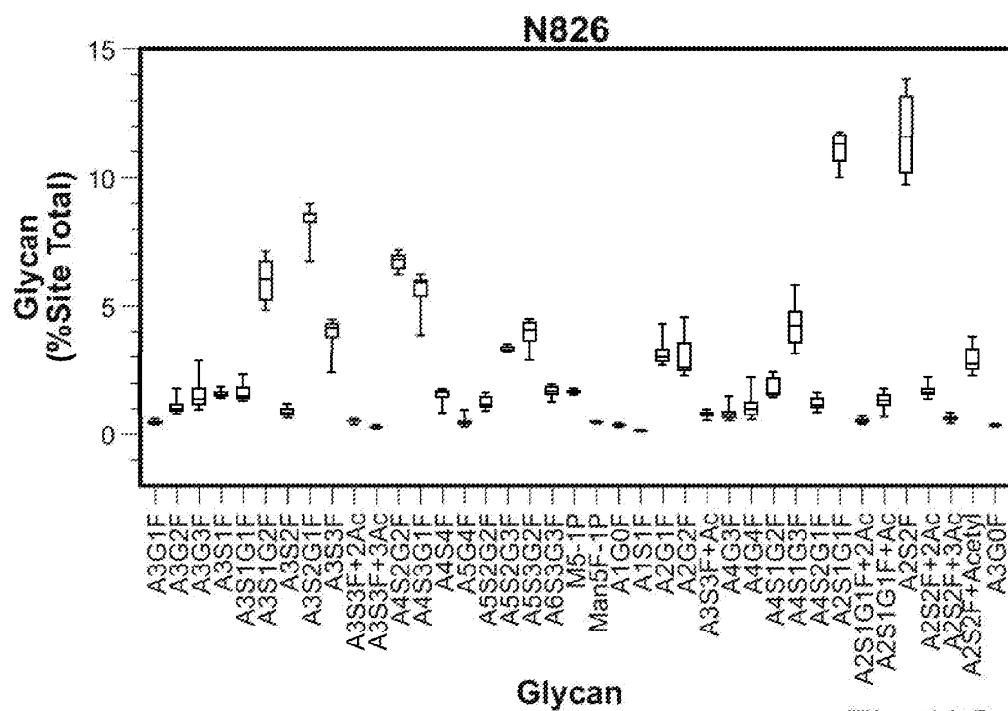


Fig. 19F



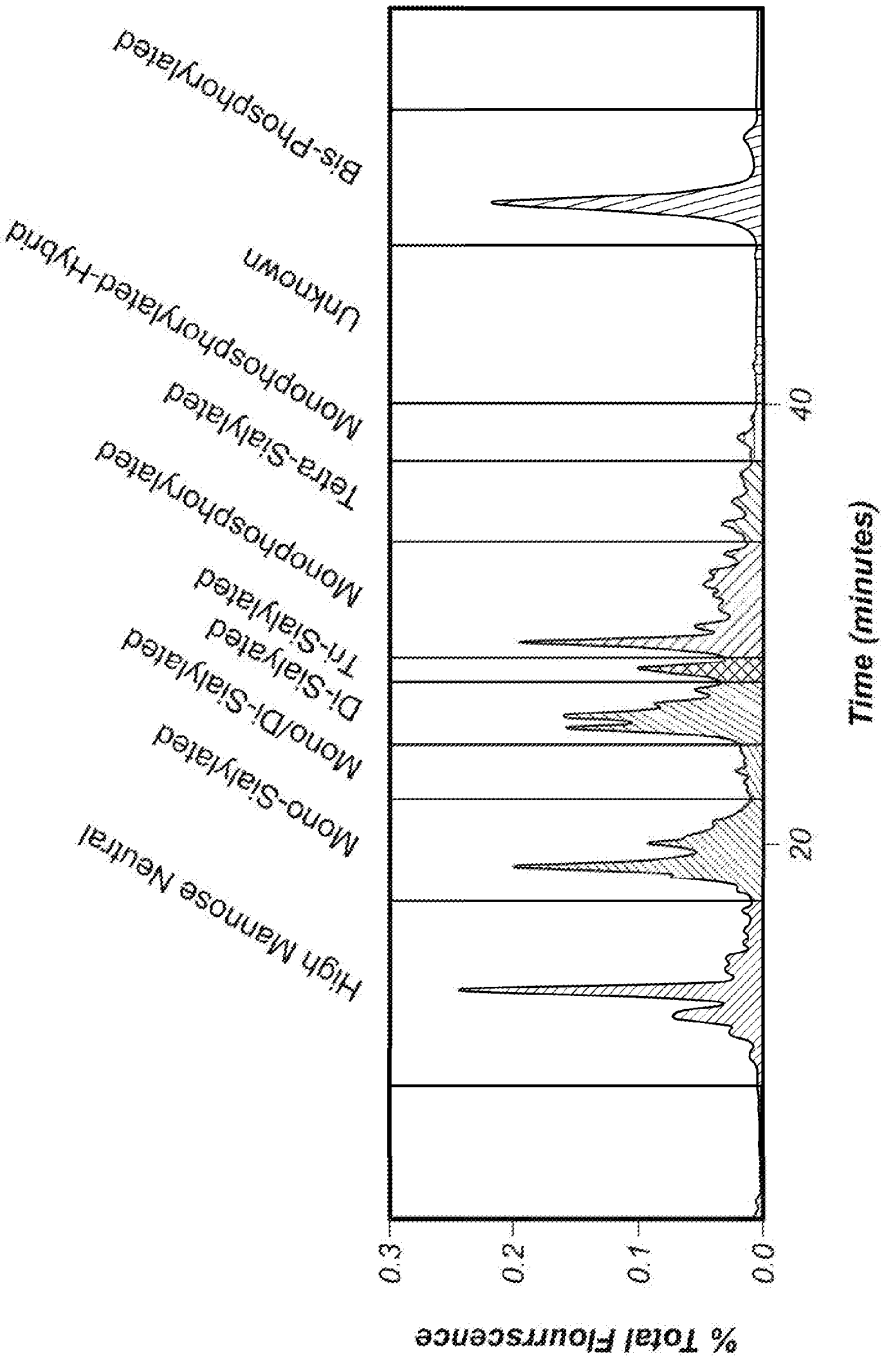


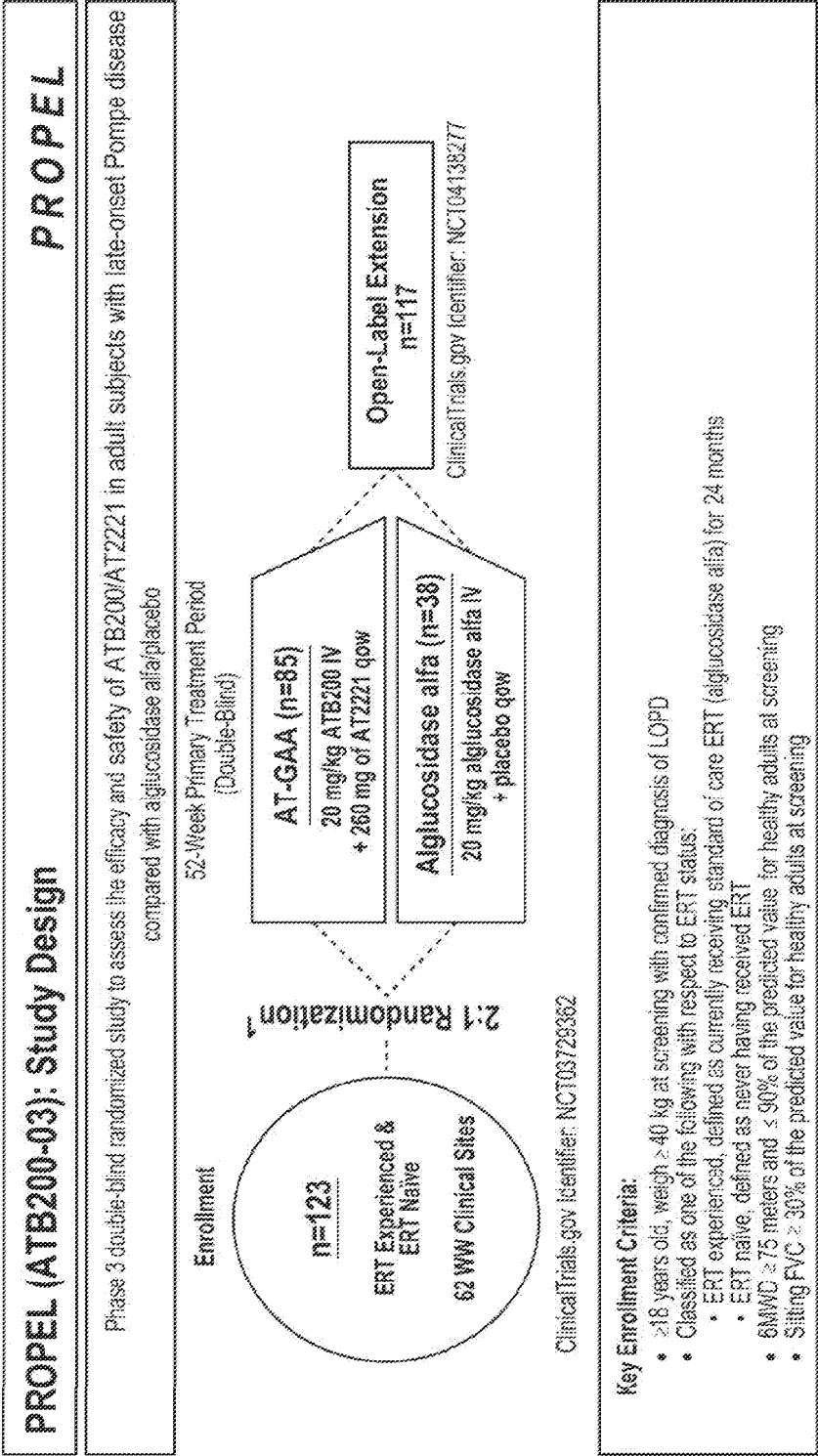
Fig. 20A

Site Specific Glycan Summary

	N84		N177		N334		N414		N596		N826		N869	
	Average	Stdev	Average	Stdev	Average	Stdev	Average	Stdev	Average	Stdev	Average	Stdev	Average	Stdev
Phosphorylated Glycans	83.2%	5.4%	48.9%	3.0%	ND		87.4%	3.1%	ND		2.1%	0.1%	ND	
Mono-Phosphorylated	25.6%	2.8%	48.0%	2.9%	ND		35.3%	1.6%	ND		2.1%	0.1%	ND	
Bis-phosphorylated	57.6%	2.6%	1.0%	0.1%	ND		52.0%	1.5%	ND		ND		ND	
Sialylated Glycans	25.0%	3.3%	6.2%	0.6%	54.6%	4.9%	11.2%	1.2%	70.4%		85.4%	10.5%	86.7%	10.8%
Fully Sialylated	13.7%	2.0%	6.2%	0.6%	19.3%	2.3%	8.6%	1.0%	26.0%		26.6%	4.0%	7.6%	1.4%
High Mannose														
Hybrid	64.9%	3.1%	88.9%	4.1%	14.4%	1.4%	84.7%	2.8%	0.1%	0.0%	2.1%	0.1%	ND	
Complex	18.7%	2.3%	10.9%	1.4%	ND		5.2%	0.6%	ND		ND		ND	
	16.4%	2.4%	0.2%	0.0%	85.6%	9.0%	10.1%	1.2%	99.9%	11.8%	97.9%	13.9%	100.0%	14.3%
Number of Glycans	24		17		39		22		25		39		46	
M6P (mol/mol Site)	1.36		0.50				1.38				0.02			
mono Glycan (mol/mol Site)	0.25		0.48				0.35				0.02			
bis Glycan (mol/mol Site)	0.56		0.01				0.52							
Sialic Acid (mol/mol Site)	0.32	0.04	0.06	0.01	0.97	0.06	0.074	0.004	0.86	0.07	4.2	0.1	0.86	0.07
Site Occupancy	96.5%	0.2%	99.9%	0.0%	100.0%	0.0%	99.3%	0.7%	84.9%	1.1%	98.6%	0.1%	41.0%	0.8%

ND=Not Detected

Fig. 20B



¹2:1 randomization with stratification factors on ERT status, baseline 6MWD

Fig. 21

Baseline Characteristics				PROPEL	
Baseline 6MWD and FVC were representative of the population and generally similar in the two treatment arms					
	AT-GAA n=85		Aglucosidase 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)	343.3 (112.5, 532.3)	385.5 (201.0, 623.0)	
	AT-GAA n=85		Aglucosidase alfa n=37		
FVC% Predicted, Sitting					
Mean (SD)	70.7 (19.6)		65.7 (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
Results exclude one clinically implausible patient who used and investigational anabolic steroid ostarine (selective androgen receptor modulator) just prior to study start.

Fig. 22

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

GMWD (m)

Treatment	Baseline	CFB 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)

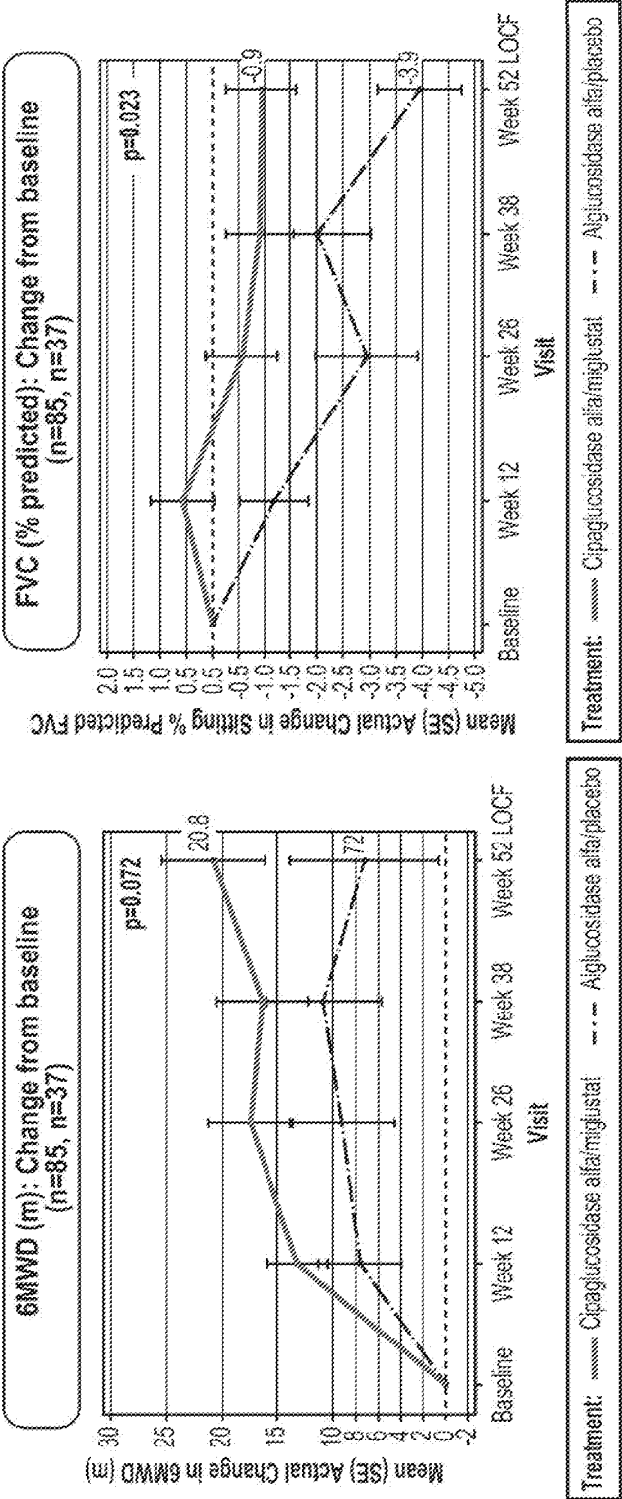
Treatment	Baseline	CFB at Week 52	Difference	P-Value
AT-GAA (n=85)	70.7 (19.6)	-0.9 (0.7)	+3.0 (1.2)	p=0.023
Alglucosidase alfa (n=37)	69.7 (21.5)	-4.0 (0.8)		

NOTES: Baseline is Mean (STDEV); CFB 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.

Fig. 23A

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

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



6MWD=6-minute walk distance; ANCOVA=analysis of covariance; CFBL=change from baseline; ERT=enzyme replacement therapy; FVC=forced vital capacity; LOCF=last observation carried forward; MMRM=mixed effect model for repeated measures; SD=standard deviation; SE=standard error; Baseline is Mean (SE); 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 MMRM P value is for non-parametric ANCOVA; 6MWD parameter: MMRM P=0.057. Results exclude one clinically implausible patient who used an investigational anabolic steroid (selective androgen receptor modulator) just prior to study start.

Fig. 23B

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

6MWD (m)

Treatment	Baseline	CFB 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	CFB 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)		

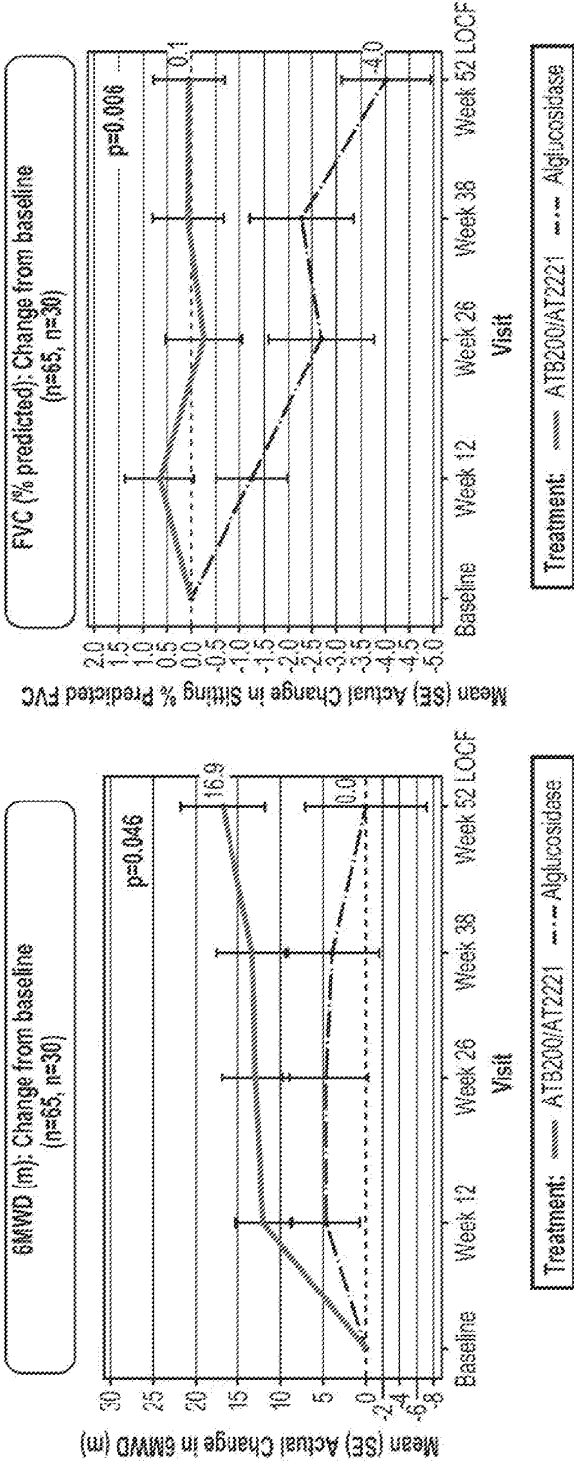
NOTE: Baseline is Mean (STDEV); CFBL is Mean LOCF (SE); P-values are nominal 2-sided; FVC data normally distributed and p-values are from ANCOVA. 6MWD data not normally distributed and 6MWD p-value is for non-parametric ANCOVA; 6MWD parametric MMRM p-value was p=0.078.

Fig. 24

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

PROPEL



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

Fig. 25

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

6MWD (m)

Treatment	Baseline	CFB 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)		

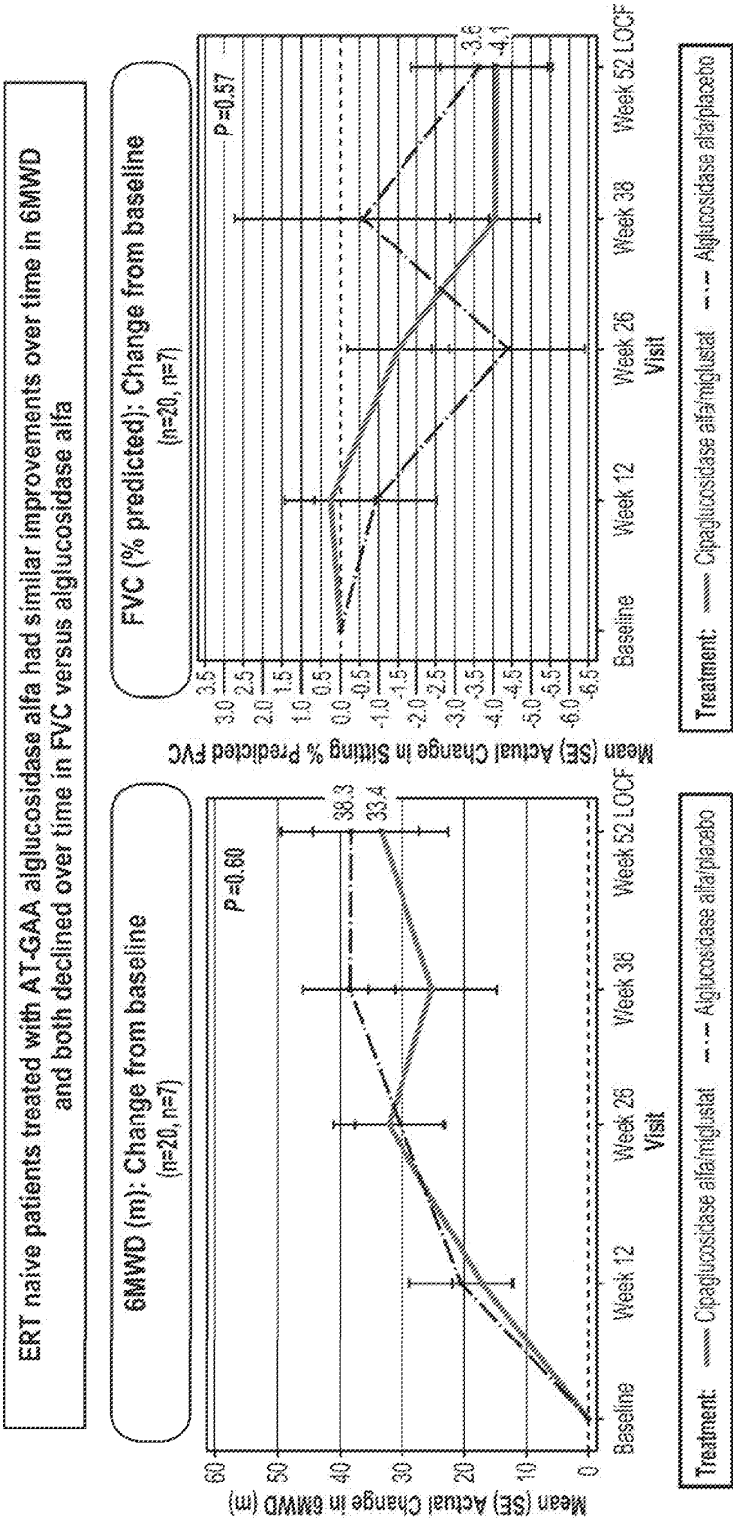
FVC(% predicted)

Treatment	Baseline	CFB 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); CFB 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.

Fig. 26A

6MWD and FVC Over Time: ERT-Naïve Population (n=27)



Baseline characteristics: Key Secondary Endpoints and Biomarkers

Parameters, mean (SD)	AT-GAA		Alglucosidase alfa	
	Overall n=85	ERT-Experienced n=65	Overall n=37	ERT-Experienced n=30
MMT lower extremities score	28.0 (5.8) ^a	26.4 (5.1) ^b	27.7 (6.2) ^c	26.1 (5.8) ^d
MMT lower extremities score	68.9 (12.3) ^a	64.4 (1.4) ^b	68.0 (13.1)	66.9 (12.3)
MMT lower extremities score	22.3 (8.3)	22.0 (7.9)	21.1 (6.1)	20.4 (5.4)
MMT lower extremities score	14.5 (5.2) ^e	15.6 (4.1) ^f	14.5 (4.7) ^g	15.5 (4.4) ^h

GSGC=Gait, Stairs, Gowers, Chair.
Results exclude 1 clinically implausible patient who used an investigational anabolic steroid ostarine (selective androgen receptor modulator) just prior to study start.
^a n=84; ^b n=64; ^c n=34; ^d n=27; ^e n=74; ^f n=55; ^g n=32; ^h n=25.

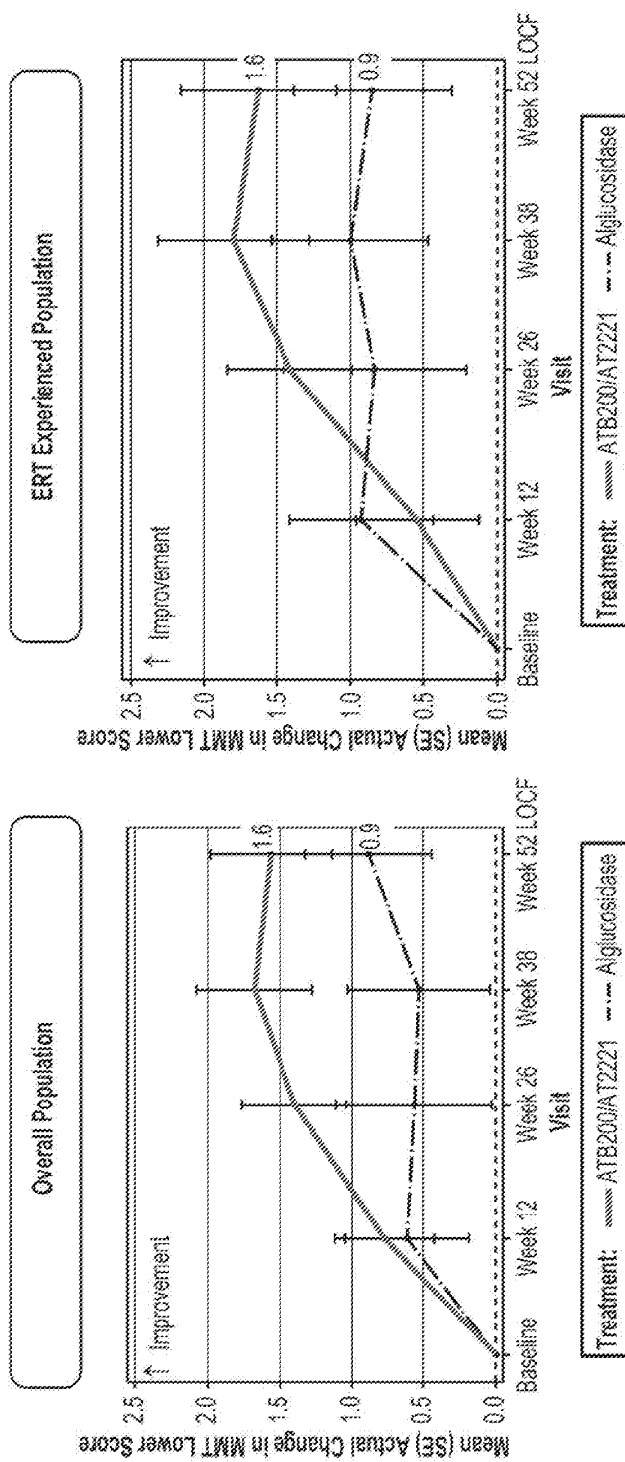
Fig. 27

Key Secondary: Lower MMT

All Patients & ERT Experienced Patients

LEAD

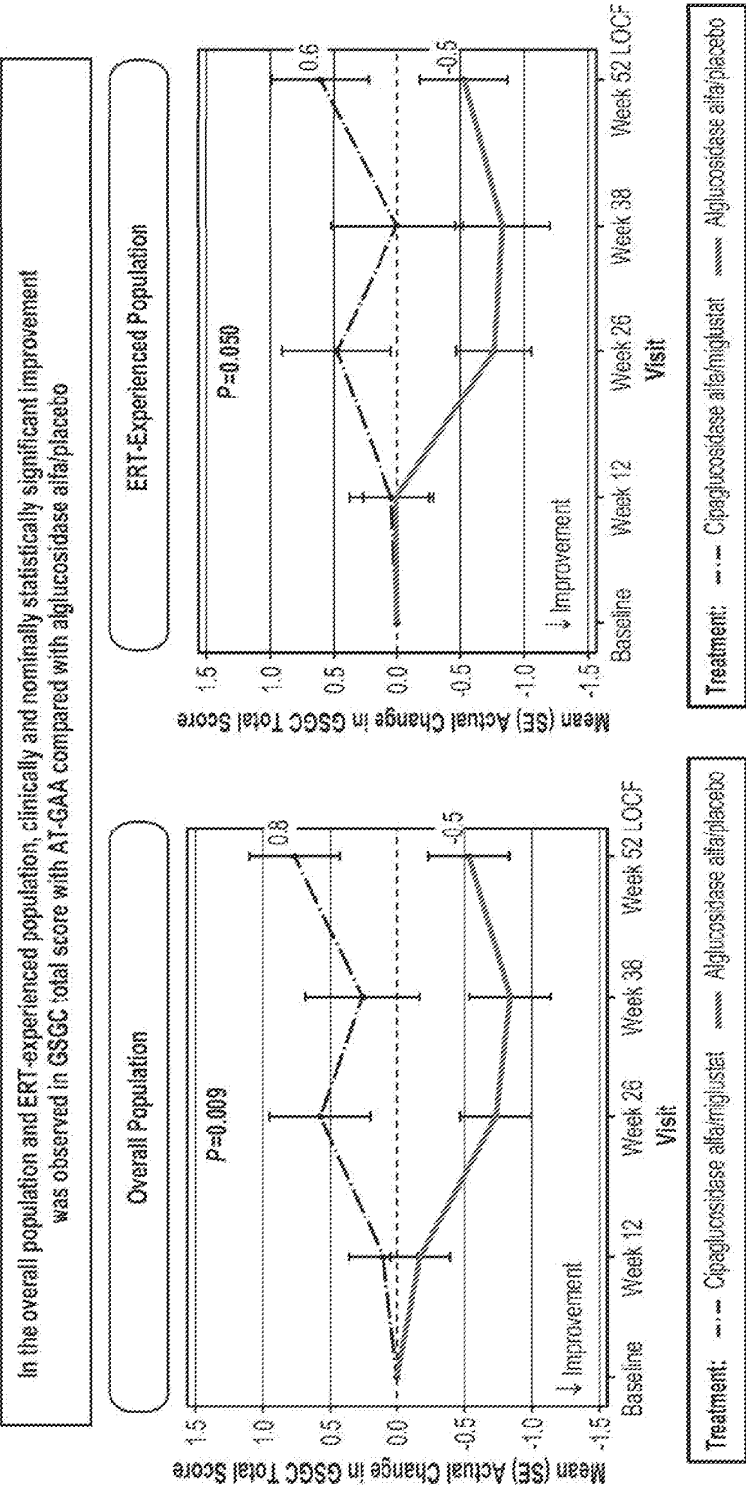
In the overall population and ERT experienced population lower MNT numerically favored AT-GAA.



Note: MMT measured via the Medical Research Criteria (MRC) scale

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Key Secondary: GSGC (Gait, Stairs, Chair)
All Patients and ERT-Experienced Patients



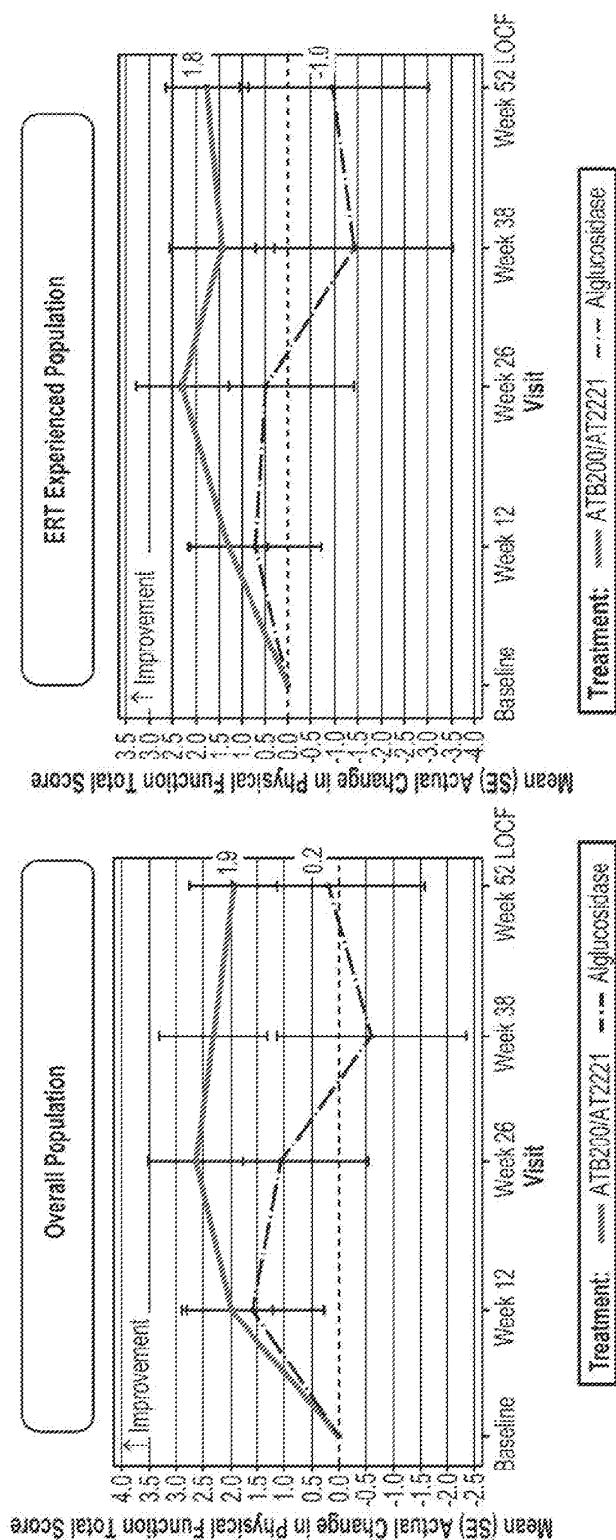
ERT=enzyme-replacement therapy; LOCF=last observation carried forward; SE, standard error.
GSGC total score is the sum of 4 tests and ranges from a minimum of 4 points (normal performance) to a maximum of 27 points (worst score).

Fig. 29

Key Secondary: PROMIS Physical Function
All Patients & ERT Experienced Patients

PROPERTY

In the overall population and EXT experienced population PROMIS physical function numerically favored AT-GAA



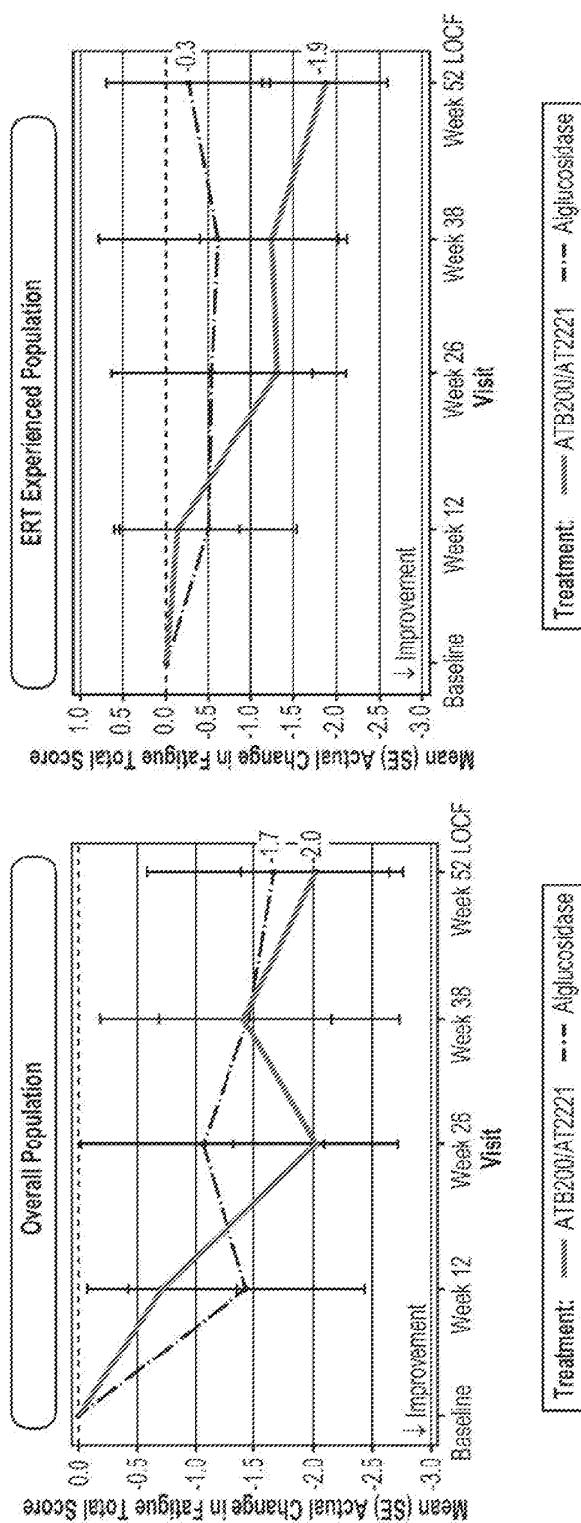
Note: PROMIS-Physical Function Short Form 20a (v2.0) consists of 20 questions scored on a scale from 1 to 5: 1 = unable to do; 5 = not at all; min score 20; max score 100



Key Secondary: PROMIS Fatigue
All Patients & ERT Experienced Patients

PROPEL

In the overall population and ERT experienced population PROMIS fatigue numerically favored AT-GAA



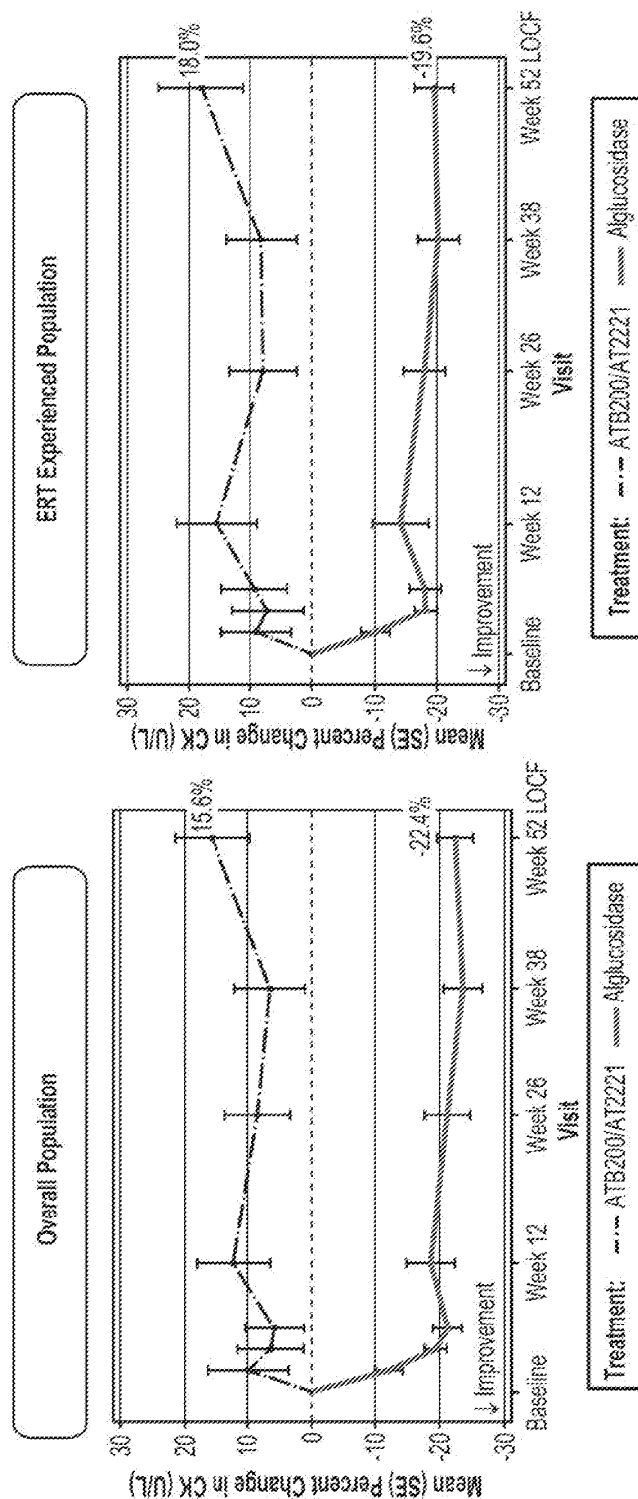
Note: PROMIS - Fatigue Short Form 8a consists of 8 questions scored on a scale from 1 to 5; 1 = not at all; 5 = very much; min score 8 max score 40

[illegible]

Biomarker: Creatine Kinase (CK)
All Patients & ERT Experienced Patients

PROPEL

In the overall population and ERT experienced population reductions in CK were significantly greater with AT-GAA

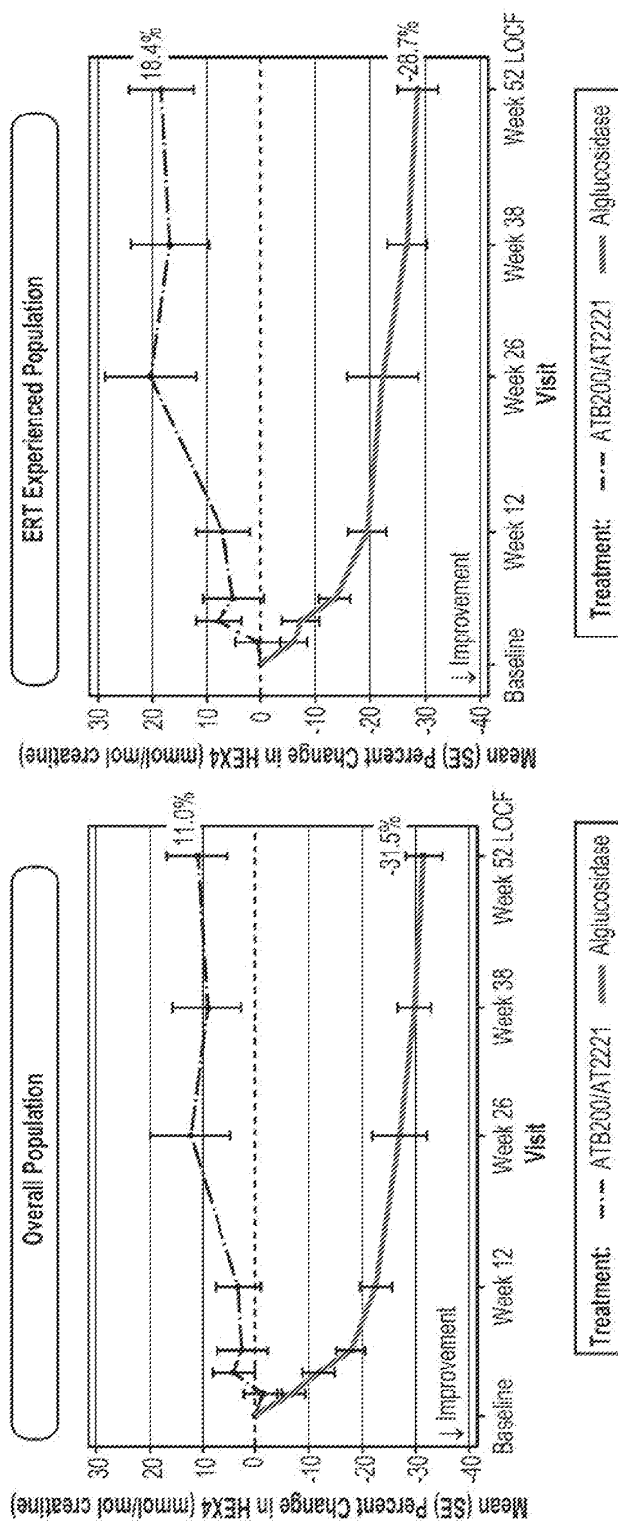


Biomarker: Urinary Hex4

All Patients & ERT Experienced Patients

PROPEL

In the overall population and ERT experienced population reductions in Hex4 were significantly greater with AT-CAA



Primary, Key Secondary and Biomarkers 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 and improved from baseline

Overall Population		ERT-Experienced	
Motor Function	Alglucosidase alfa	AT-GAA	
		6MWD	
		%Predicted 6MWD	
		GSGC*	
		10-meter walk*	
		4-stair climb*	
Pulmonary Function	Gowers		
		Rising from Chair	
		FVC*	
		MIP	
Muscle Strength		MEP	
		Lower MMT	
		Upper MMT	
		Total MMT	
PROs		PROMIS-Physical	
		PROMIS-Fatigue	
Biomarkers		Hex4*	
		CK*	

6MWD=6-minute walk distance; CK=creatinine kinase; FVC=forced vital capacity; GSGC=Gait Stairs; Gowers: Chair; Hex4=hexose tetraaccharide 4; LOCF=last observation carried forward; MEP=maximum expiratory pressure; MIP=maximum inspiratory pressure; MMT=manual muscle test; PRO=patient reported outcome; PROMIS=Patient-reported Outcomes Measurement Information System.
Base on LOCF means; *Nominal P-value <0.05

Fig. 34

Safety Summary		PROPEL	
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

Fig. 35

Executive Summary

- Patients switching to AT-GAA from the approved ERT, aiglucosidase alfa, walked +16.9 meters farther than those treated with standard of care ERT (p=0.046)
- Patients switching to AT-GAA also showed an improvement in percent-predicted forced vital capacity (FVC), the most important measure of respiratory function in Pompe disease, compared to a decline in patients treated with the currently approved ERT (FVC Diff. + 4.1% p=0.006)
- In the overall study population of ERT experienced and ERT naive patients, 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 compared to patients treated with the currently approved ERT (FVC Diff. + 3.0%; p=0.023)
- In the overall study population of ERT experienced and ERT naive patients, AT-GAA outperformed the currently approved ERT (+21 meters compared to +7 meters) which was not statistically significant for superiority (p=0.072)
- 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 (p<0.001)
- 8 of 8 Key Secondary and Biomarker Endpoints favored AT-GAA compared to standard of care in the overall and ERT experienced population

Fig. 36

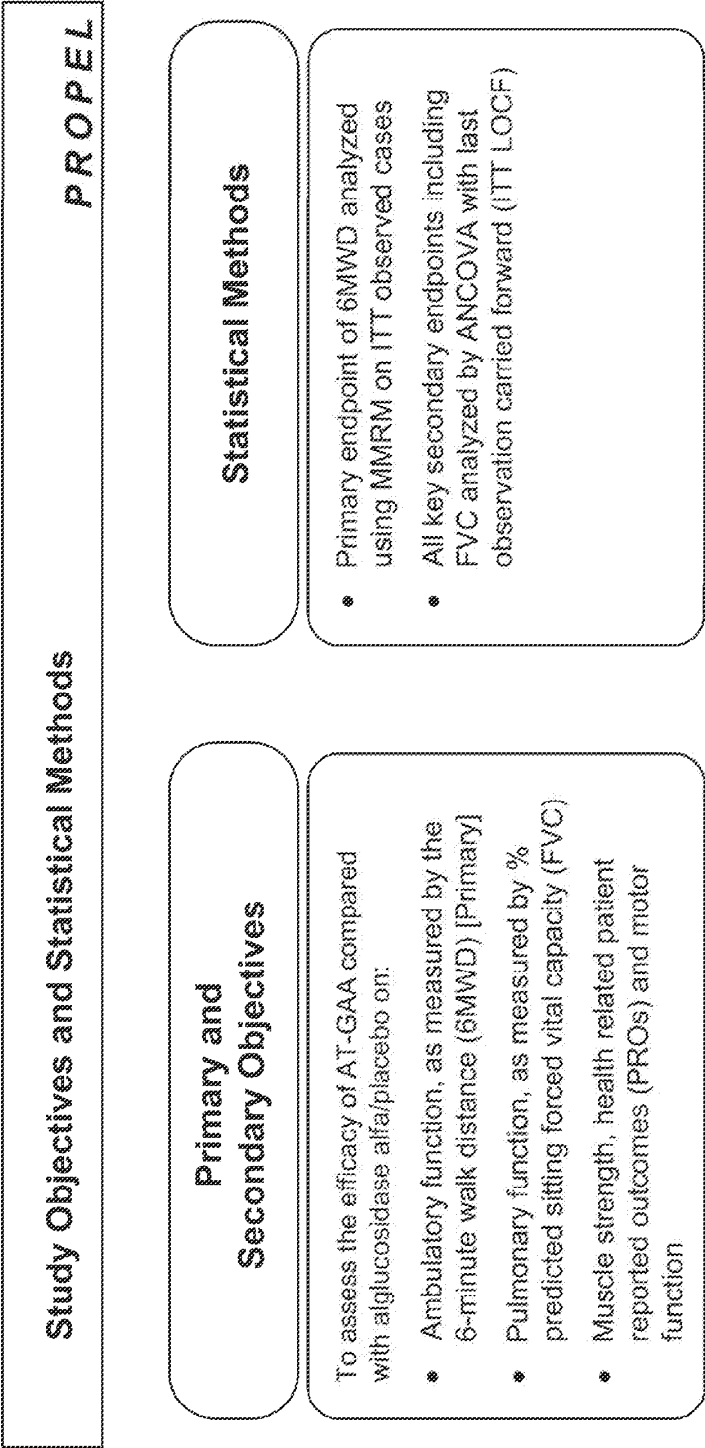


Fig. 37

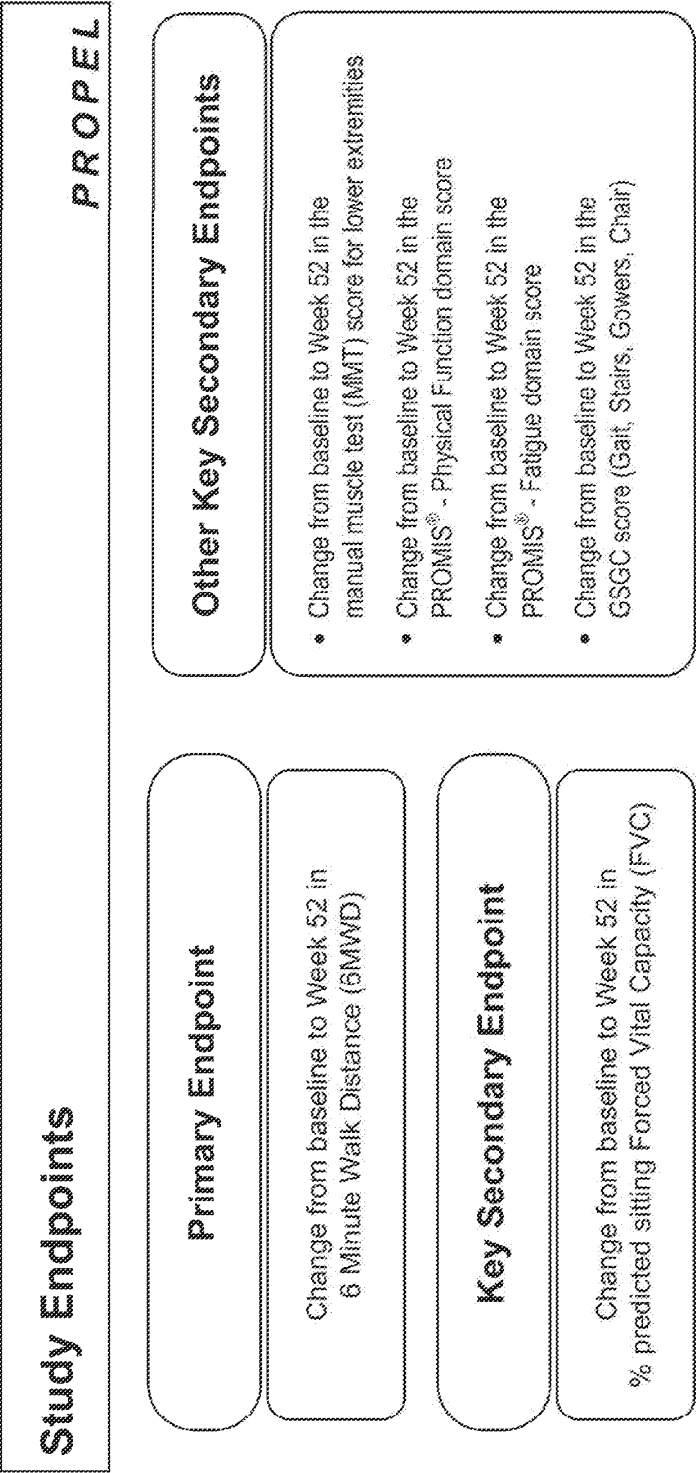


Fig. 38

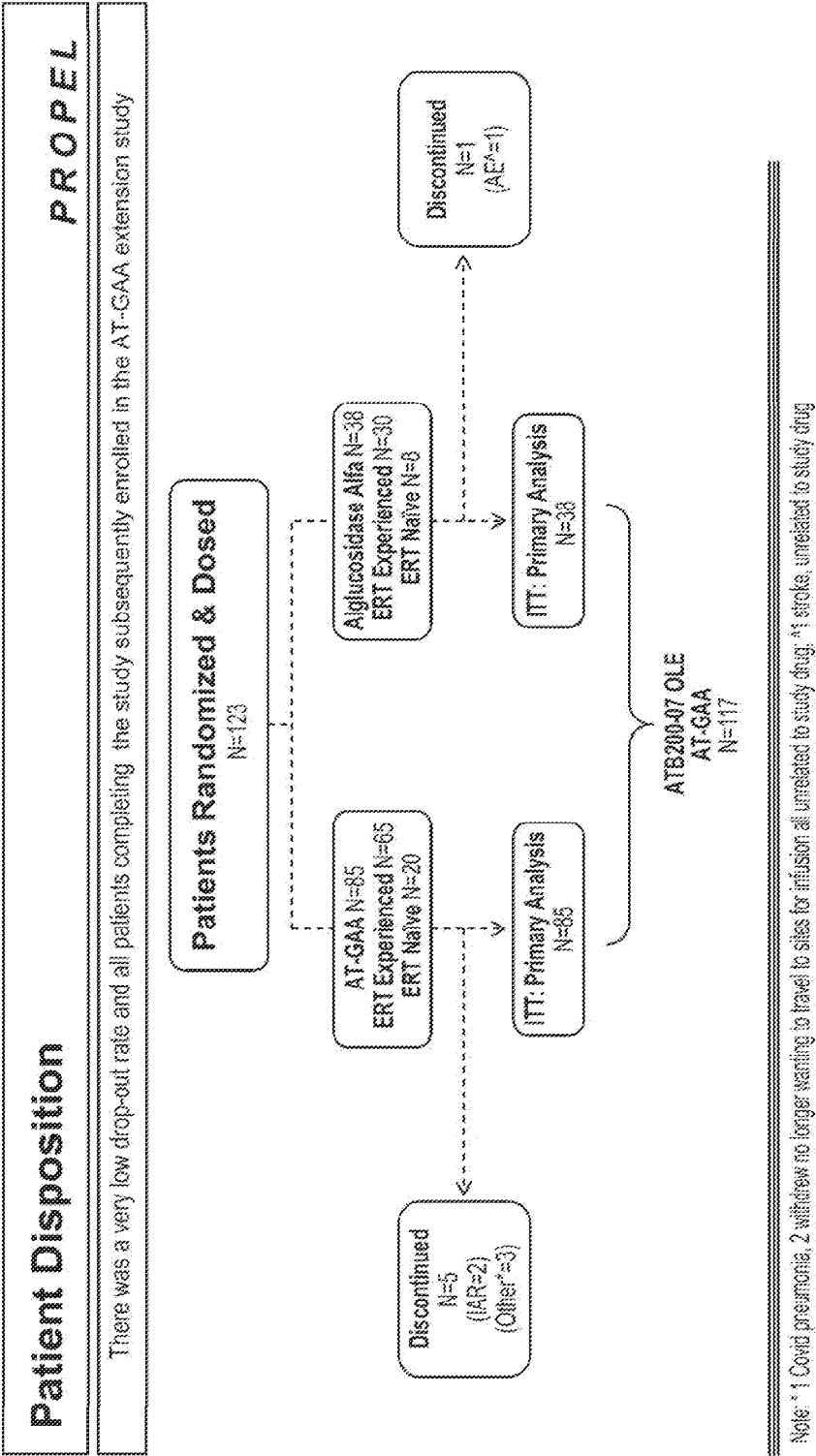


Fig. 39

Baseline Demographics		PROPEL	
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 (57.4)
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)

Fig. 40

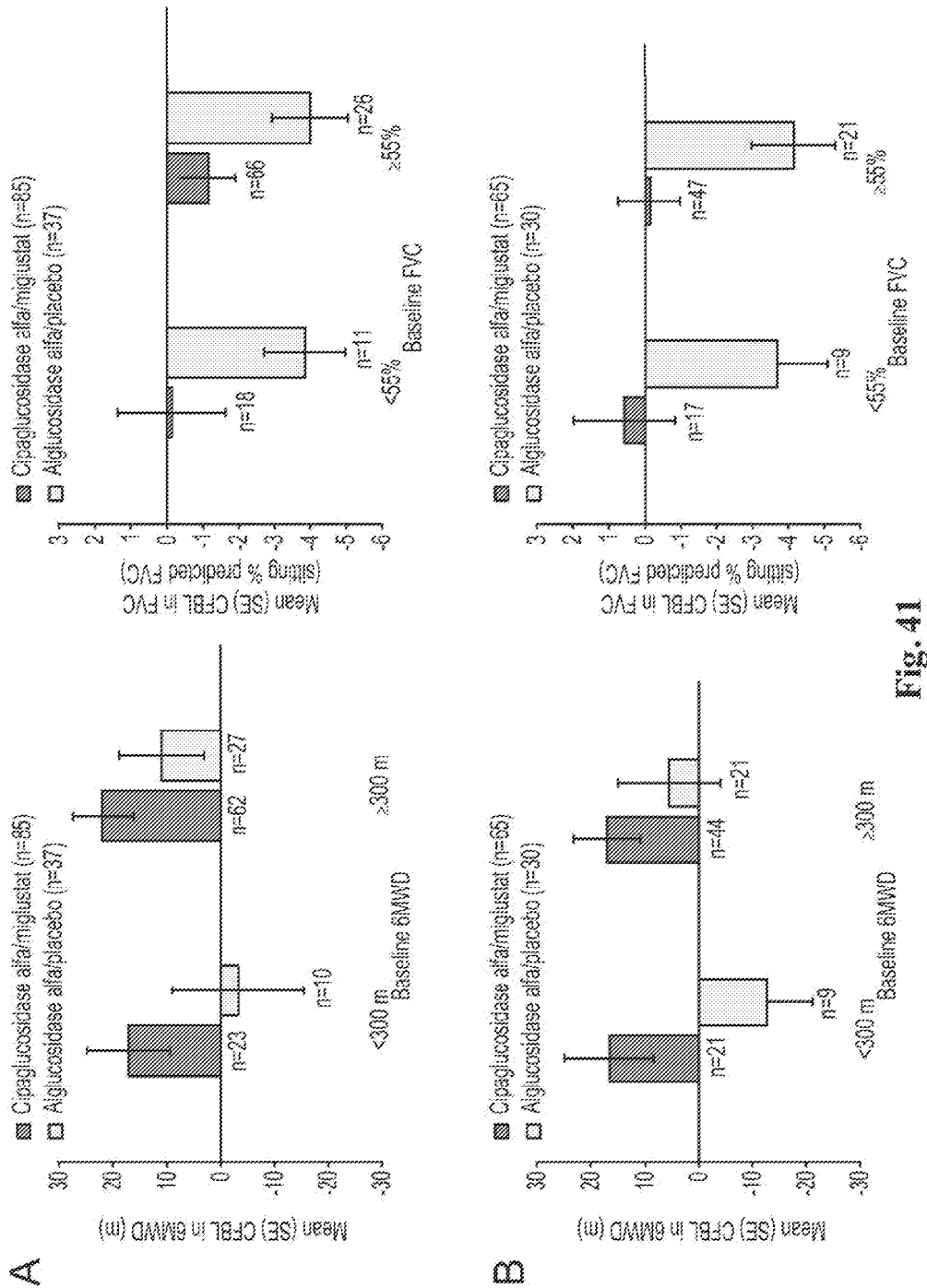
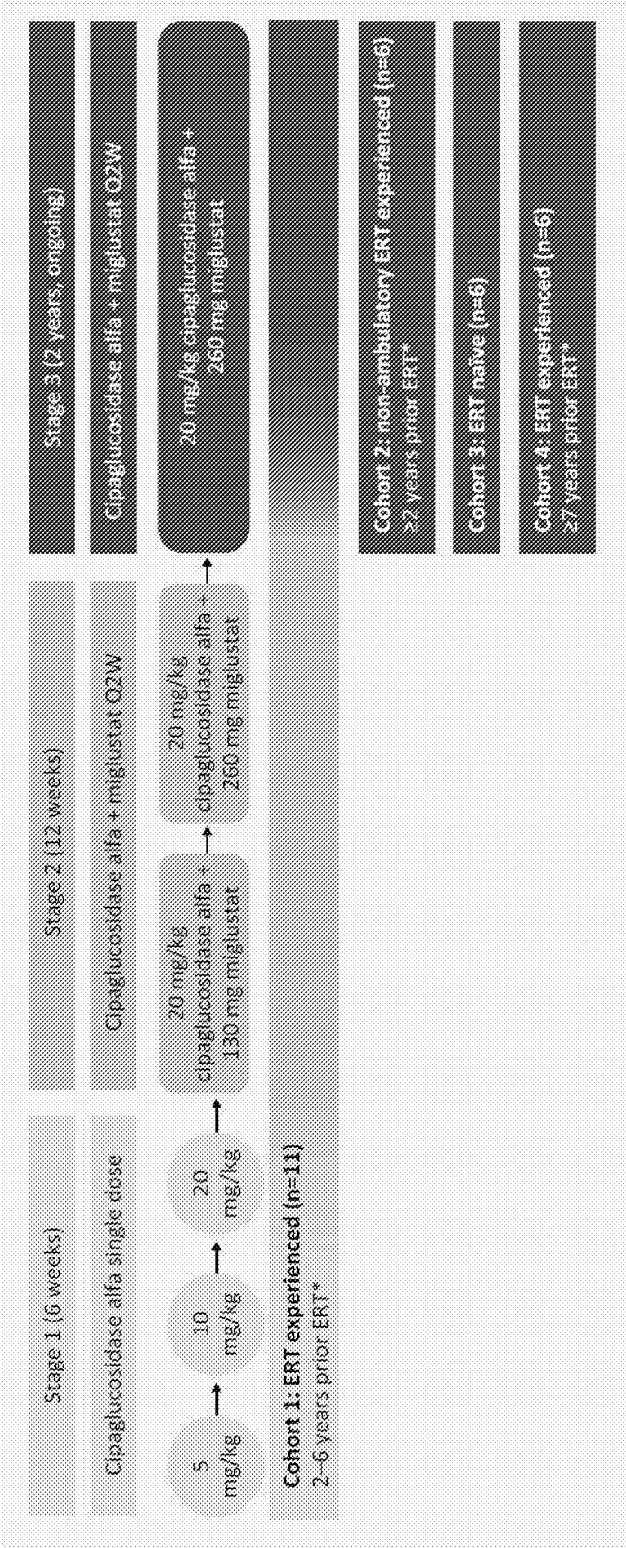


Fig. 41

TEAE	Cipaglucosidase alfa/ mglustat n=85	Alglucosidase alfa/ placebo n=38
Fall	25 (29.4)	15 (39.5)
Headache	20 (23.5)	9 (23.7)
Nasopharyngitis	19 (22.4)	3 (7.9)
Myalgia	14 (16.5)	5 (13.2)
Arthralgia	13 (15.3)	5 (13.2)
Urinary tract infection	12 (14.1)	2 (5.3)
Diarrhoea	11 (12.9)	4 (10.5)
Pain in extremity	11 (12.9)	2 (5.3)
Nausea	10 (11.8)	8 (21.1)
Musculoskeletal pain	10 (11.8)	2 (5.3)
Oropharyngeal pain	10 (11.8)	2 (5.3)
Back pain	9 (10.6)	7 (18.4)
Fatigue	8 (9.4)	5 (13.2)

Data are n (%).

Fig.42



*With 20 mg/kg alglucosidase alfa Q2W, every 2 weeks.

FIG. 43

Assessments	ERT experienced*		ERT naïve Cohort 3
	Cohort 1 (2–6 years)	Cohort 4 (≥7 years)	
Motor function • 6MWD	Pooled data		✓
Respiratory function • FVC	Pooled data		✓
Muscle strength • MMT lower extremity score	Pooled data		✓
Biomarkers • Hex4 and CK	Pooled data		✓
Safety	Pooled data		✓
	Pooled data		

*With 20 mg/kg alglucosidase alfa Q2W. 6MWD, 6-minute walk distance; CK, creatine kinase; FVC, forced vital capacity; Hex4, glucose tetrasaccharide; MMT, manual muscle test.

FIG. 44

	ERT experienced		ERT naïve Cohort 3 n=6
	Cohort 1 2–6 years prior ERT n=11*	Cohort 4 ≥7 years prior ERT n=6	
Baseline characteristics			
Median (range) age, years	50.0 (28–66)	43.0 (20–65)	51.0 (24–65)
Sex, M:F	9:2	2:4	1:5
Mean (SD) time on alglucosidase alfa, years	4.7 (1.4)	9.4 (1.2)	N/A†
Mean (SD) 6MWD, m	397.2 (96.8)	387.3 (161.3)	396.0 (75.2)
Mean (SD) sitting FVC, % predicted	52.6 (13.9)	65.3 (21.1)	57.2 (20.8)
Mean (SD) MMT lower extremity score	31.8 (1.9)	27.3 (3.7)	29.0 (1.7)
Patient disposition			
Ongoing in study, n (%)	9 (82)	6 (100)	6 (100)

*All enrolled patients were included in both the efficacy and safety populations, except one patient in Cohort 1 who was excluded from the efficacy population as the patient withdrew consent prior to post-baseline efficacy assessments. †1 ERT-naïve patient had received 1 dose of alglucosidase alfa >6 months prior to study entry. m, meters; M:F, male:female; N/A, not applicable; SD, standard deviation.

FIG. 45

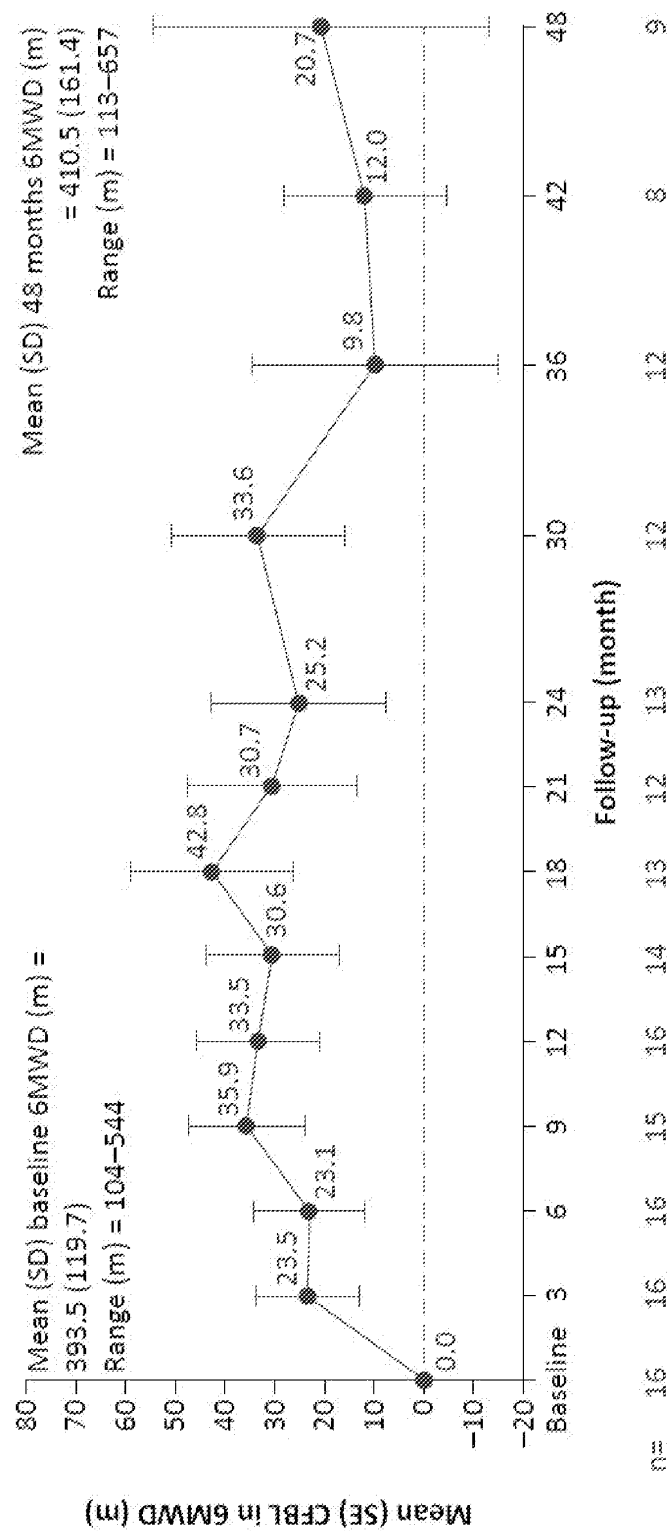


FIG. 46A

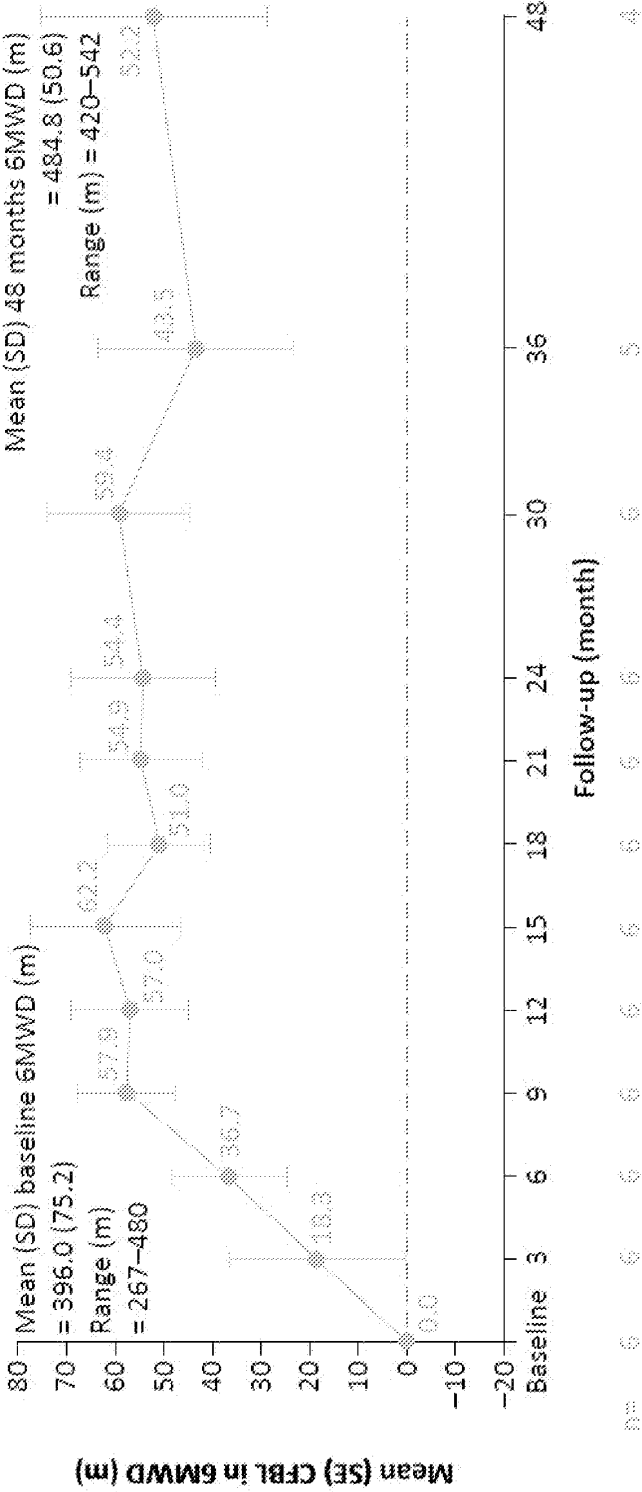


FIG. 46B

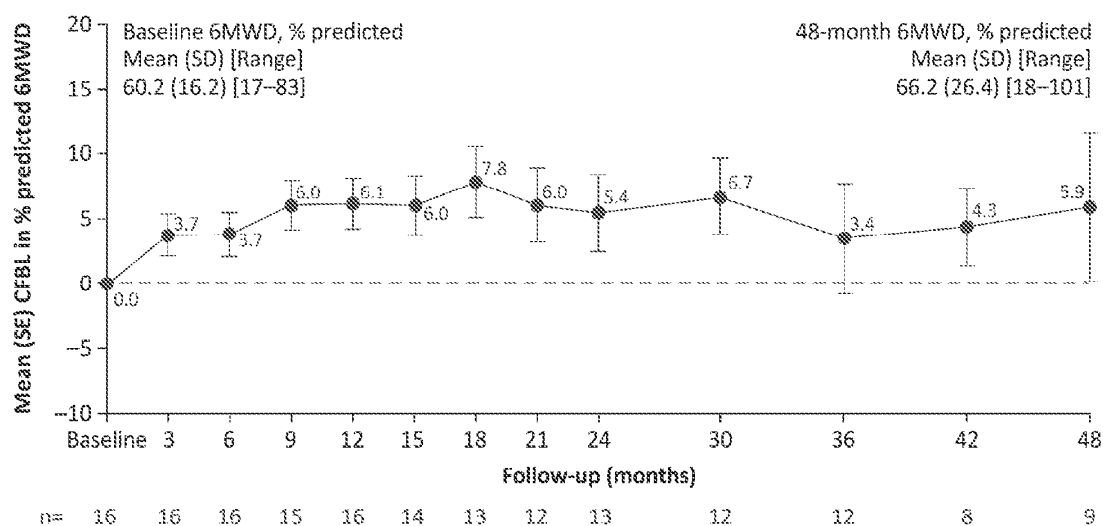


FIG. 46C

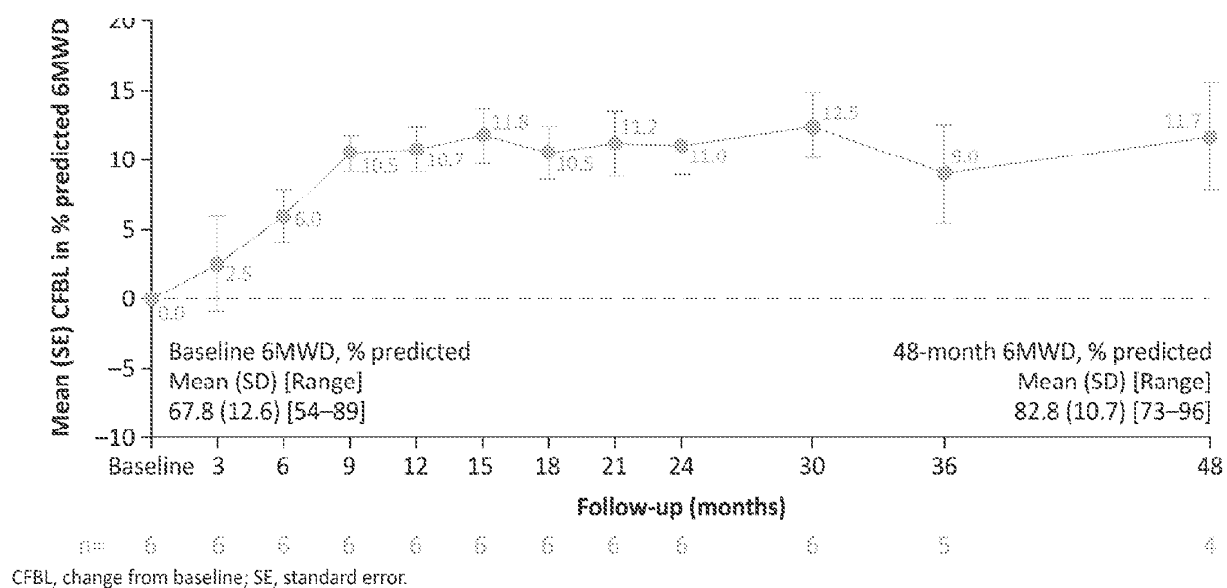


FIG. 46D

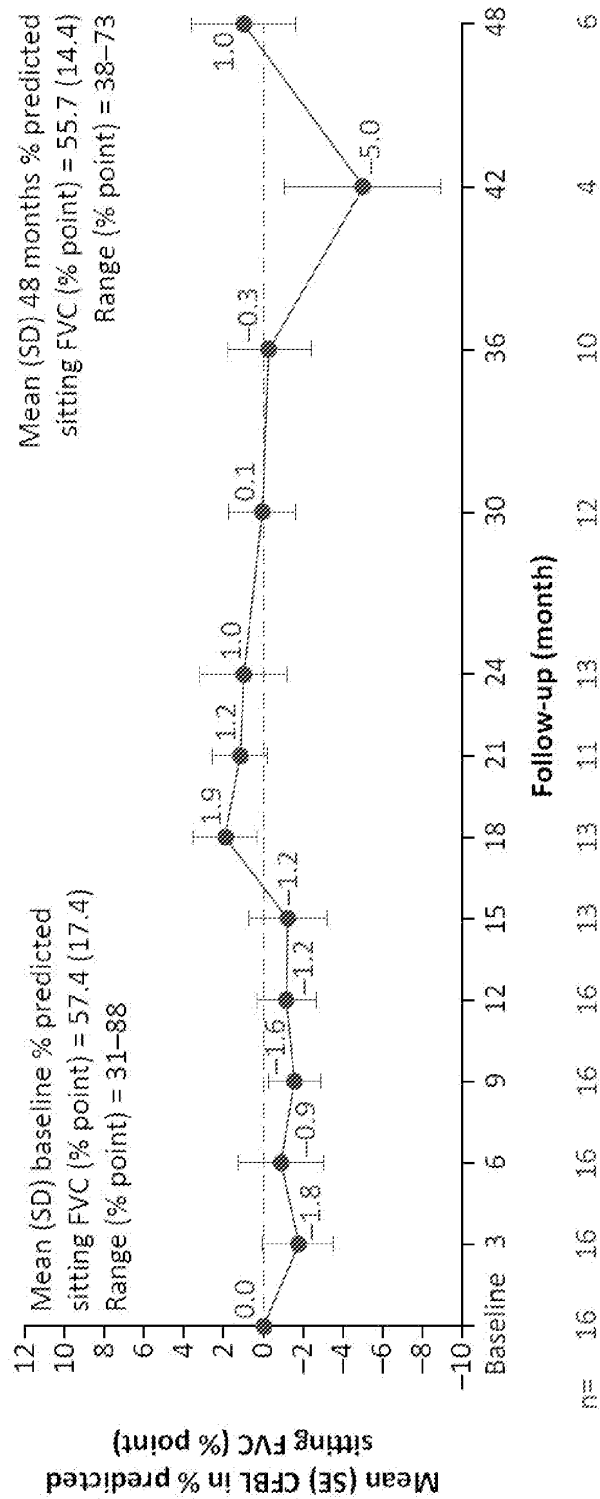
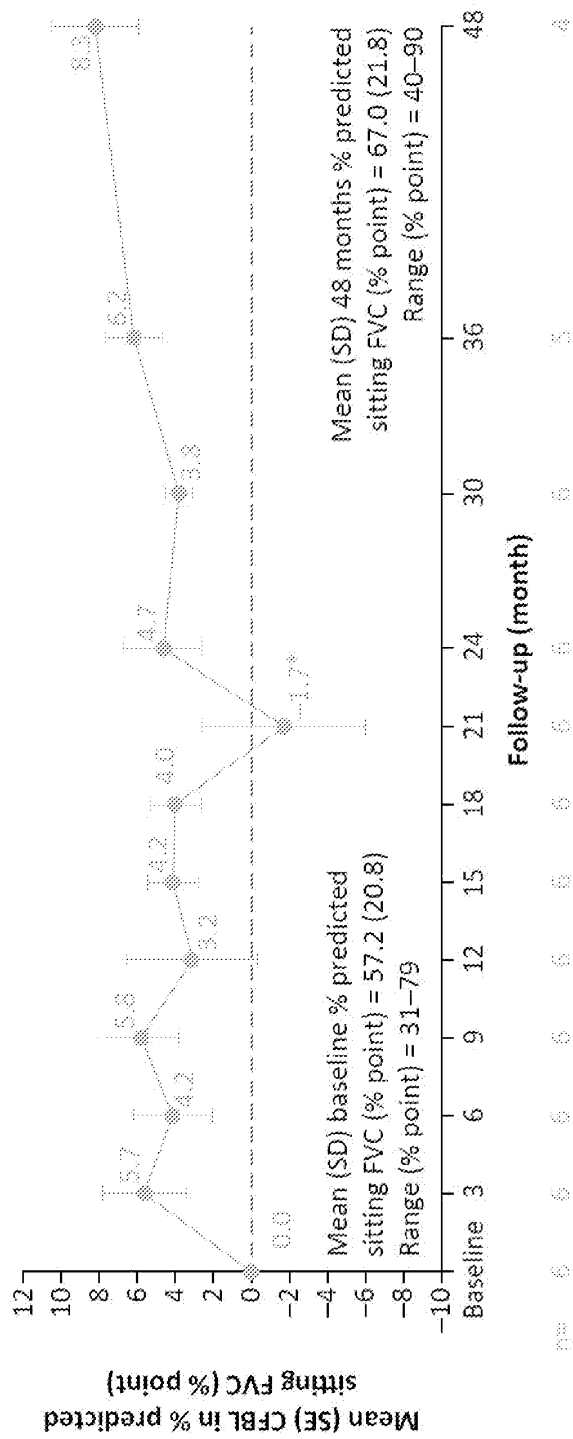


FIG. 47A



*One patient in the ERT-naïve cohort experienced a large drop in % predicted FVC at month 21, which returned to previous levels at the following visit (month 24).

FIG. 47B

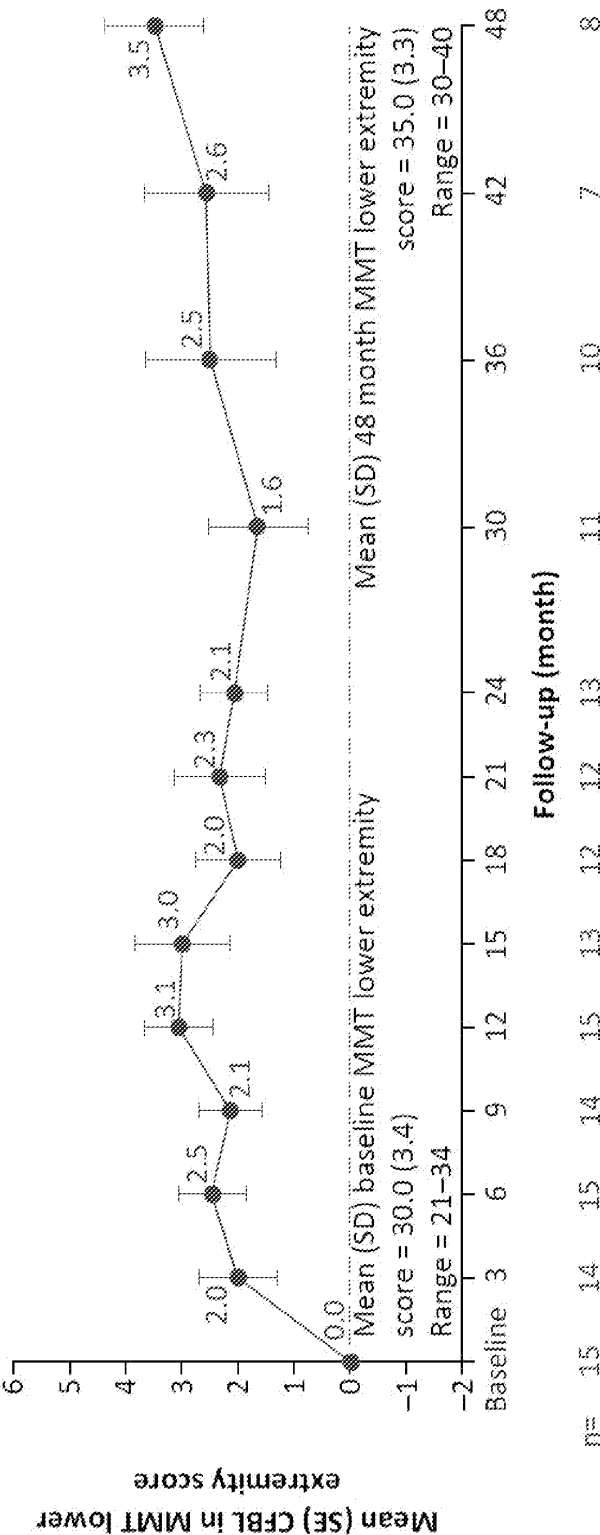


FIG. 48A

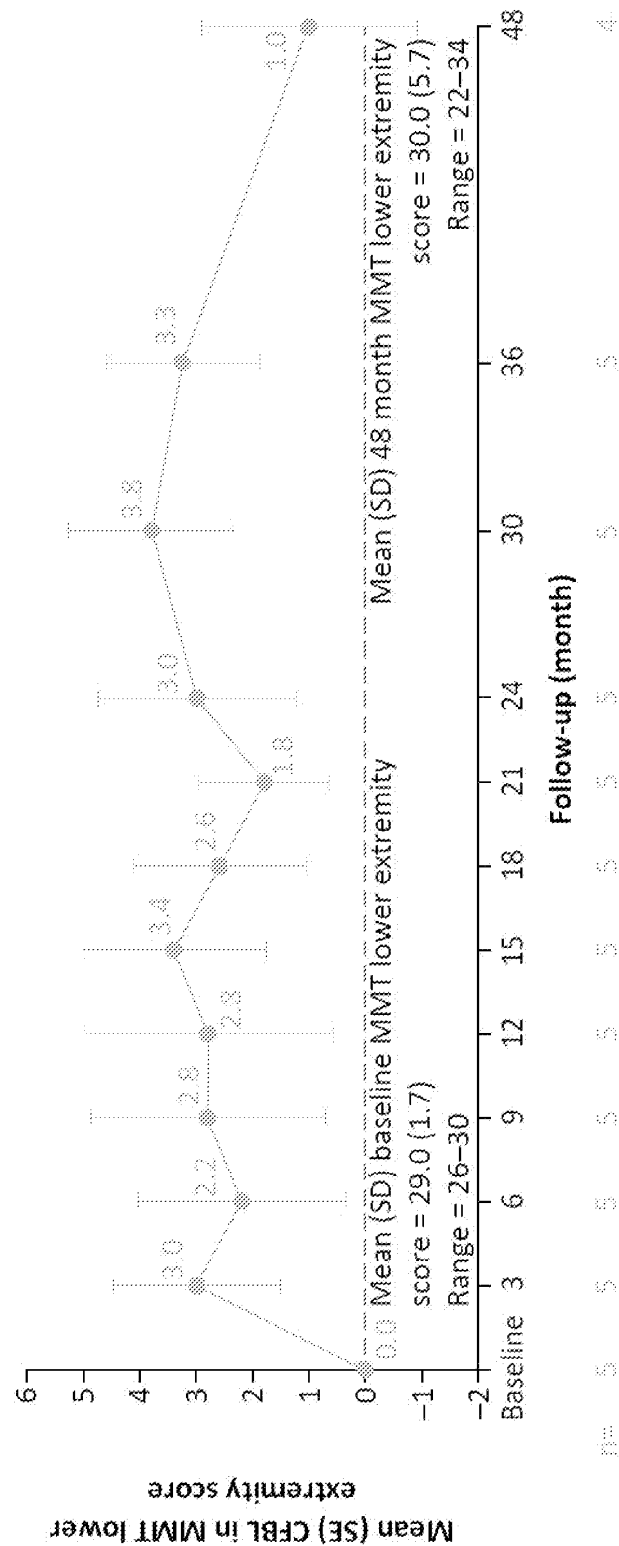


FIG. 48B

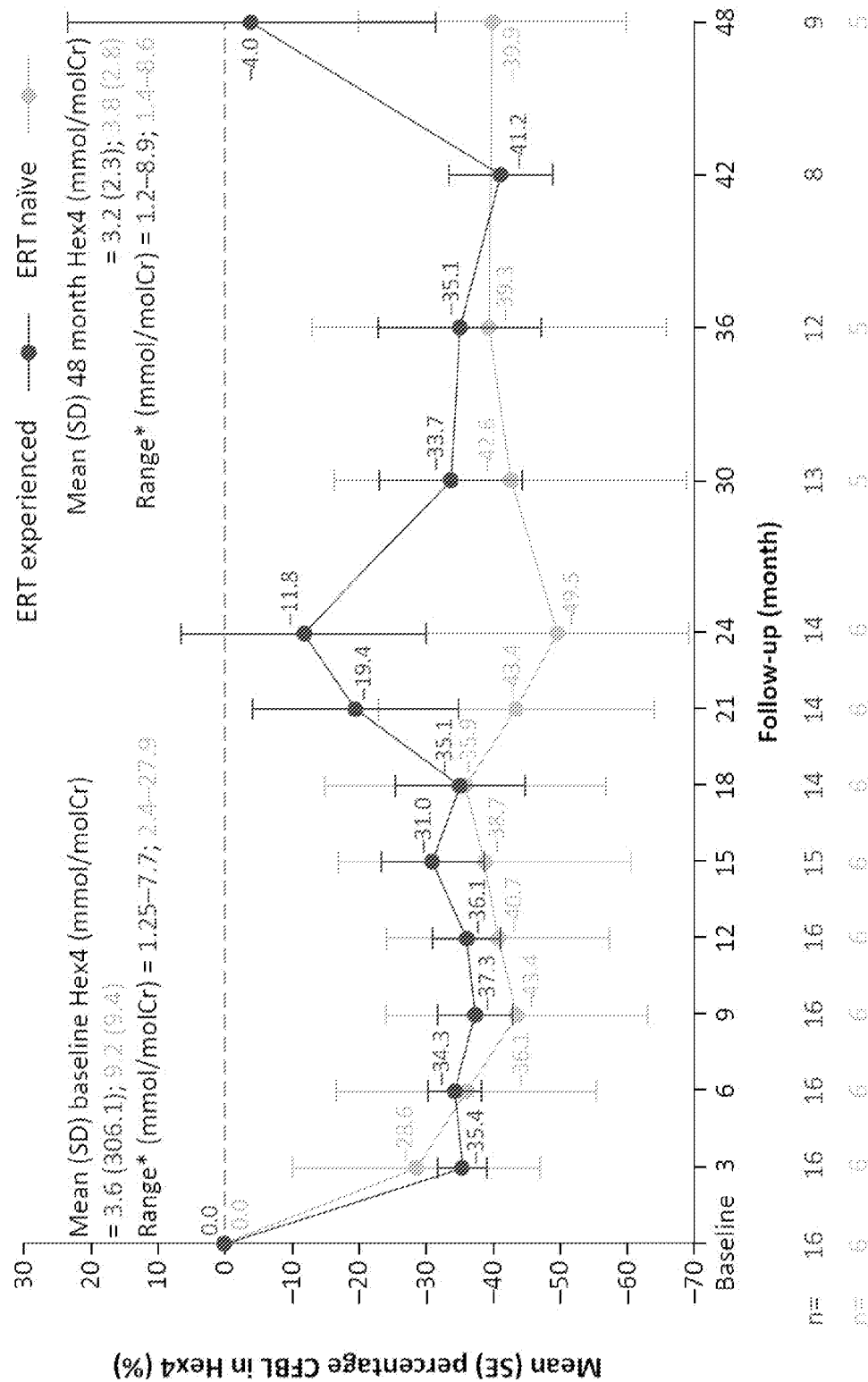


FIG. 49A

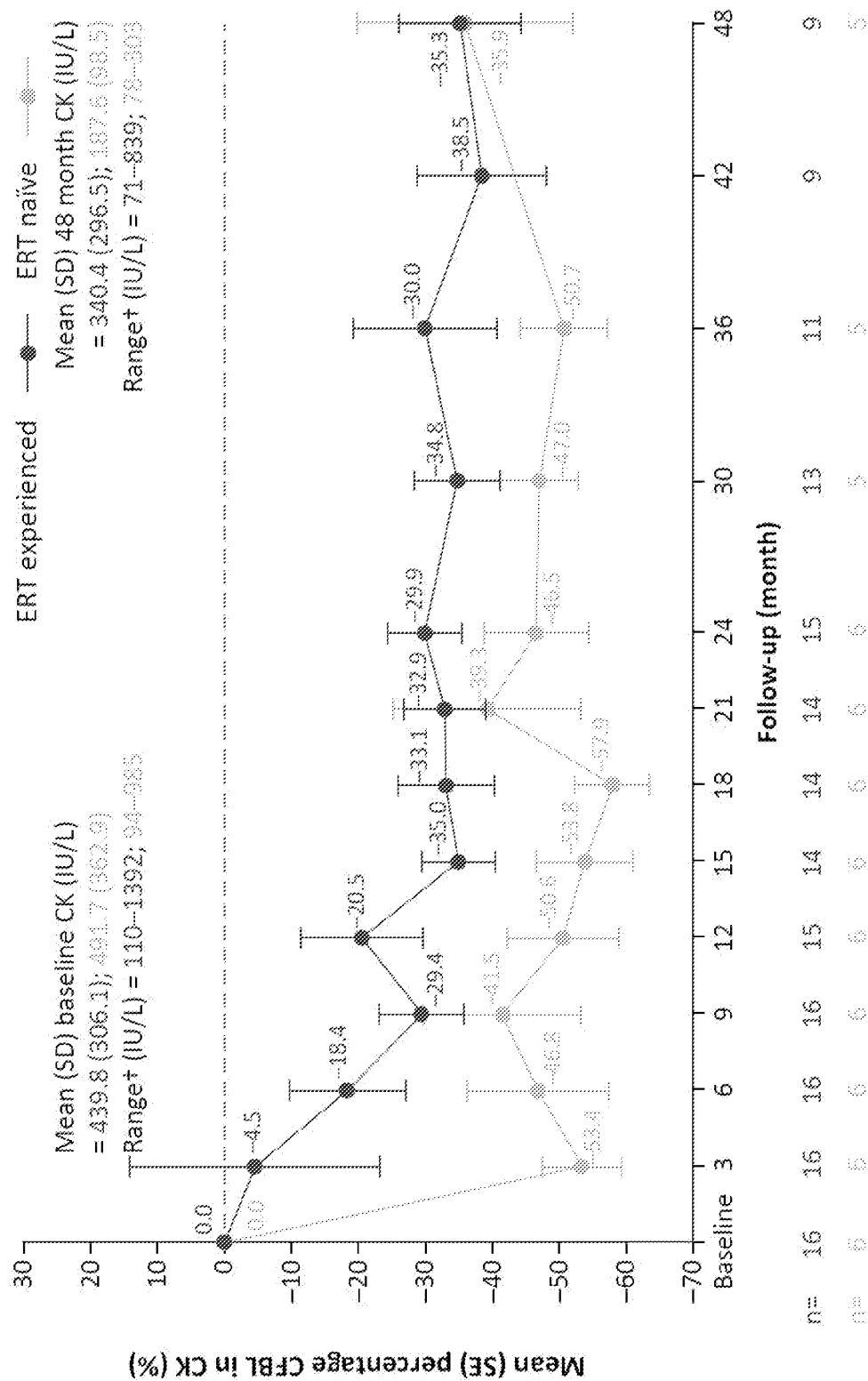
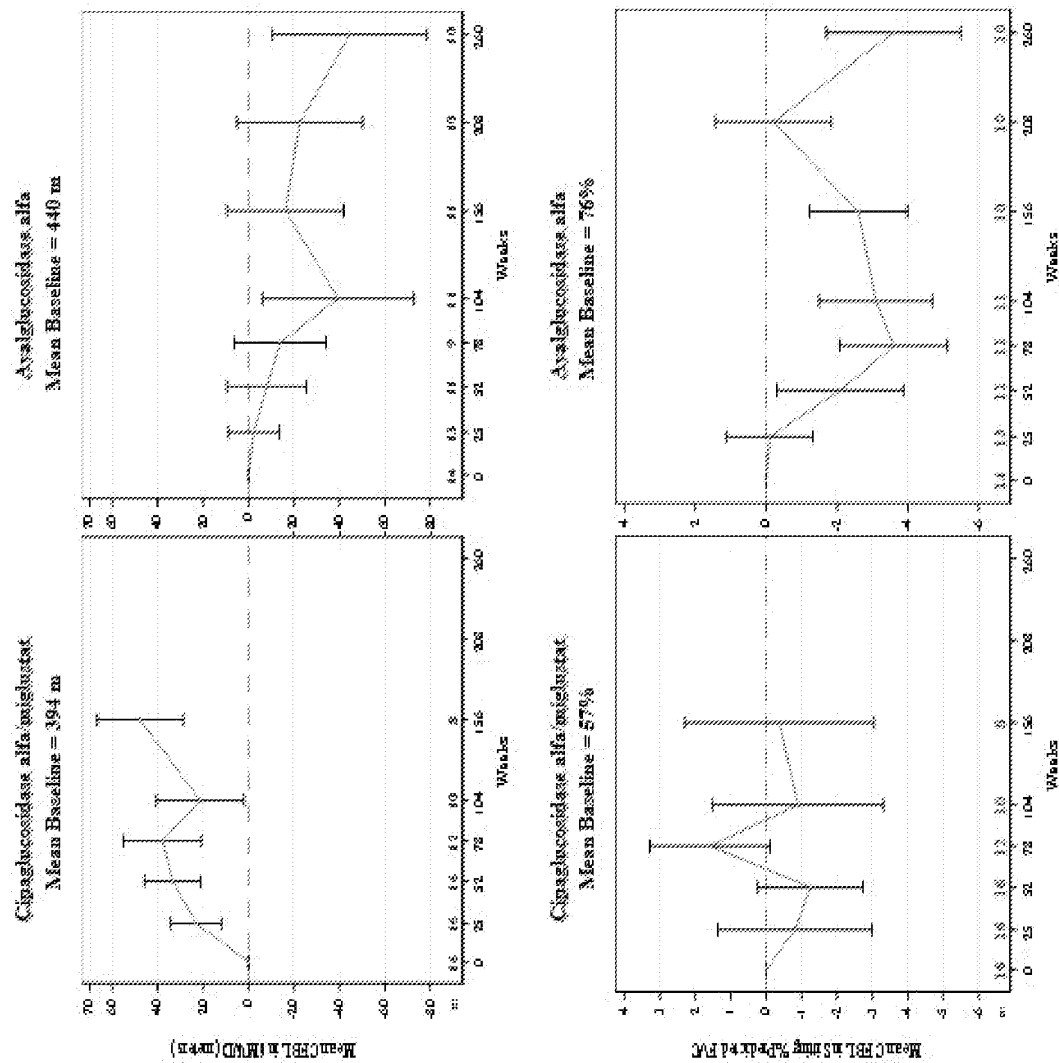


FIG. 49B

	ERT experienced n=17	ERT naive n=6	Overall N=23
TEAEs, n (%)	17 (100)	6 (100)	23 (100)
TEAEs potentially related to treatment	11 (65)	4 (67)	15 (65)
Serious TEAEs	6 (35)	4 (67)	10 (44)
Serious TEAEs potentially related to treatment	1 (6)	2 (33)	3 (13)
TEAEs leading to study withdrawal	1 (6)*	0 (0)	1 (4)
TEAEs leading to death	0 (0)	0 (0)	0 (0)
IARs	8 (47)	3 (50)	11 (48)

TEAEs have an onset date on or after first dose of study drug. *Diffuse large B-cell lymphoma. IAR, infusion-associated reaction.

FIG. 50



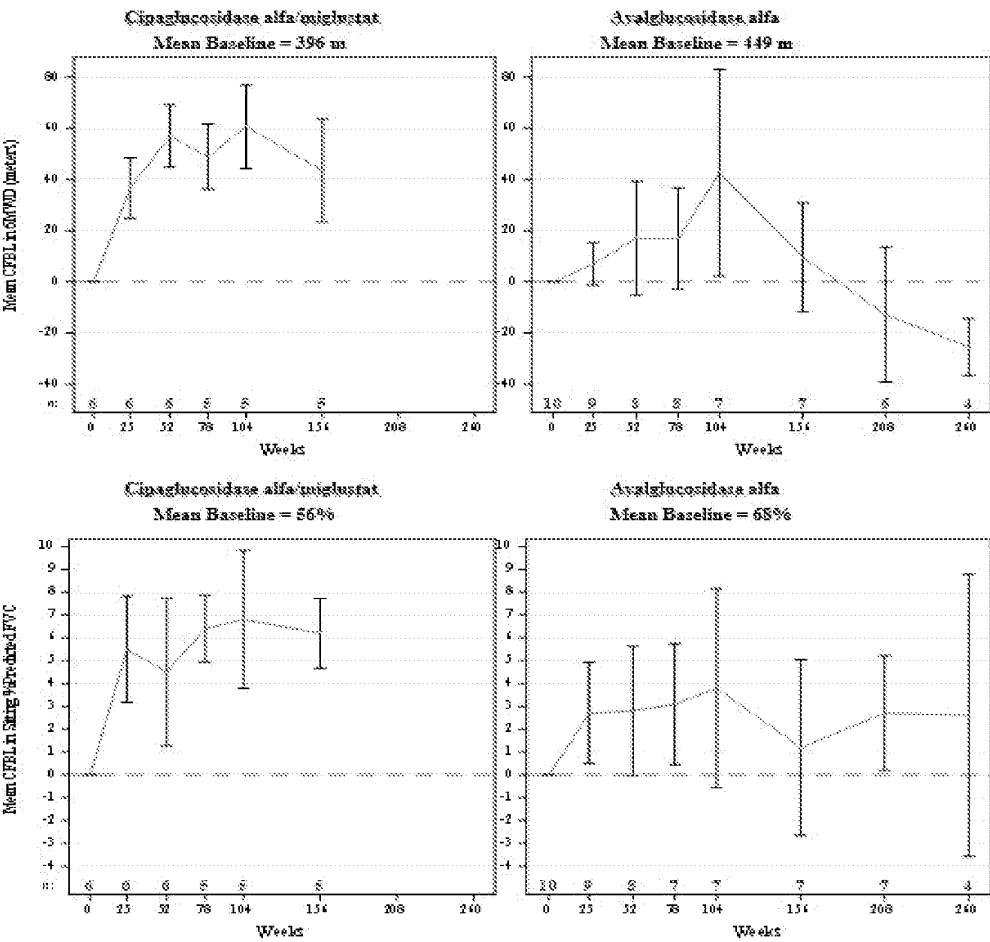


FIG. 52

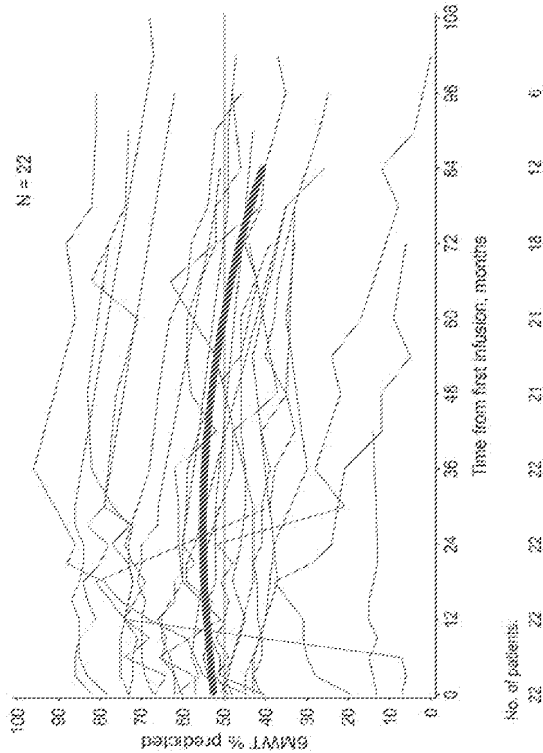


FIG. 53A

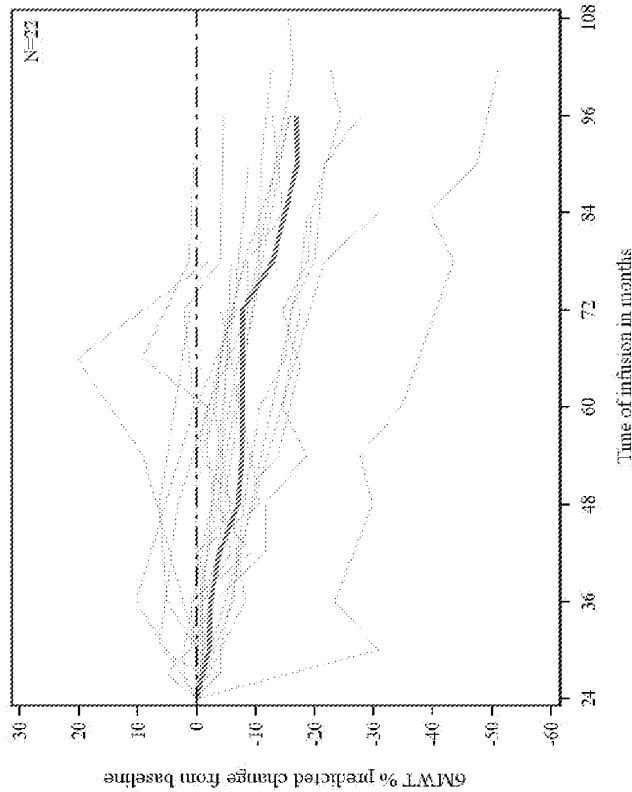


FIG. 53B

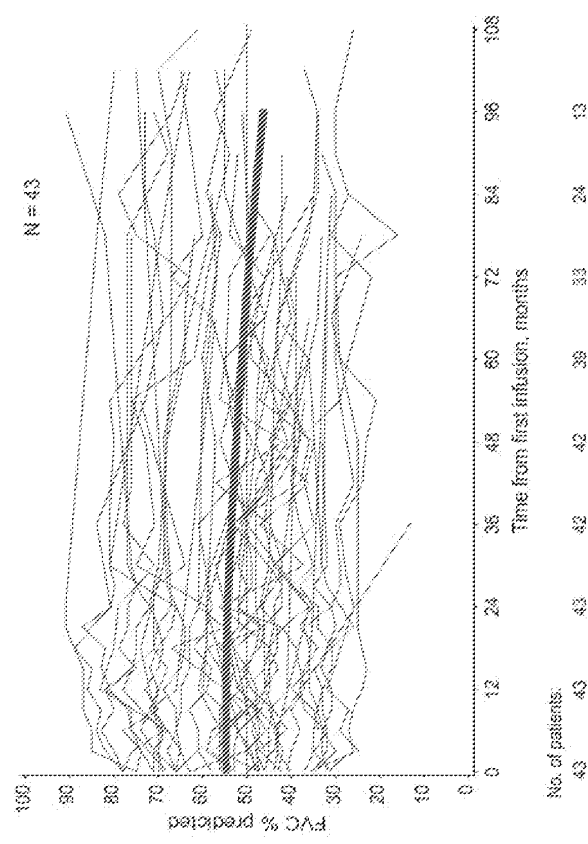


FIG. 54

Summary of endpoints and cohorts reported in non-ambulatory ERT-experienced patients (cohort 2)

- Cohort 2 included 6 non-ambulatory ERT-experienced patients
 - Non-ambulatory was defined as those who use a wheelchair and are unable to walk assisted

Cohort 2 ≥2 years prior ERT*	
Assessments	
6MWD	Data not collected
FVC	✓
MMT lower extremity score	Data not collected
MMT total score (upper body)	✓
CK and Hex4	✓
Safety	✓

*With 20 mg/kg alglucosidase alfa Q2W. 6MWD, 6-minute walk distance; CK, creatine kinase; ERT, enzyme replacement therapy; FVC, forced vital capacity; Hex4, glucose tetrasaccharide; MMT, manual muscle test.

FIG. 55

Baseline characteristics and patient disposition of non-ambulatory ERT-experienced patients (cohort 2)

Cohort 2 ≥2 years prior ERT N=6	
Baseline* characteristics	
Median (range) age, years	49.5 (18–57)
Sex, M:F	4:2
Mean (SD) time on alglucosidase alfa, years	10.1 (4.8)
Mean (SD) sitting FVC, % predicted	42.3 (28.2)
Mean (SD) MMT total score (upper body)	18.4 (14.0)
Patient disposition	
Ongoing in study, n (%)	5 (83)

*Baseline assessment is the last non-missing result on or prior to the administration of the first dose of study medication (20 mg/kg cipagucosidase alfa + 260 mg miglustat co-administration dose). M:F, male:female; SD, standard deviation.

FIG. 56

CFBL in multiple endpoints and biomarkers for non-ambulatory ERT-experienced patients (cohort 2)

Endpoint	Follow-up (months)							
	12		24		36		48	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
% predicted sitting FVC, % point	2	2.5 (9.2)	1	2.0 (N/A)	2	-2.0 (7.1)	1	-1.0 (N/A)
MMT total score (upper body)	4	1.3 (3.4)	4	2.0 (6.6)	4	-0.8 (10.7)	N/A	N/A
Hex4, %	5	-15.6 (16.7)	5	-34.1 (14.1)	4	-36.5 (23.1)	2	-4.0 (82.6)
CK, %	5	-20.8 (8.8)	5	-25.3 (16.8)	4	-27.1 (32.4)	2	-23.7 (23.9)

CFBL, change from baseline; N/A, not applicable.

FIG. 57

Safety summary in non-ambulatory ERT-experienced patients (cohort 2)

	Cohort 2 ≥2 years prior ERT N=6
TEAEs, n (%)	6 (100)
TEAEs potentially related to treatment	5 (83)
Serious TEAEs	2 (33)
Serious TEAEs potentially related to treatment	1 (17)
TEAEs leading to study withdrawal	1 (17)*
Severe TEAEs	2 (33)
TEAEs leading to death	0 (0)
IARs	2 (33)

- Mean (SD) duration of treatment was 46.3 (22.86) months
- The most common TEAEs were nasopharyngitis and diarrhea (both occurred in 3 patients); most TEAEs were mild or moderate in severity and did not lead to study withdrawal

*Urticaria considered to be an IAR. IAR, infusion-associated reaction; TEAE, treatment-emergent adverse event with onset date on or after first dose of study drug.

FIG. 58

Trial name	Population	Treatment	N	Age, mean (SD)	Male (%)	White (%)	ERT duration in years, mean (SD)	6MWD in metres, mean (SD)	Sitting FVC (% predicted), mean (SD)
LOTS ¹	ERT naïve	Aglu	60	45.3 (12.4)	57.0	95.0	0 (0)	332.2 (126.7)	55.4 (14.4)
	ERT naïve	Placebo	30	42.6 (11.6)	37.0	90.0	0 (0)	317.9 (132.3)	53.0 (15.7)
LOTS OLE ²	ERT naïve	Aglu	28	44.1 (11.6)	37.0	90.0	0 (0)	313.0 (147.0)	51.1 (15.8)
	ERT naïve	Aval	10	44.6 (20.3)	30.0	80.0	0 (0)	449.0 (116.0)	59.2 (13.3)
NEO-1/EXP ³	ERT experienced	Aval	14	46.7 (14.1)	64.0	93.0	4.0 (2.0)	440.0 (141.0)	77.3 (16.5)
	ERT naïve	Aval	51	46.0 (14.5)	52.9	92.2	0 (0)	399.3 (110.9)	62.5 (14.4)
COMET ⁴	ERT naïve	Aglu	49	50.3 (13.7)	51.0	96.9	0 (0)	376.1 (116.2)	61.6 (12.4)
	ERT experienced	Aval	43	50.3 (13.7)	51.0	96.0	0.94 (0)	384.0 (141.0)	61.2 (13.5)
ATB200-02 ⁵	ERT experienced	Cipa+mg	17	46.7 (36.0)	85.0	81.0	6.36 (1.3)	394.0 (120.0)	57.1 (17.9)
	ERT naïve	Cipa+mg	6	46.1 (39.1)	17.0	70.0	0 (0)	396.0 (75.0)	55.8 (15.1)
PROPEL ⁷	ERT naïve and ERT experienced	Cipa+mg	85	47.6 (13.3)	42.4	87.1	5.7 (4.3)	357.9 (111.6)	70.7 (19.6)
	ERT naïve and ERT experienced	Aglu ⁶	37	45.4 (13.4)	51.4	78.4	5.6 (4.3)	351.0 (121.3)	70.0 (21.3)

¹One patient in the Aglu placebo group who completed the study was deemed to have deliberately underperformed in eligibility assessments at baseline and was excluded from the efficacy analyses.

6MWD, 6-minute walking distance; ERT, enzyme replacement therapy; FVC, forced vital capacity; SD, standard deviation.

²van der Ploeg AT et al. *N Engl J Med* 2010;362:1195–1402. ³van der Ploeg AT et al. *Mol Genet Metab* 2012;107:485–91. ⁴Center for Drug Evaluation and Research, FDA Integrated Review 76184 Nervazyme (Avalglucosidase Alfa-Napp). ⁵2021. ⁶Comanche Mill et al. *Neurology* 2022;99:5536–43. ⁷Dias-Narves J et al. *Lancet Neurol* 2021;20:1012–26. ⁸Pyne BJ et al. Poster presented at Muscular Dystrophy Association (MDA) Clinical & Scientific Conference 2022. P92. <https://www.mdaonline.org/2022/03/2022-03-27>.

FIG. 59

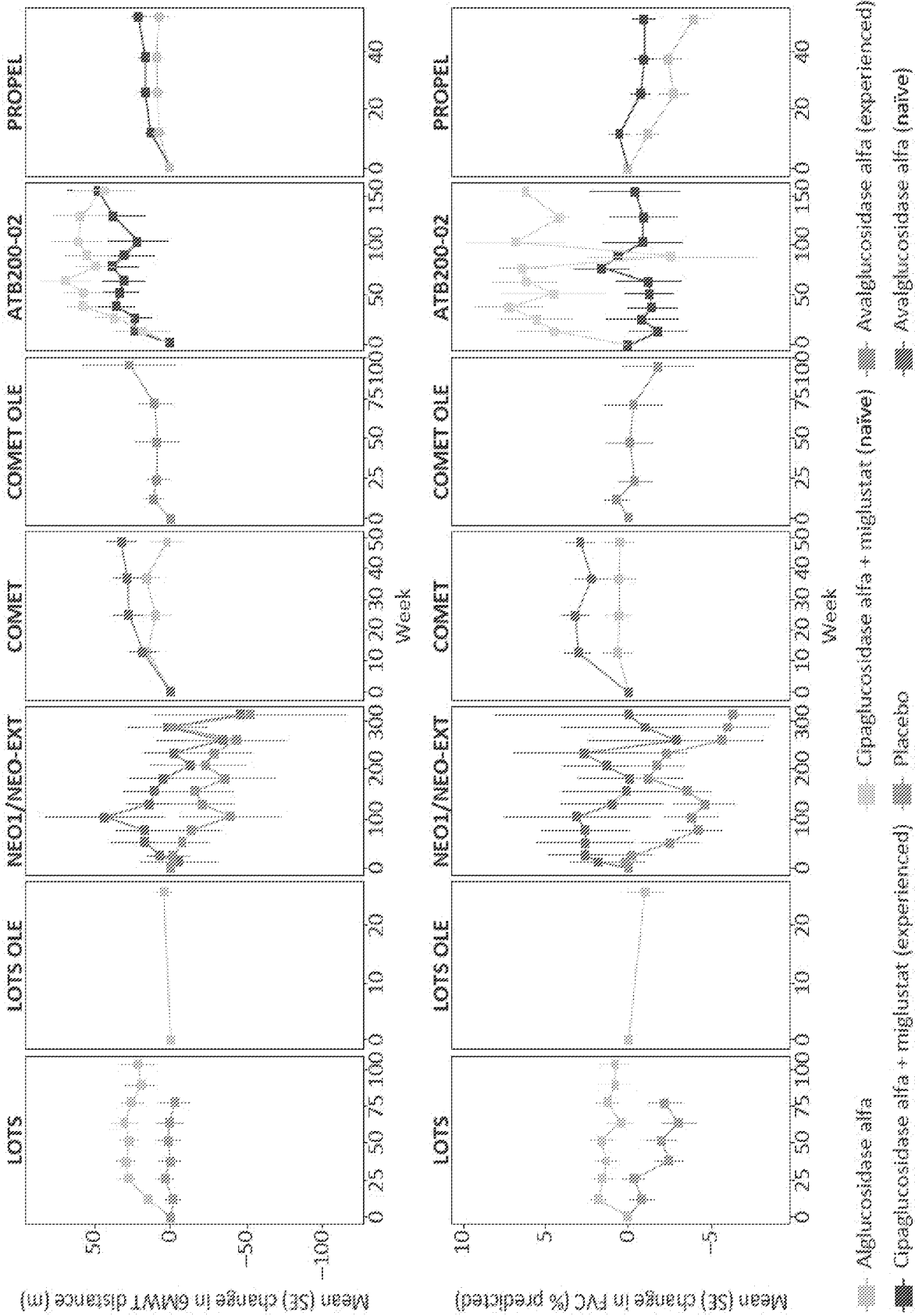


FIG. 60

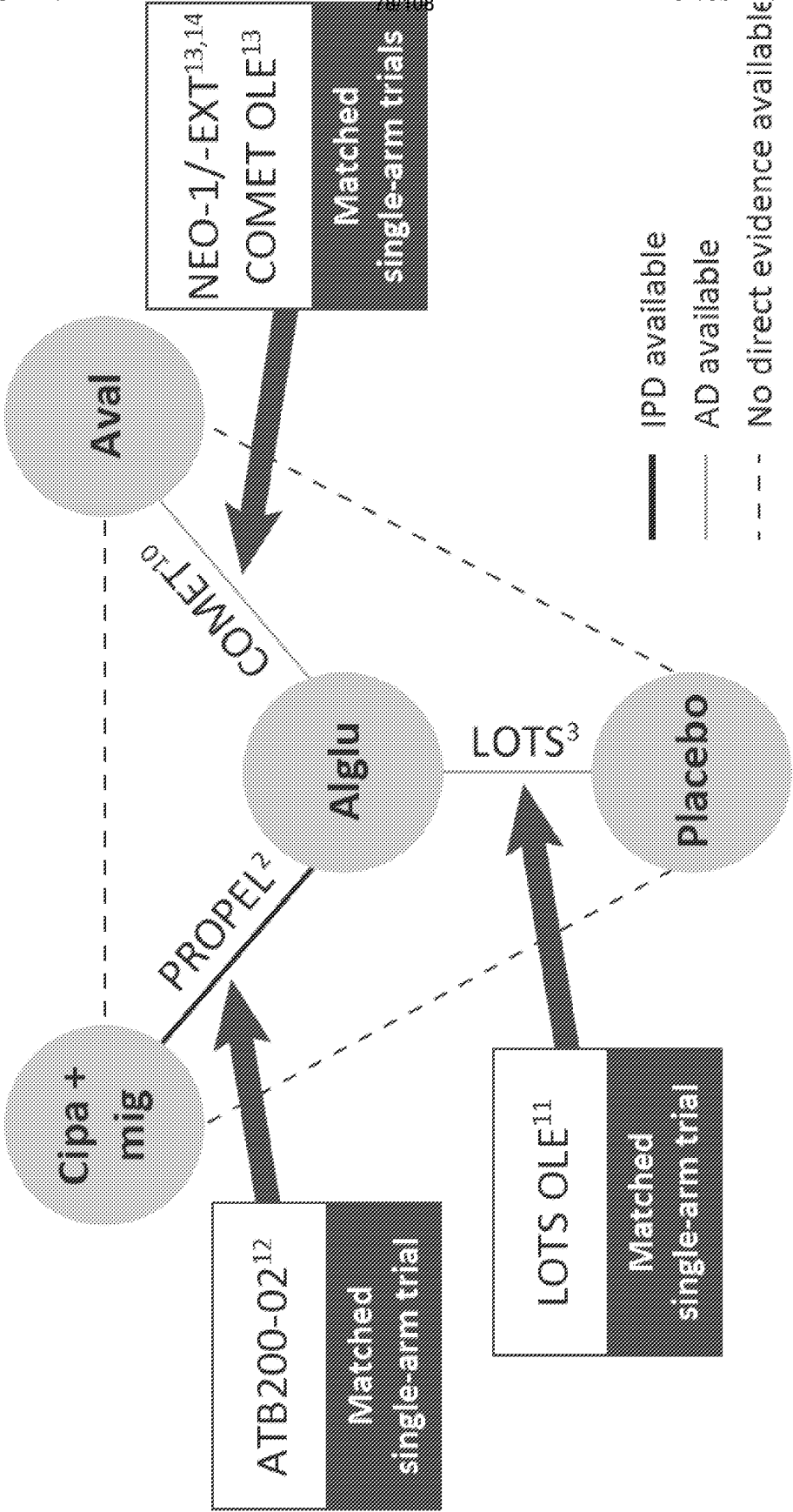


FIG. 61

Relative effect (95% CrI)	P-value
16.3 (9.6, 24.3)	<0.001
29.5 (7.4, 52.6)	0.011
27.6 (-84.1, 144.4)	0.648
-13.2 (-35.9, 7.2)	0.233
-1.8 (-114.7, 114.2)	0.977
11.3 (-102.6, 127.6)	0.857

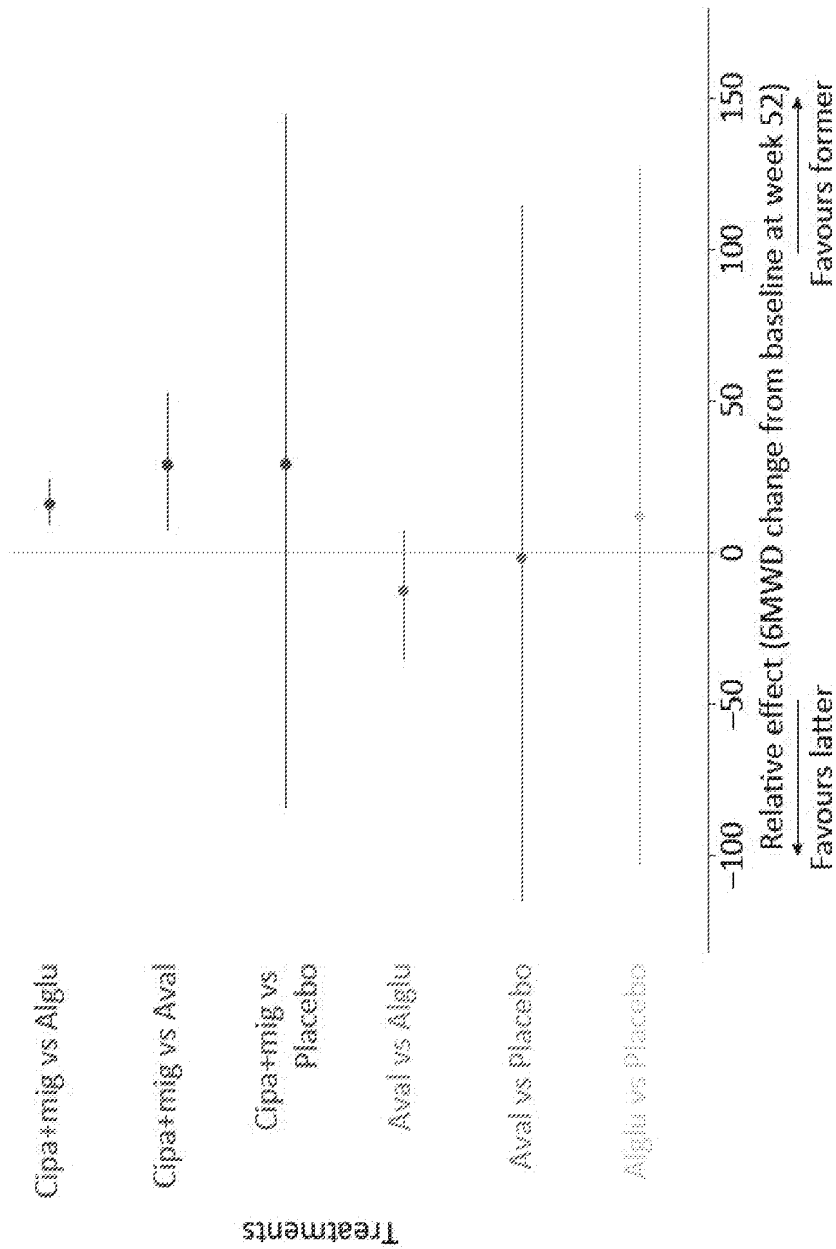


FIG. 62

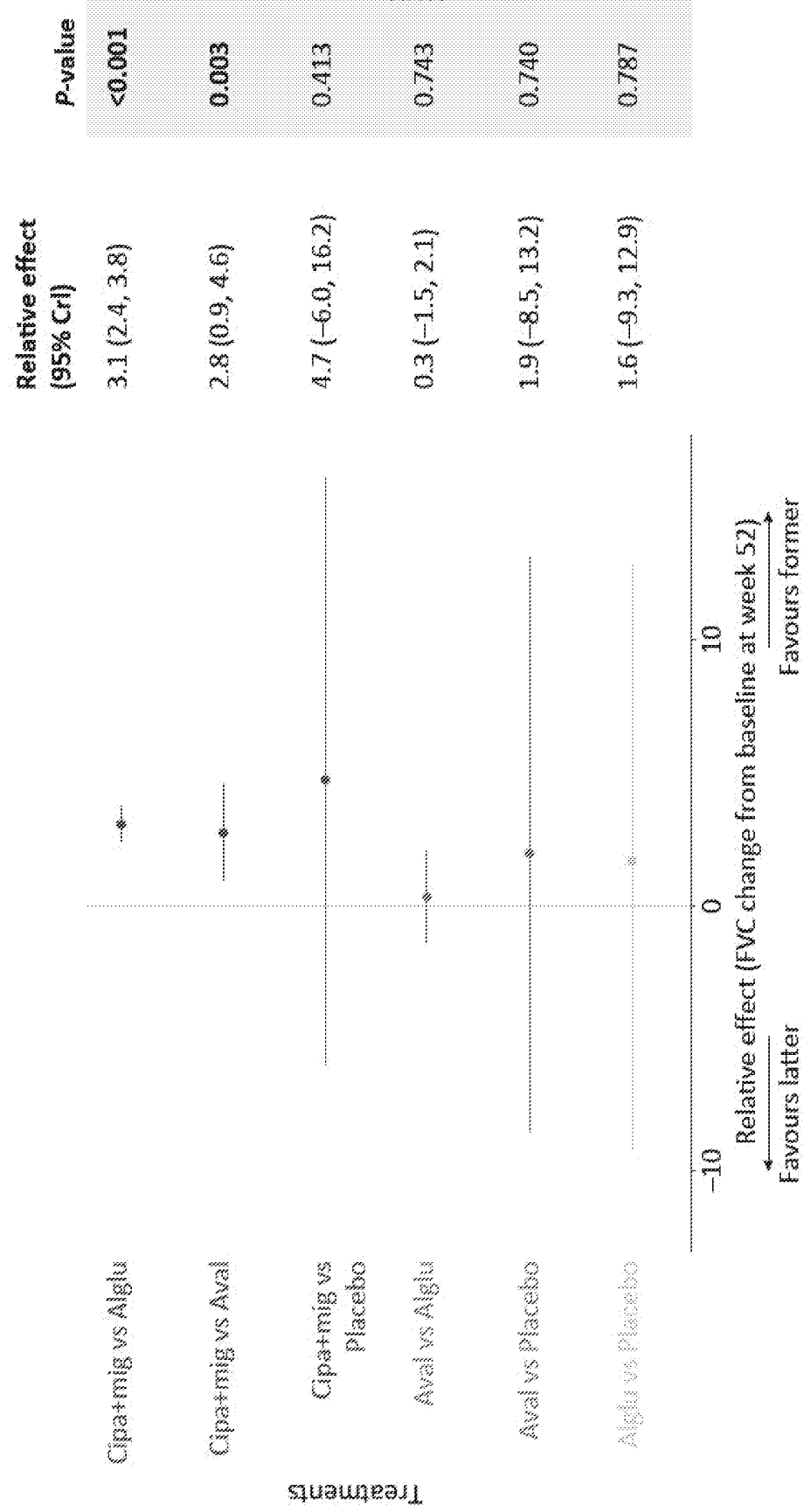


FIG. 63

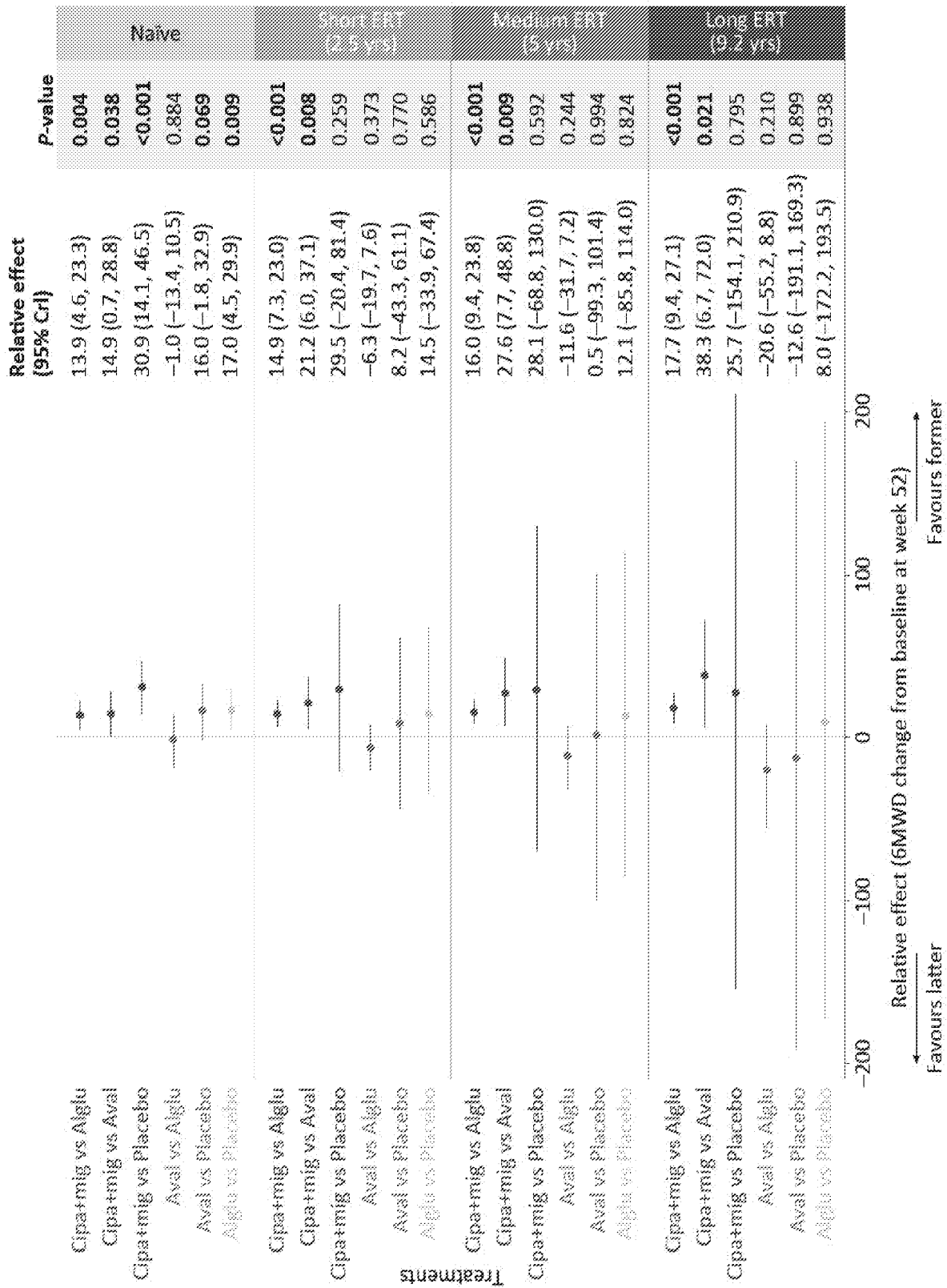


FIG. 64

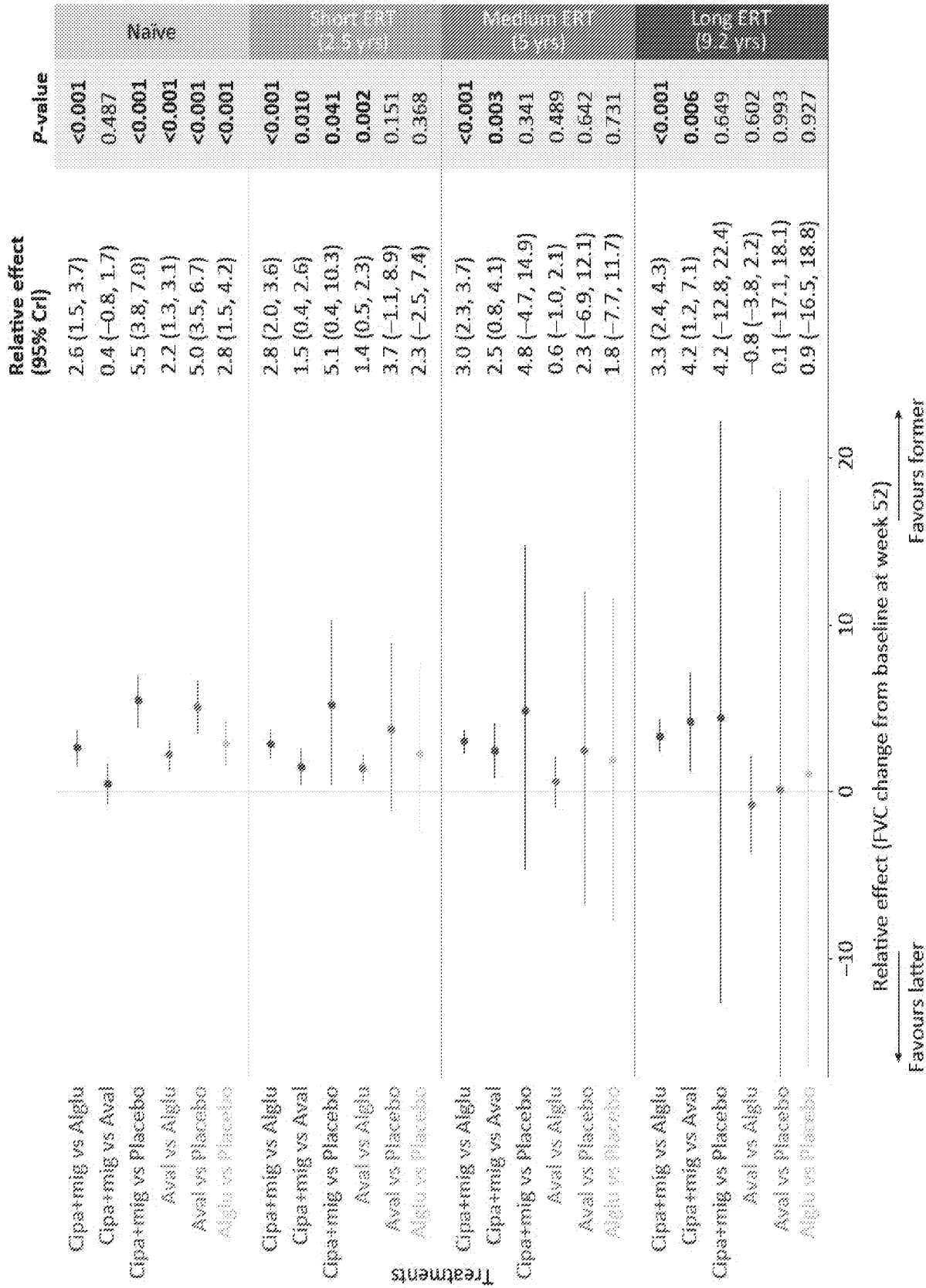


FIG. 65

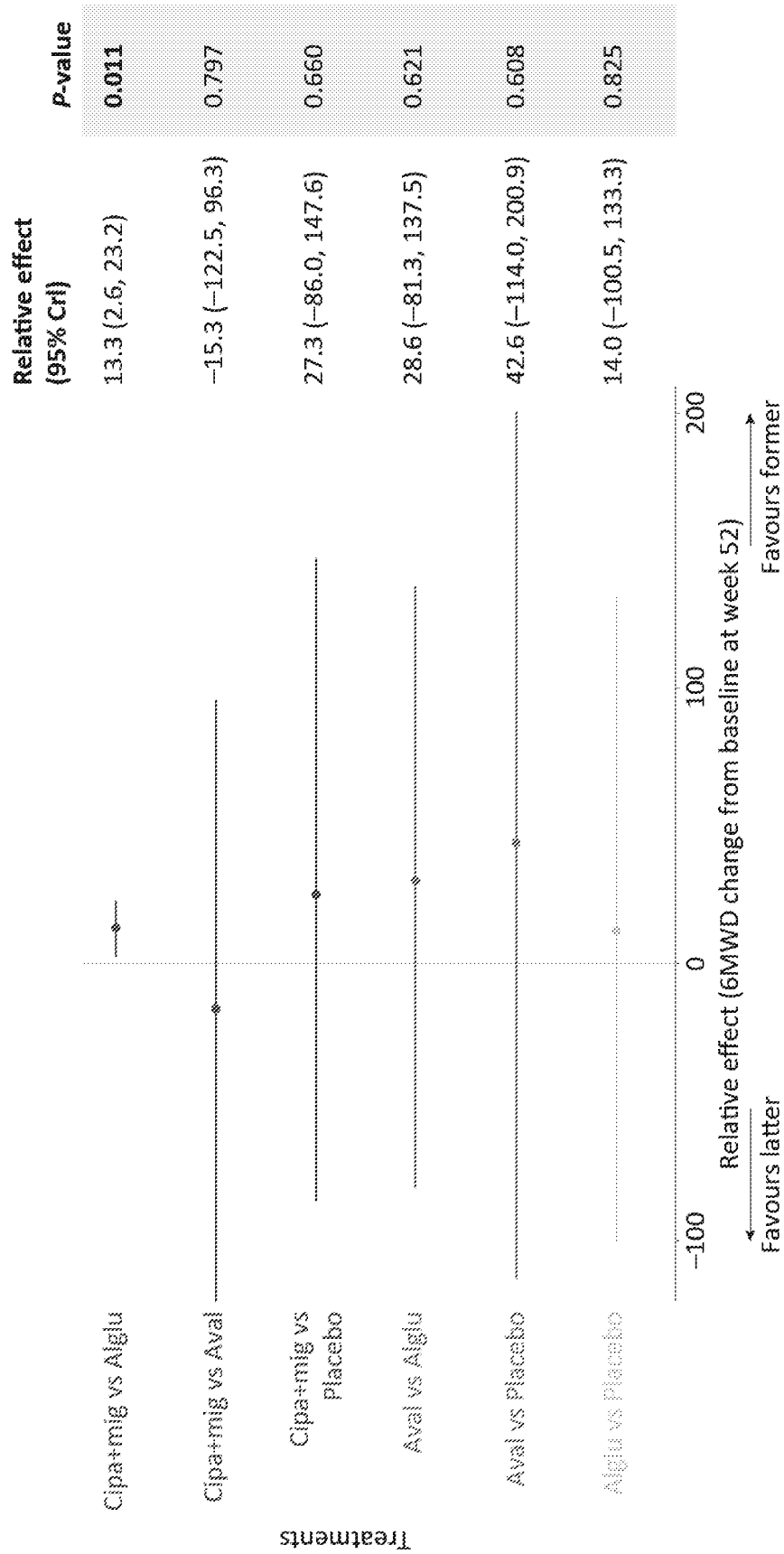


FIG. 66

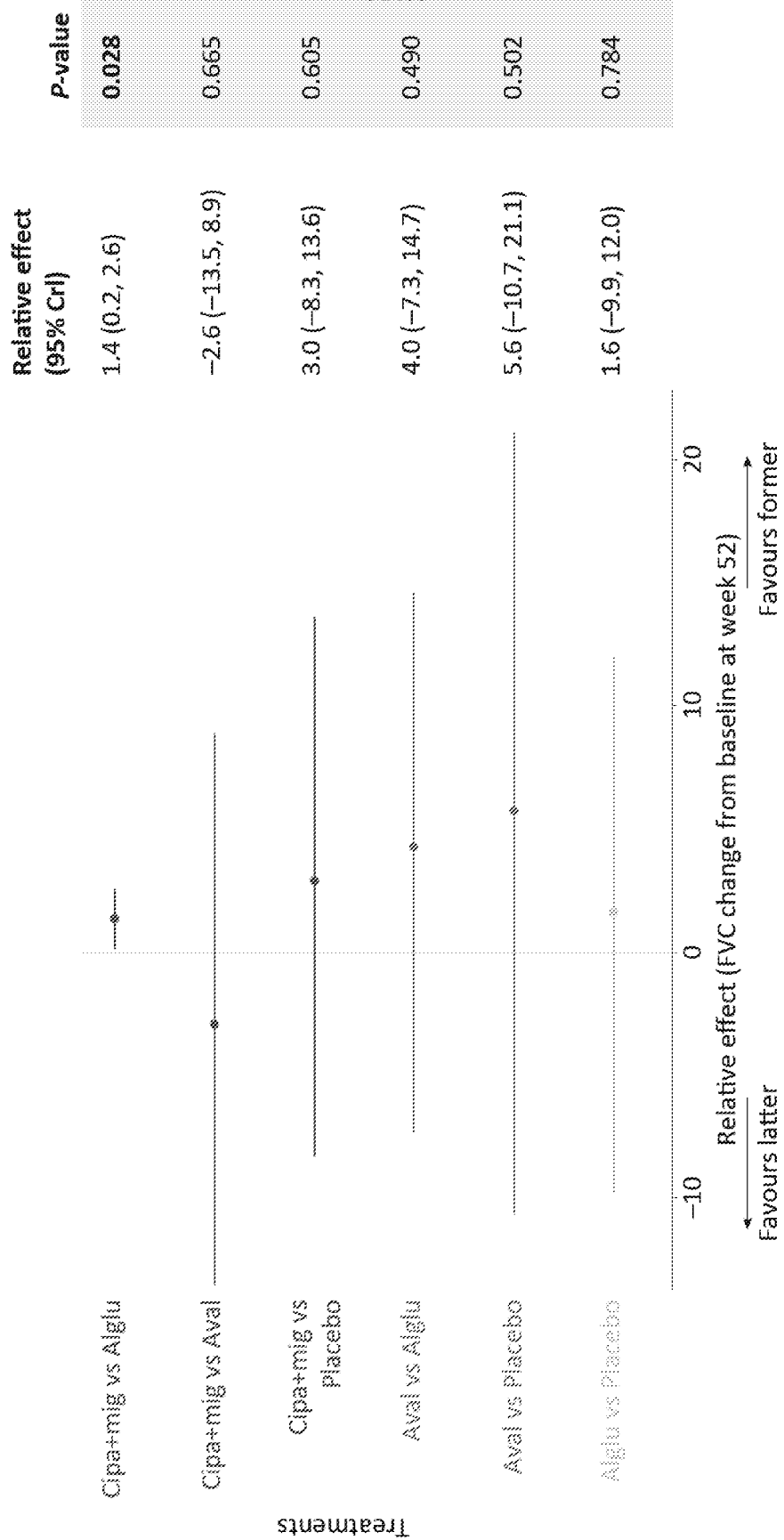
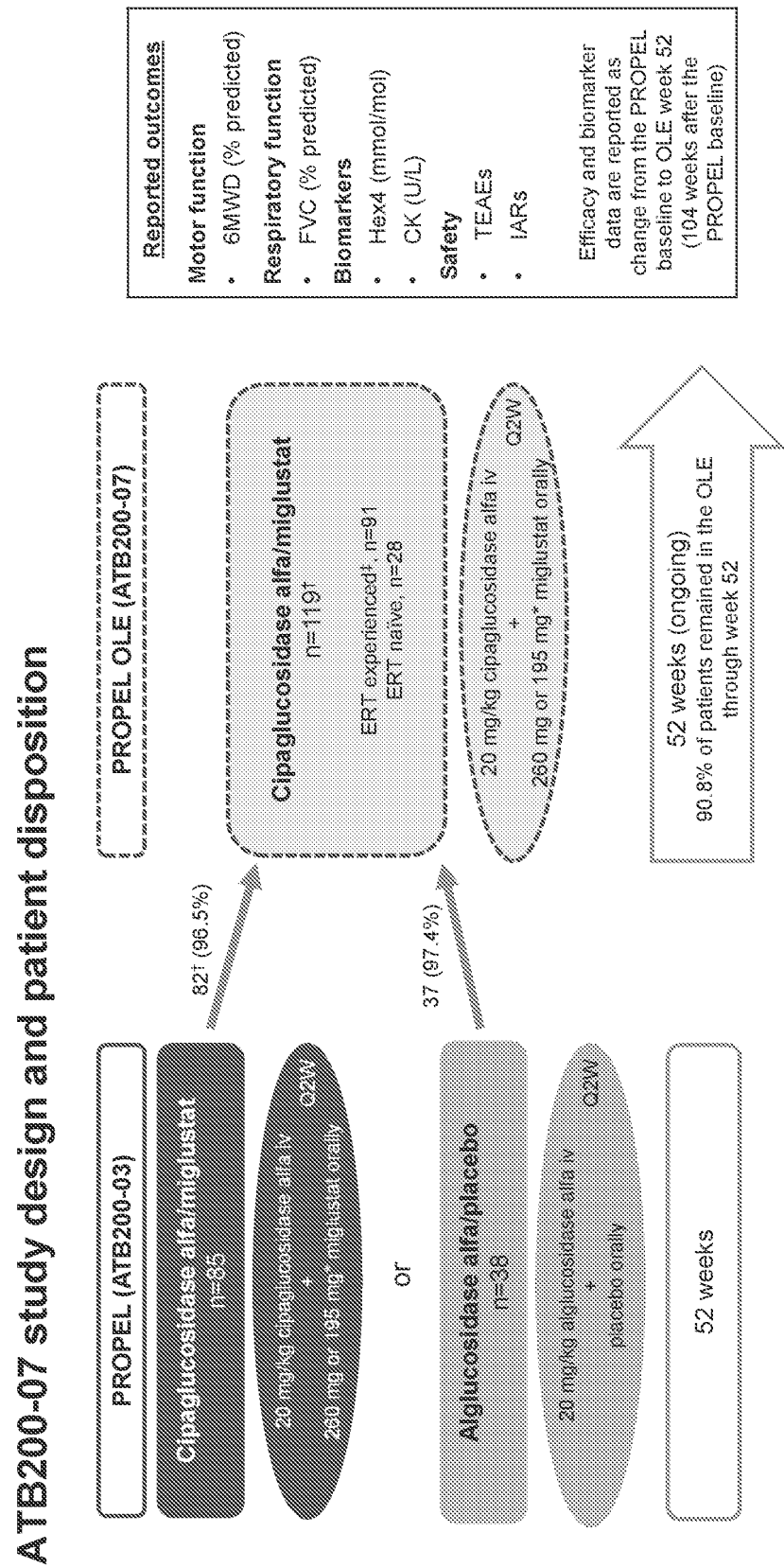


FIG. 67



*260 mg miglustat for patients weighing ≥ 50 kg and 195 mg for patients weighing ≥ 40 kg to < 50 kg; [†]includes 1 patient who enrolled on ATB200-07 but was never dosed; ERT-experienced patients are defined as those treated with ERT (alglucosidase alfa) prior to their participation in the PROPEL study; 6MWD, 6-minute walk distance; CK, creatine kinase; FVC, forced vital capacity; Hex4, hexose tetrasaccharide; IAR, infusion-associated reaction; iv, intravenous; OLE, open-label extension; Q2W, every 2 weeks; TEAE, treatment-emergent adverse event.

FIG. 68

Patient baseline characteristics in the OLE

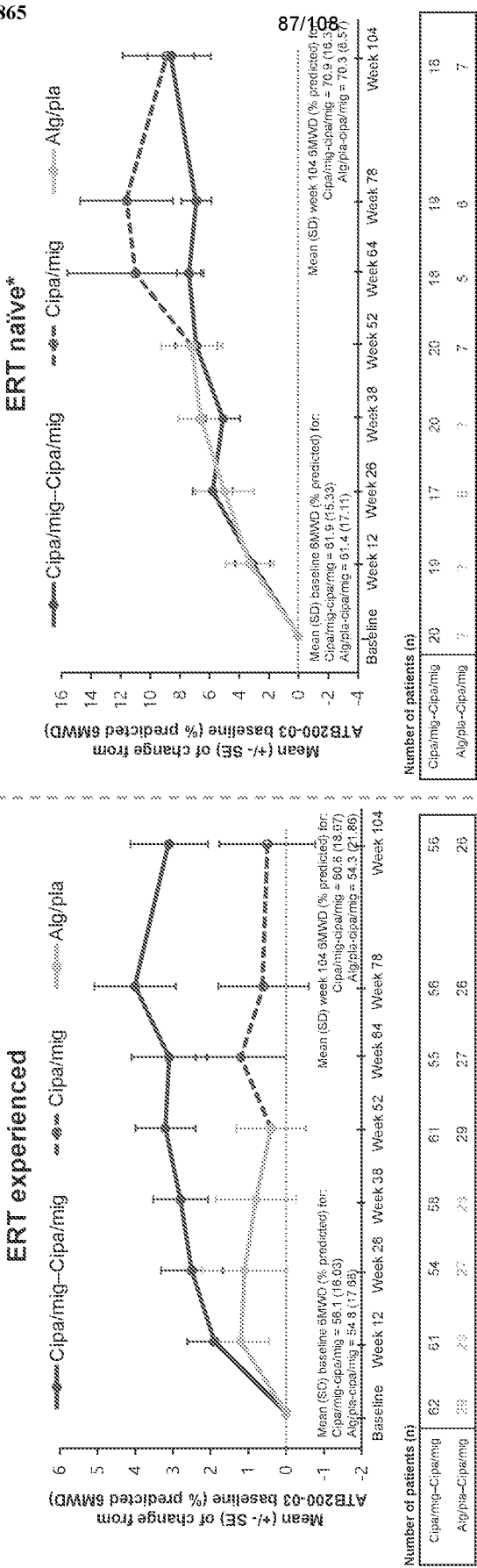
	Ciparmig-ciparmig n=81*	Alg/pla-ciparmig n=37
Median (range) age, years	49 (20–75)	47 (23–67)
Male patients, n (%)	34 (41.5)	19 (51.4)
ERT experienced, n (%)	61 (75.3)	29 (78.4)
Median (Q1–Q3) ERT duration, years	7.6 (4.3–10.2)	7.10 (3.8–10.4)

- As only 4 patients in PROPEL did not continue into the OLE, patients in the OLE are representative of all randomized patients in PROPEL

*excludes 1 participant who enrolled in ATE200-07 but was not treated. Alg/pla, alglucosidase alfa/placebo; ciparmig, cipaglucosidase alfa/miglustat.

FIG. 69

Improvement from the PROPEL baseline in % predicted 6MWD was maintained throughout the OLE for ERT-experienced and naïve patients



- ERT-experienced and -naïve patients treated with cipa/mig throughout showed durable improvements in % predicted 6MWD in PROPEL which were maintained throughout the OLE to week 104
- ERT-experienced and -naïve patients who received alg/pla in PROPEL and switched to cipa/mig in the OLE showed stability in % predicted 6MWD throughout the OLE

*Excludes 1 outlier, SE, standard error.

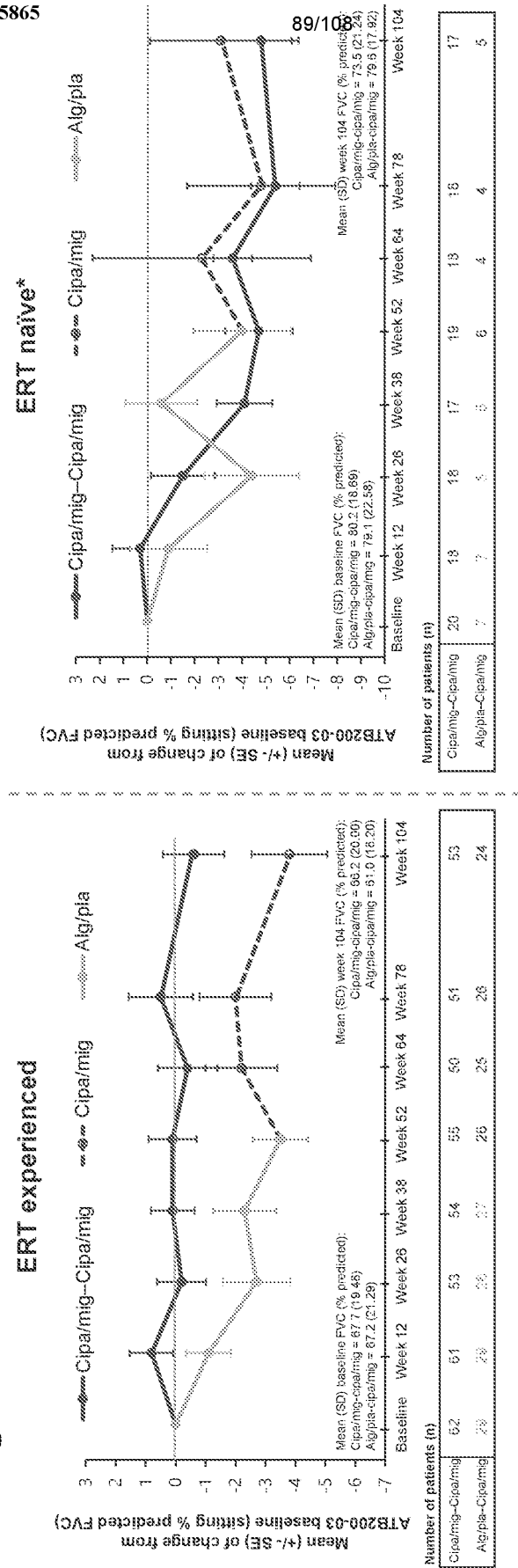
FIG. 70 A

	ERT experienced				ERT naïve*			
	Cipaglicoside afa/migliostat		Alogliquin afa/migliostat		Cipaglicoside afa/migliostat		Alogliquin afa/migliostat	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
6 MWD, m								
Baseline	62	342.4 (100.40)	29	335.0 (116.03)	20	393.6 (112.39)	7	420.9 (135.75)
Week 104	56	367.1 (129.11)	26	330.5 (142.54)	18	428.0 (107.74)	7	469.3 (106.30)
Change from ATB200-03 baseline in 6MWD, m								
Week 12	61	10.9 (23.19)	29	5.3 (21.68)	19	17.1 (20.97)	7	20.5 (22.12)
Week 26	55	12.9 (30.64)	27	5.6 (26.60)	17	32.2 (36.75)	6	30.3 (17.94)
Week 38	58	13.3 (32.82)	28	4.0 (28.90)	20	25.2 (46.25)	7	38.5 (19.46)
Week 52	61	16.3 (39.46)	29	0.7 (39.84)	20	33.4 (48.70)	7	36.3 (29.32)
Week 64	55	14.2 (43.27)	27	5.7 (49.81)	18	35.5 (47.65)	5	63.3 (49.66)
Week 78	56	19.8 (53.17)	26	0.8 (44.88)	19	31.8 (47.83)	6	65.2 (49.47)
Week 104	56	14.2 (53.44)	26	-8.8 (46.19)	18	38.8 (51.03)	7	48.3 (70.66)

*Excludes one outlier 6MWD, 6-minute walk distance; SD, standard deviation.

FIG. 70B

Sitting % predicted FVC remained stable in ERT-experienced and naïve patients throughout the OLE



- ERT-experienced patients treated with cipa/mig throughout remained stable while patients who received alg/pla in PROPEL experienced a decline in sitting % predicted FVC that stabilized after switching to cipa/mig in the OLE
- ERT-naïve patients in both treatment groups experienced some decline in PROPEL that stabilized in the OLE to week 104

FIG. 71

*Excludes 1 outlier.

Cipa/mig treatment was associated with a durable reduction in serum CK during PROPEL and the OLE in both ERT-experienced and ERT-naïve patients

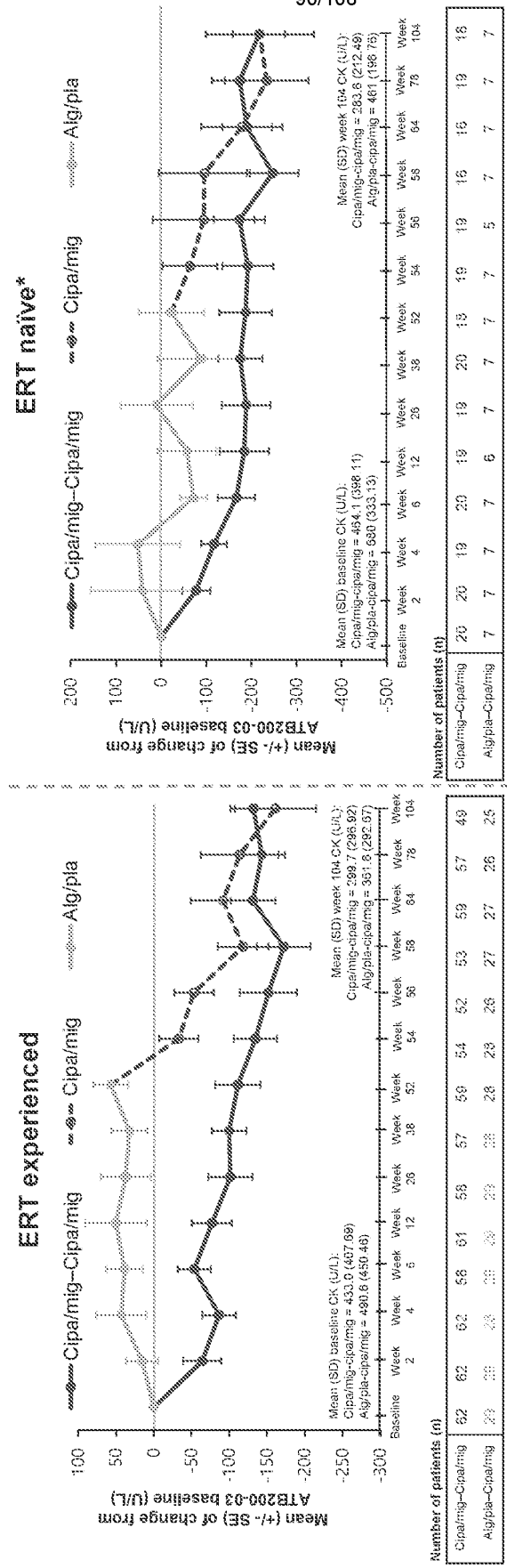
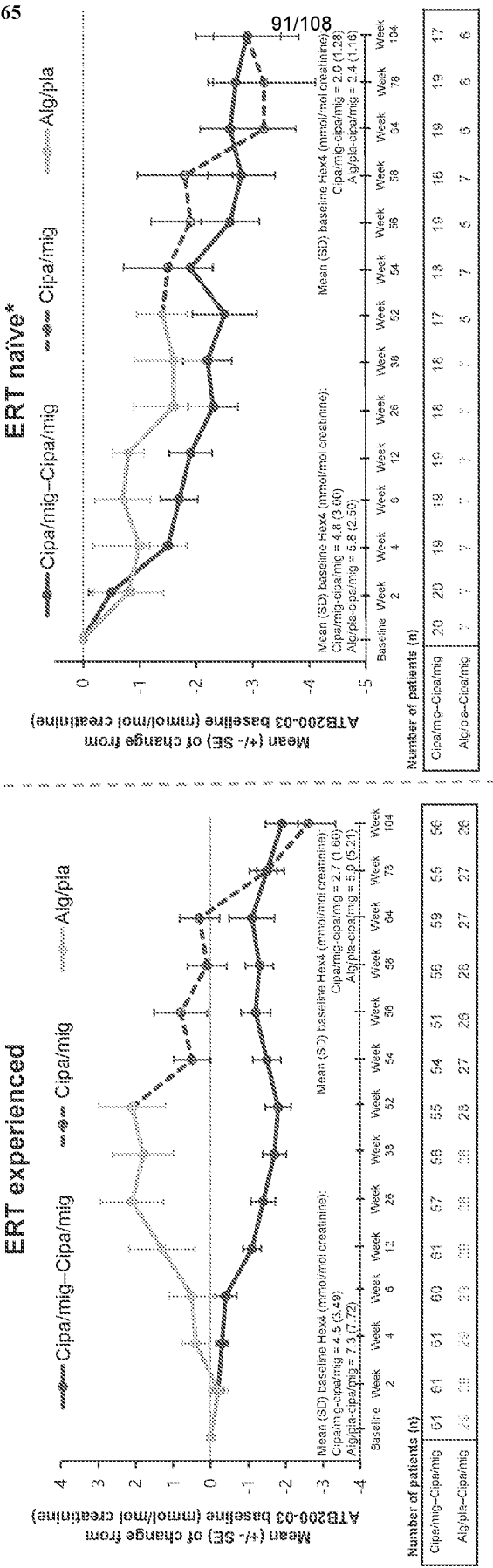


FIG. 72

- ERT-experienced and -naïve patients treated with cipa/mig throughout showed a decline in serum CK levels during PROPEL that was maintained throughout the OLE
- ERT-experienced and -naïve patients who received alg/pla in PROPEL showed a slight increase or stability in serum CK levels to week 52 and a marked decline after switching to cipa/mig in the OLE

*Excludes 1 outlier.

Cipa/mig treatment was associated with a durable reduction in urine Hex4 during PROPEL and the OLE in both ERT-experienced and ERT-naïve patients



- ERT-experienced patients treated with cipa/mig throughout experienced a decline in urine Hex4 levels in PROPEL that stabilized during the OLE. Patients who received alg/pla in PROPEL experienced an increase in Hex4 and a marked decline after switching to cipa/mig in the OLE
- ERT-naïve patients experienced a decline in Hex4 levels during PROPEL in both treatment groups that stabilized or declined further during the OLE to week 104

*Excludes 1 outlier.

FIG. 73

Safety summary

	Cipalmig-cipalmig n=85*	Alipia-cipalmig n=37†
TEAEs, n (%)	84 (98.8)	36 (97.3)
TEAEs potentially related to treatment	37 (43.5)	15 (40.5)
Serious TEAEs	14 (16.5)	6 (16.2)
Serious TEAEs potentially related to treatment‡	1 (1.2)	2 (5.4)
TEAEs leading to study withdrawal during OLE	1 (1.2) ^s	2 (5.4) [‡]
TEAEs leading to death	0 (0)	0 (0)
IARs	27 (31.8)	10 (27.0)

- Most TEAEs were mild or moderate in severity
- The most common TEAEs included fall, headache, arthralgia, nasopharyngitis, myalgia and back pain
- Three patients withdrew from the study due to TEAEs experienced during the OLE
- No new safety signals were identified during the OLE

*Includes data from patients treated with cipa/mig in PROPEL who may or may not have continued cipalmig in the OLE, including data from both PROPEL and the OLE; †includes data from the OLE only; ‡relatedness to treatment was determined by the investigator; ^sUrticaria; [‡]Urticaria and hypotension, and anaphylaxis.

FIG. 74

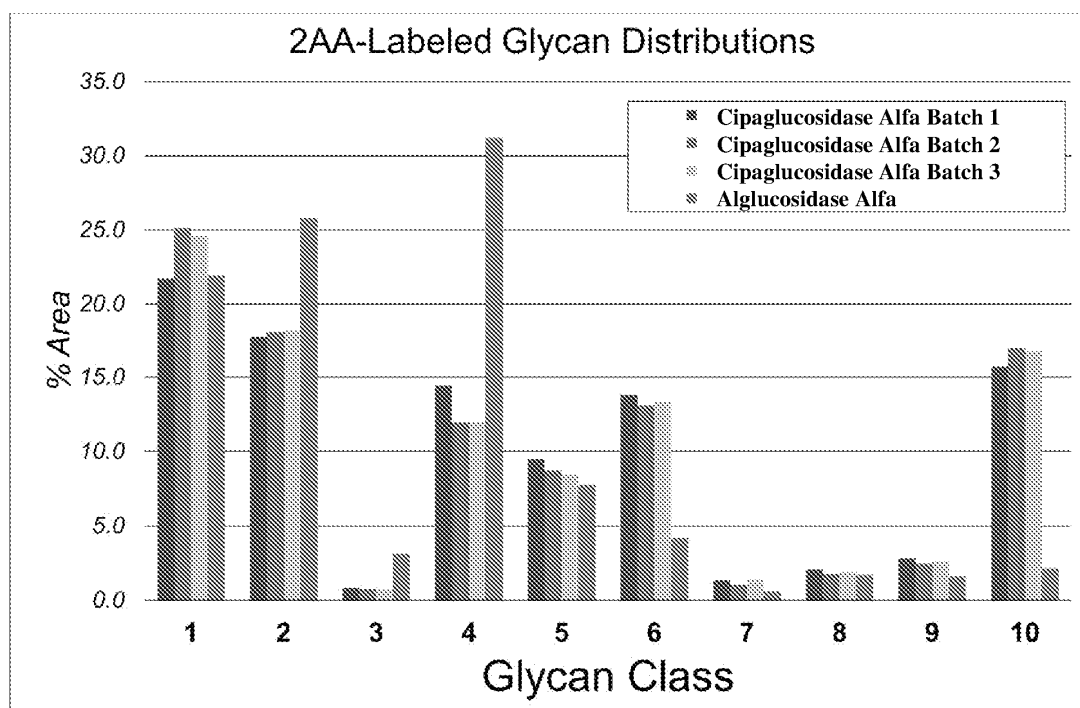


FIG. 75

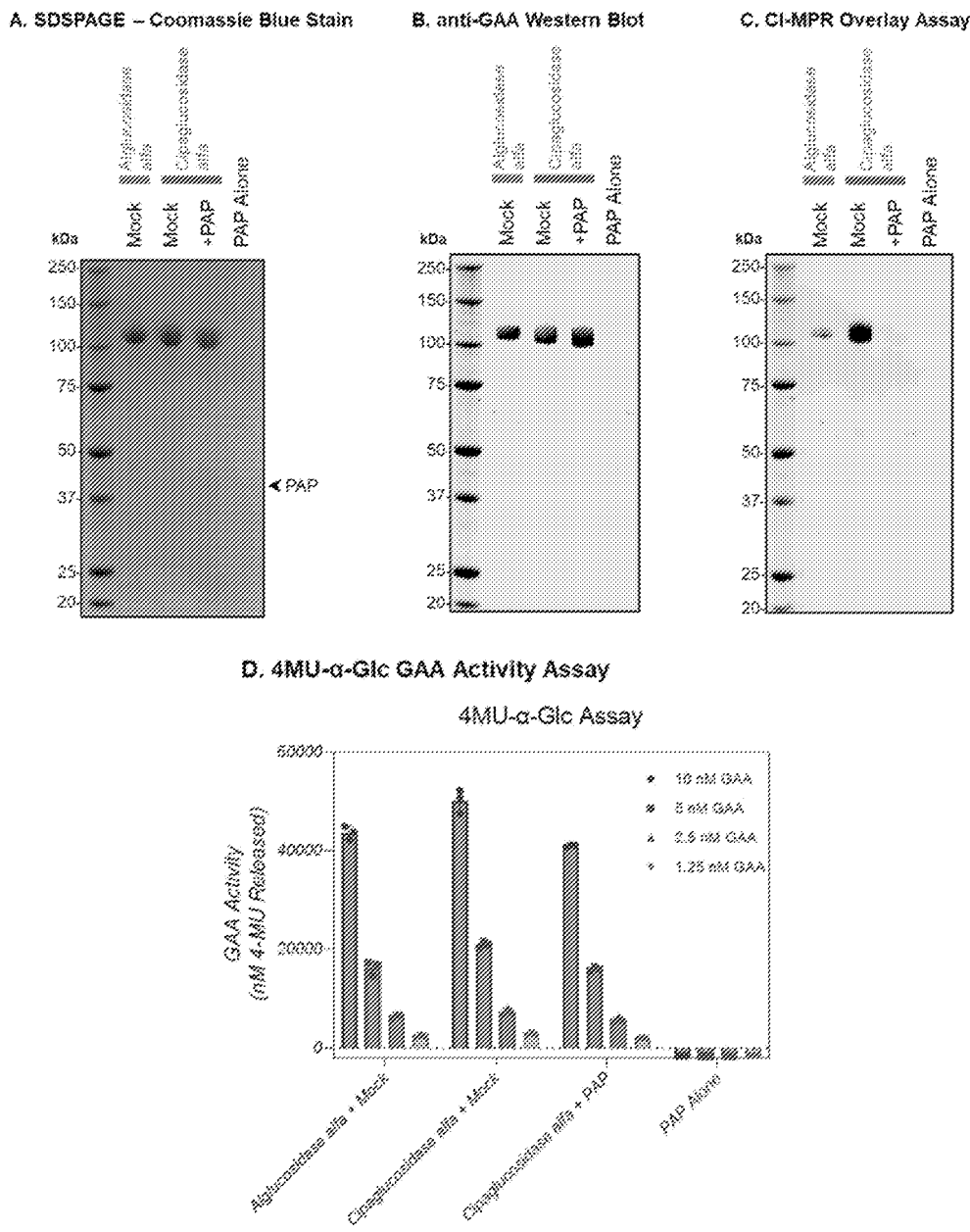


FIG. 76

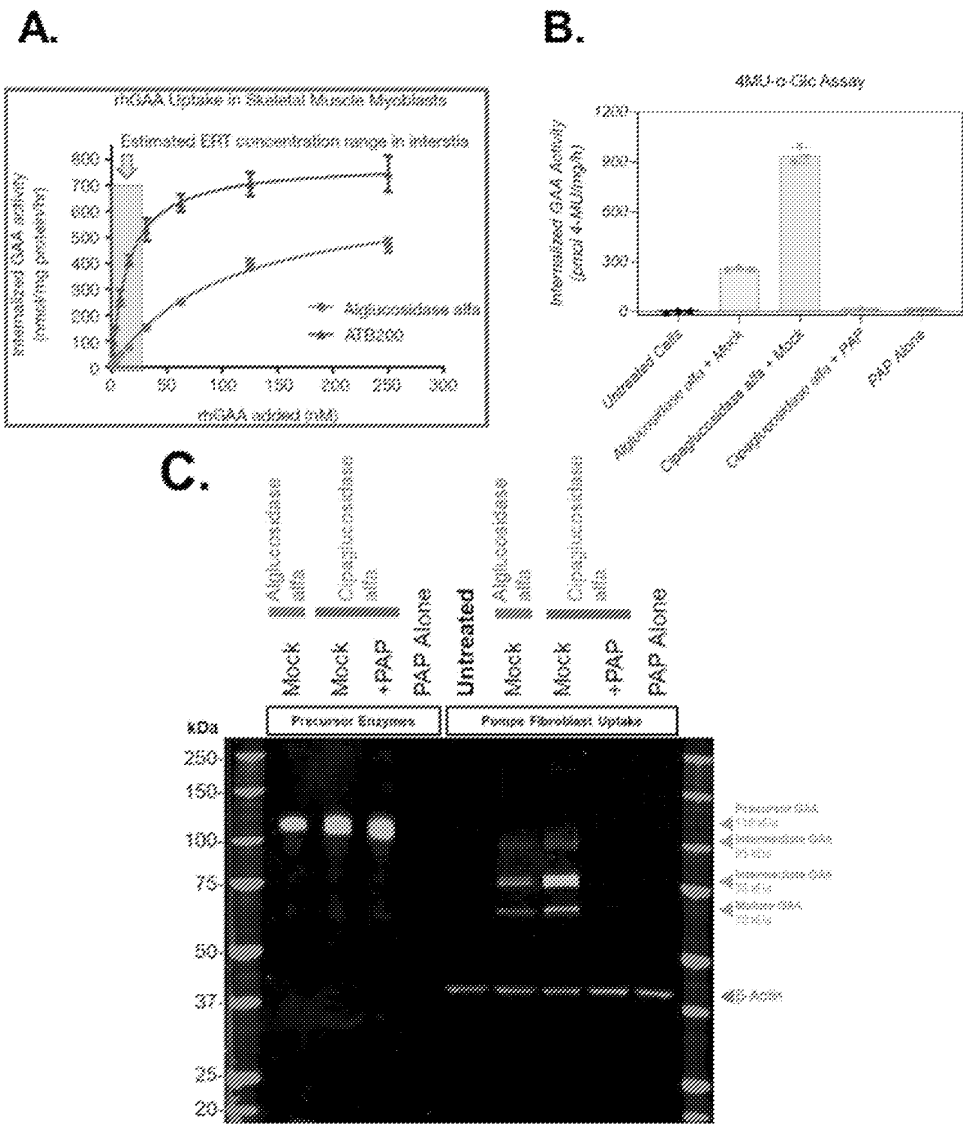


FIG. 77

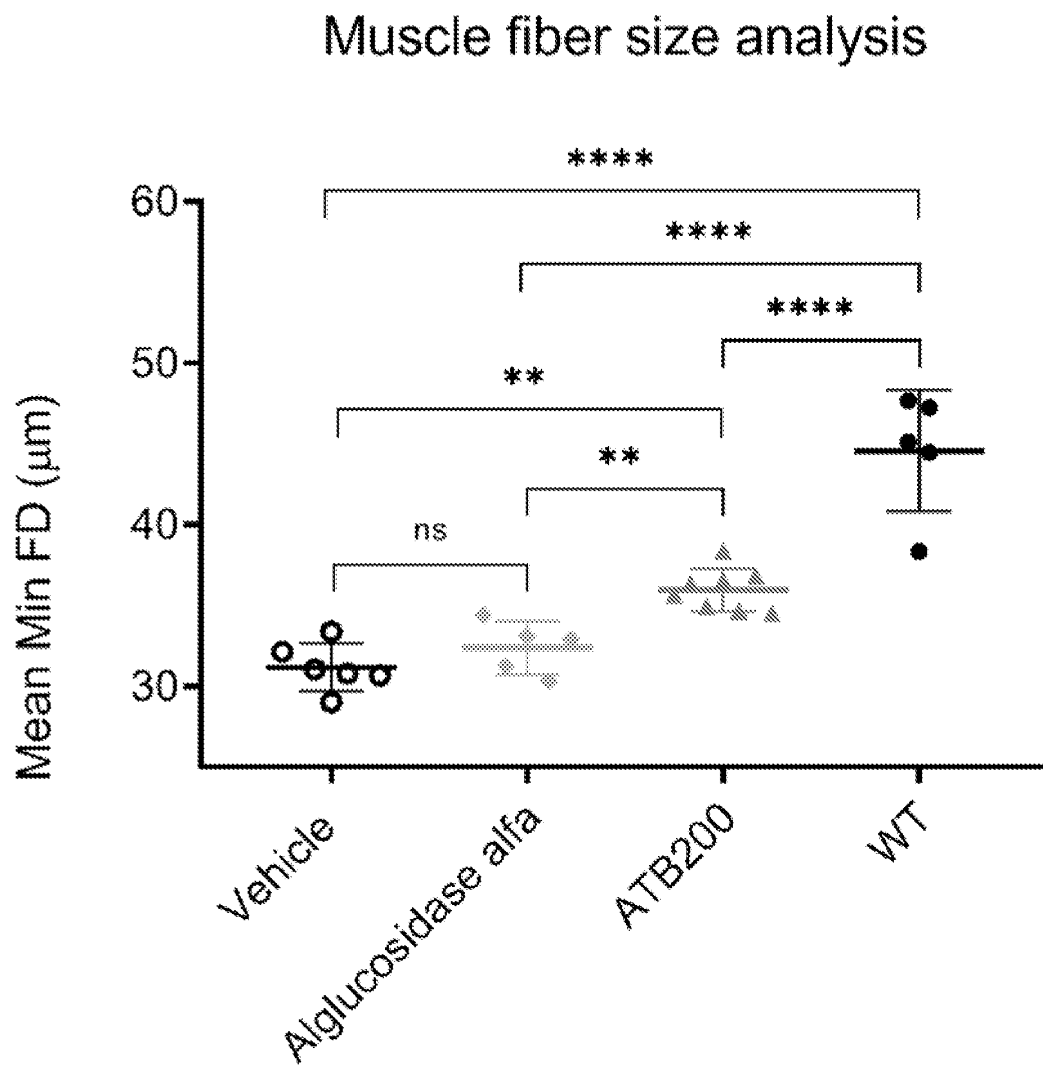
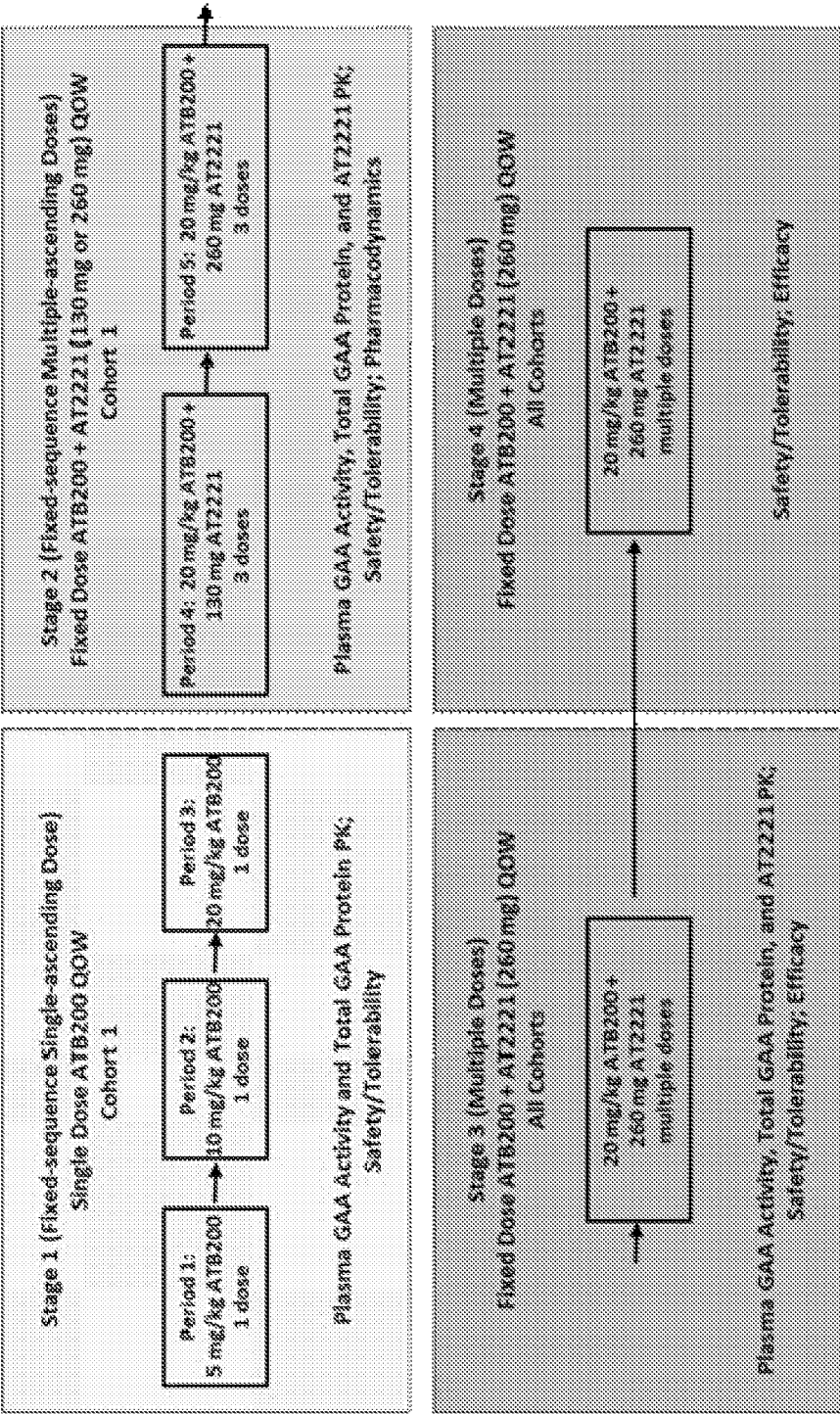


FIG. 78



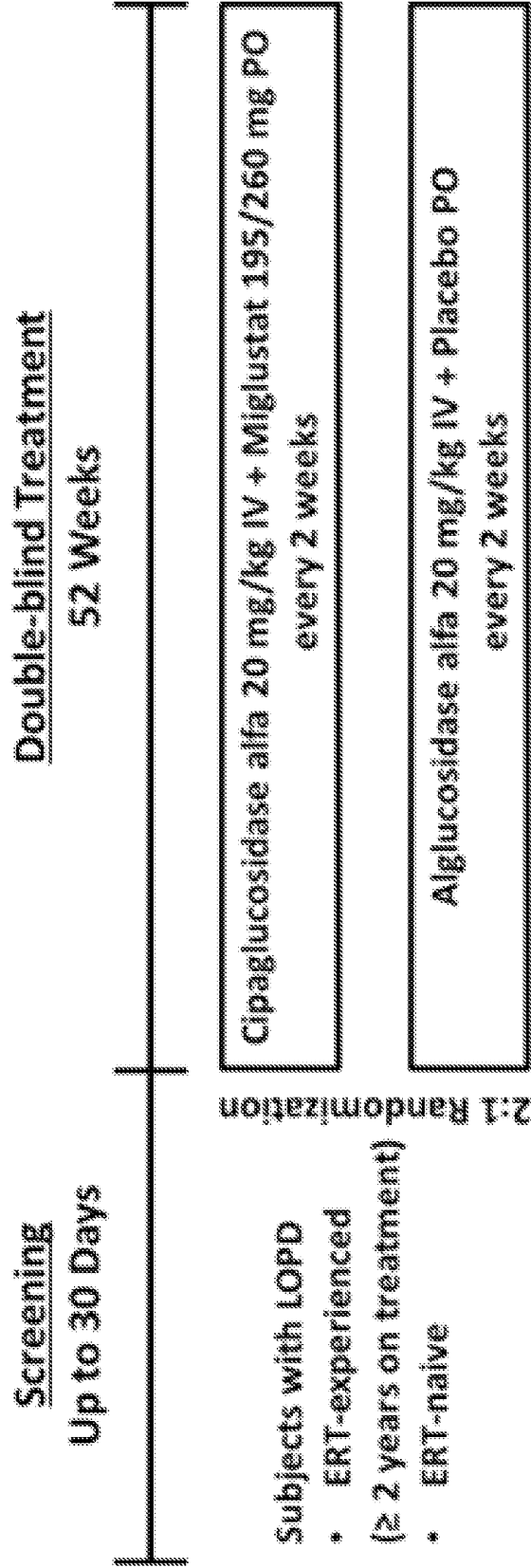
Abbreviations: AT2221 = miglustat; ATB200 = cipaglucosidase alfa; GAA = human acid α -glucosidase; PK = pharmacokinetics; QOW = every other week; rhGAA = recombinant human acid α -glucosidase

Note: PK assessments for GAA activity, total GAA protein, and AT2221 in Stage 3 were only performed for the first and third doses for Cohort 3. Sparse blood sampling for total GAA protein was performed after at least 18 months of treatment in Cohorts 1 and 3. If the subject had completed Stage 3, sparse PK sampling was performed in Stage 4.

Note: GAA activity represents both endogenous GAA and exogenous rhGAA; refers to the acid Alfa-glucosidase activity measured using the artificial substrate 4 MU- α -Glc in a fluorometric assay.

Note: Efficacy was also evaluated in Stage 3 and 4.

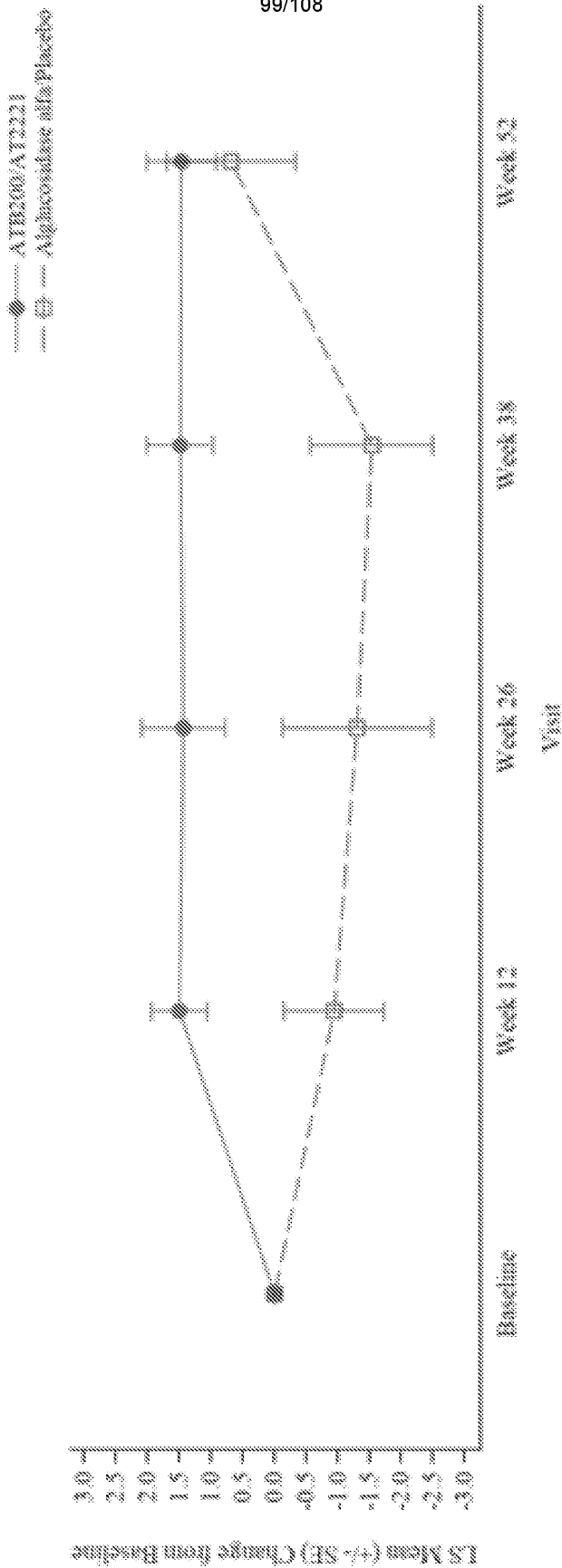
FIG. 79



Abbreviations: ERT = enzyme replacement therapy; IV = intravenous(y); LOPD = late onset Pompe disease; PO = by mouth

FIG. 80

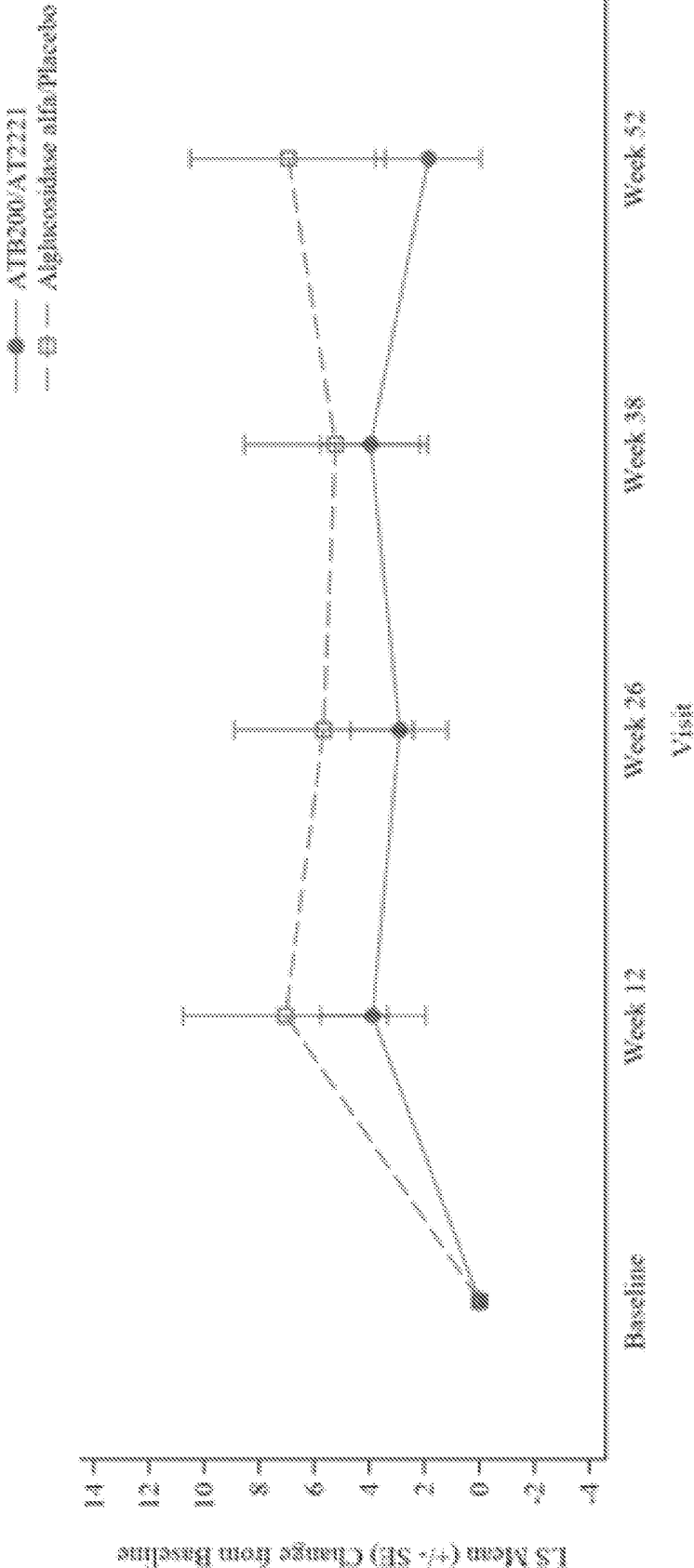
Line Chart for LS Mean (SE) of Change from Baseline in MMT Lower Extremity Score over Time
(ITT-LOCF Population) – ERT-naïve Population Excluding Subject 4005-2511 – Study
ATB200-03



Abbreviations: ANCOVA = analysis of covariance; AT2221 = miglustat; ATB200 = cipagucosidase alfa; ERT = enzyme replacement therapy; ITT = Intent-to-Treat; LOCF = last observation carried forward; LS = least squares; MMT = manual muscle testing; SE = standard error
Note: LS mean and SE are obtained from the ANCOVA model.

FIG. 81

Line Chart for LS Mean (SE) of Change from Baseline in PROMIS-Physical Function Total Score over Time (ITT-LOCF Population) – ERT-naïve Population Excluding Subject 4005-2511 – Study ATB200-03

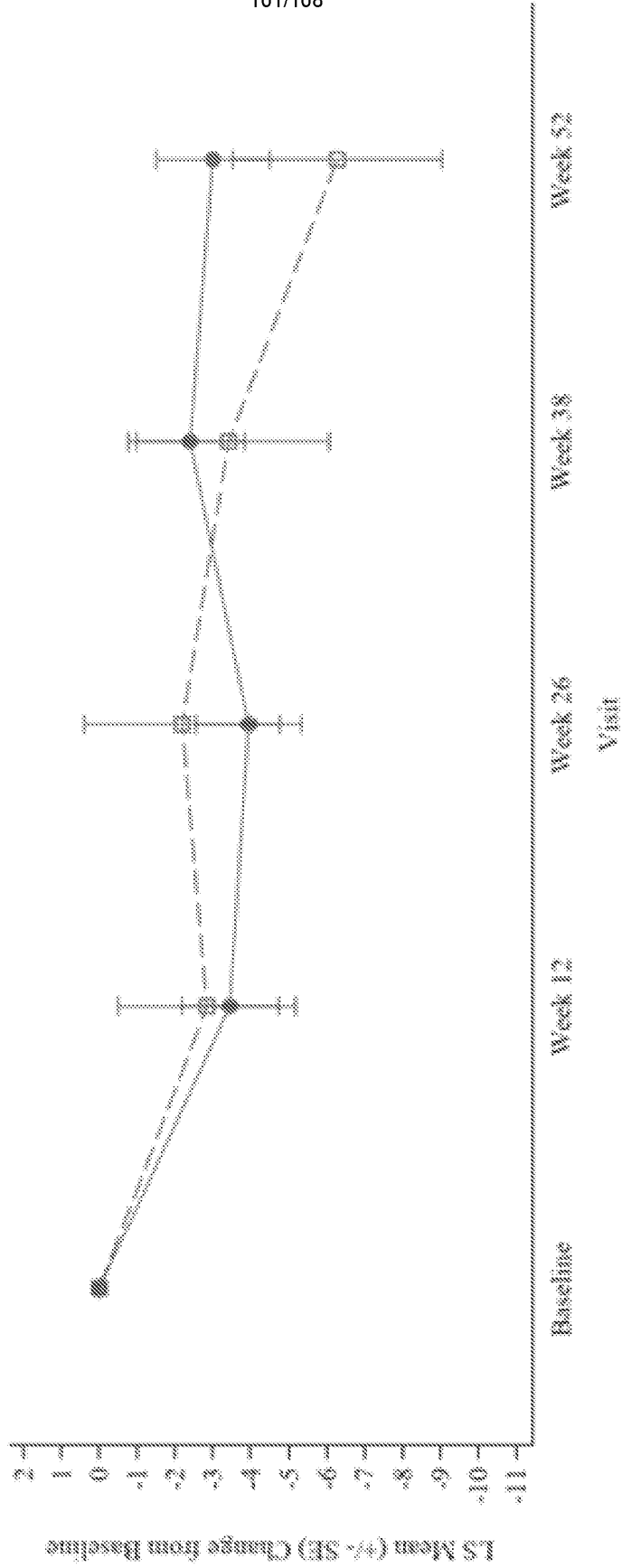


Abbreviations: ANCOVA = analysis of covariance; AT2221 = miglustat; ATB200 = cipaglucosidase alfa; ERT = enzyme replacement therapy; ITT = Intent-to-Treat; LOCF = last observation carried forward; LS = least squares; PROMIS = Patient-reported Outcomes Measurement Information System; SE = standard error

Note: LS mean and SE were obtained from the ANCOVA model.

FIG. 82

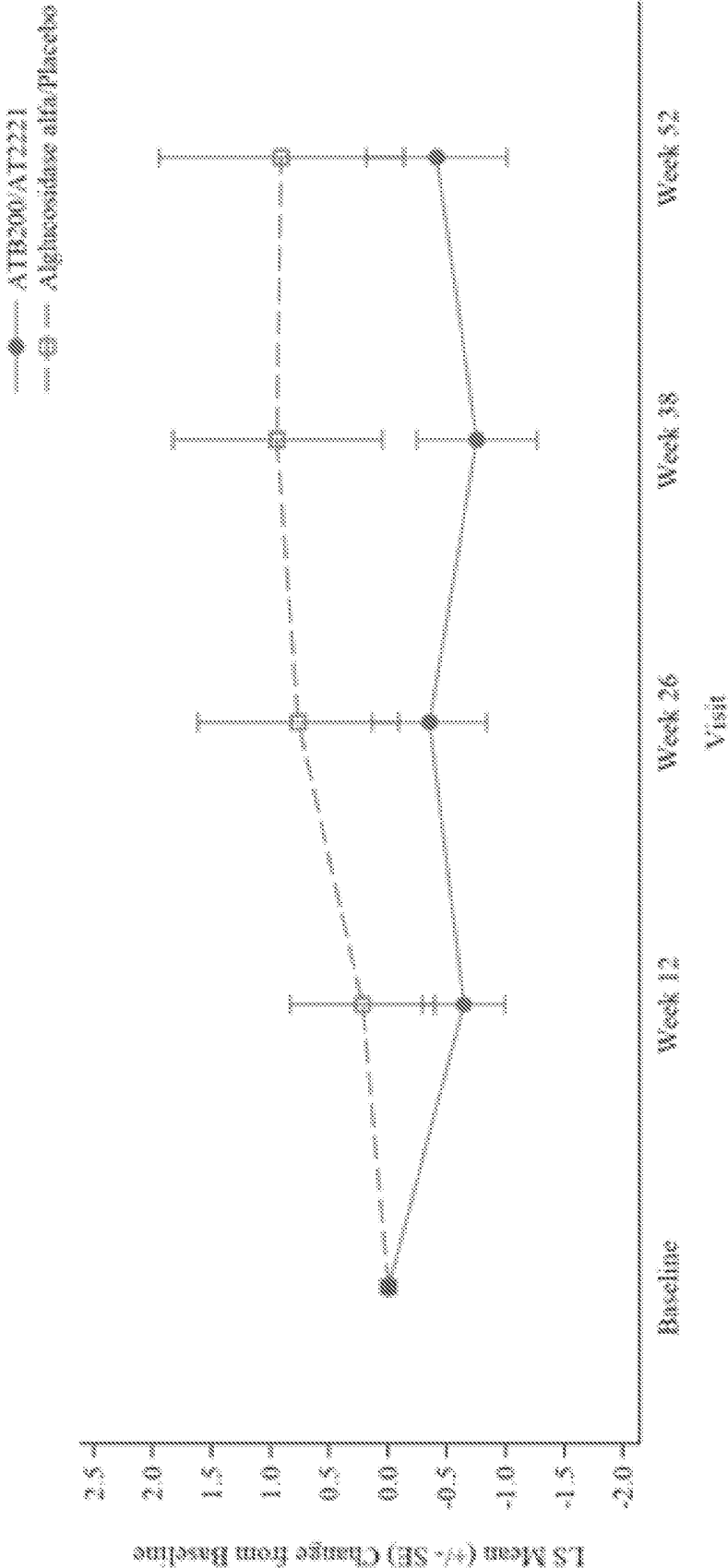
Chart for LS Mean (SE) of Change in PROMIS-Fatigue Total Score (ITT-LOCF Population) – ERT-naive Population Excluding Subject 4005 2511 – Study ATB200-03



Abbreviations: ANCOVA = analysis of covariance; AT2221 = miglustat; ATB200 = cipaglucosidase alfa; ERT = enzyme replacement therapy; ITT = Intent-to-Treat; LOCF = last observation carried forward; LS = least squares; PROMIS = Patient-reported Outcomes Measurement Information System; SE = standard error
 Note: LS mean and SE were obtained from the ANCOVA model.

FIG. 83

Line Chart for LS Mean (SE) of Change from Baseline in GSGC Total Score over Time (ITT-
LOCF Population) – ERT-naïve Population Excluding Subject 4005 2511 – Study ATB200-03

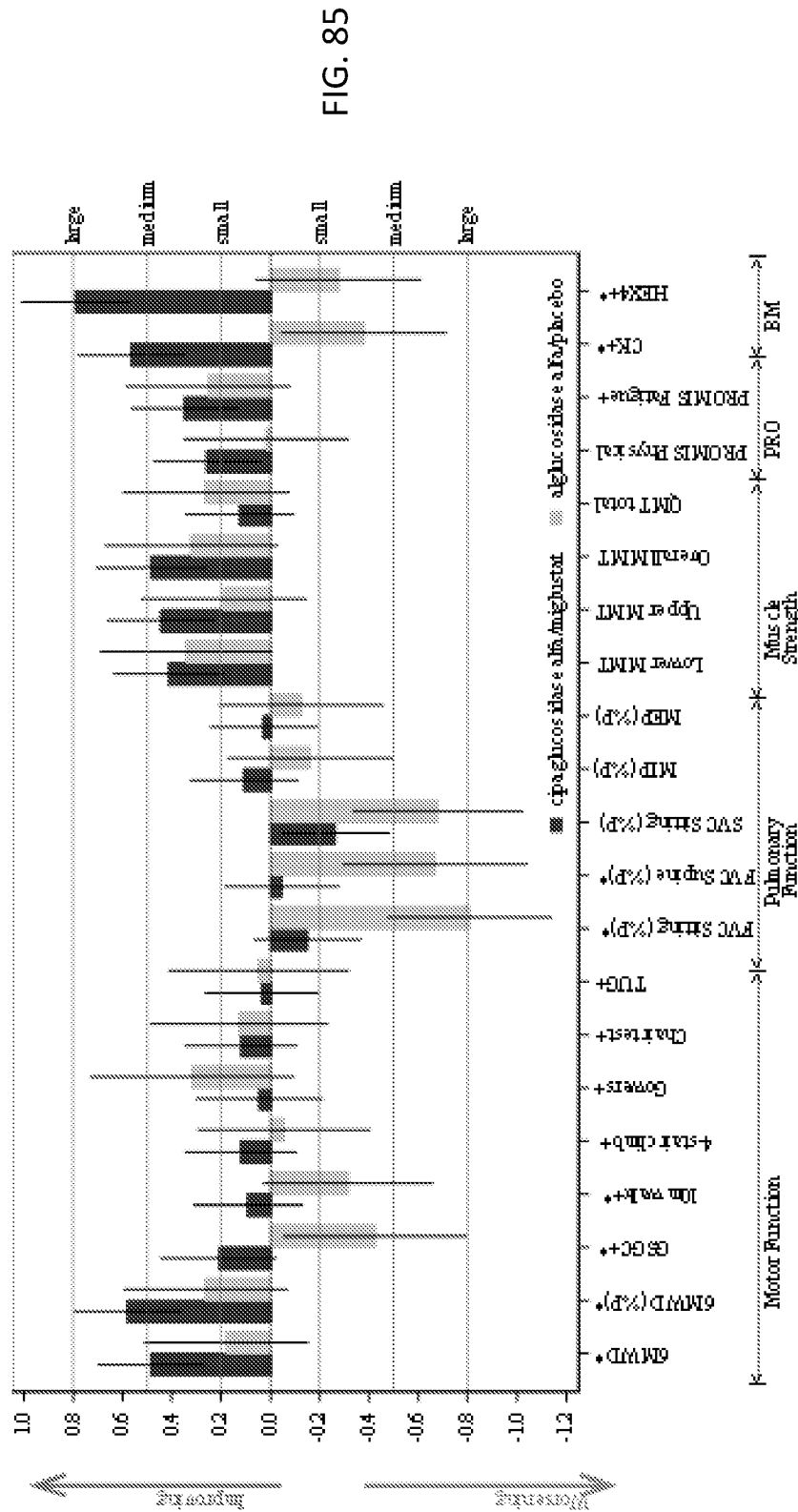


Abbreviations: ANCOVA = analysis of covariance; ATB200 = miglustat; AT2221 = cipaglucosidase alfa; ERT = enzyme replacement therapy; GSGC = Gait, Stairs, Gowers' maneuver, and Chair test; ITT = Intent-to-Treat; LOCF = last observation carried forward; LS = least squares; SE = standard error

Note: Gait score was based on the 10-m walk test; Stairs score was based on the subject climbing stairs; Gowers' maneuver score was based on the subject lying down on the floor, then rising from the floor to get to a standing position; Chair score was based on the subject arising from a sitting position in a chair to a standing position. GSGC total score was the sum of 4 tests and ranges from a minimum of 4 points (normal performance) to a maximum of 27 points (worst score).

Note: LS mean and SE were obtained from the ANCOVA model.

FIG. 84



Abbreviations: 6MWD = 6-minute walk distance; BM = biomarkers; CFBL = change from baseline; CI = confidence interval; CK = creatine kinase; FVC = forced vital capacity; GSGC = Gait, Stairs, Gowers' maneuver, and Chair test; Hex4 = hexose tetrasaccharide; ITT = Intent-to-Treat; MEP = maximum expiratory pressure; MIP = maximal inspiratory pressure; MMT = manual muscle testing; P = predicted; PRO = patient-reported outcomes; PROMIS = Patient-reported Outcomes Measurement Information System; QMT = quantitative muscle testing; SVC = slow vital capacity; TUG = Timed Up and Go

Note: The original mean CFBL values and 95% CIs were scaled by the standard deviation to get the standardized effect sizes and 95% CIs, and then plotted.

A plot from the standardized mean value to the zero line is indicated by a solid bar; the error bars (standardized 95% CIs) are plotted by a black line.

Note: Results were reversed before plotting to reflect the fact that negative CFBL values indicate improvement.

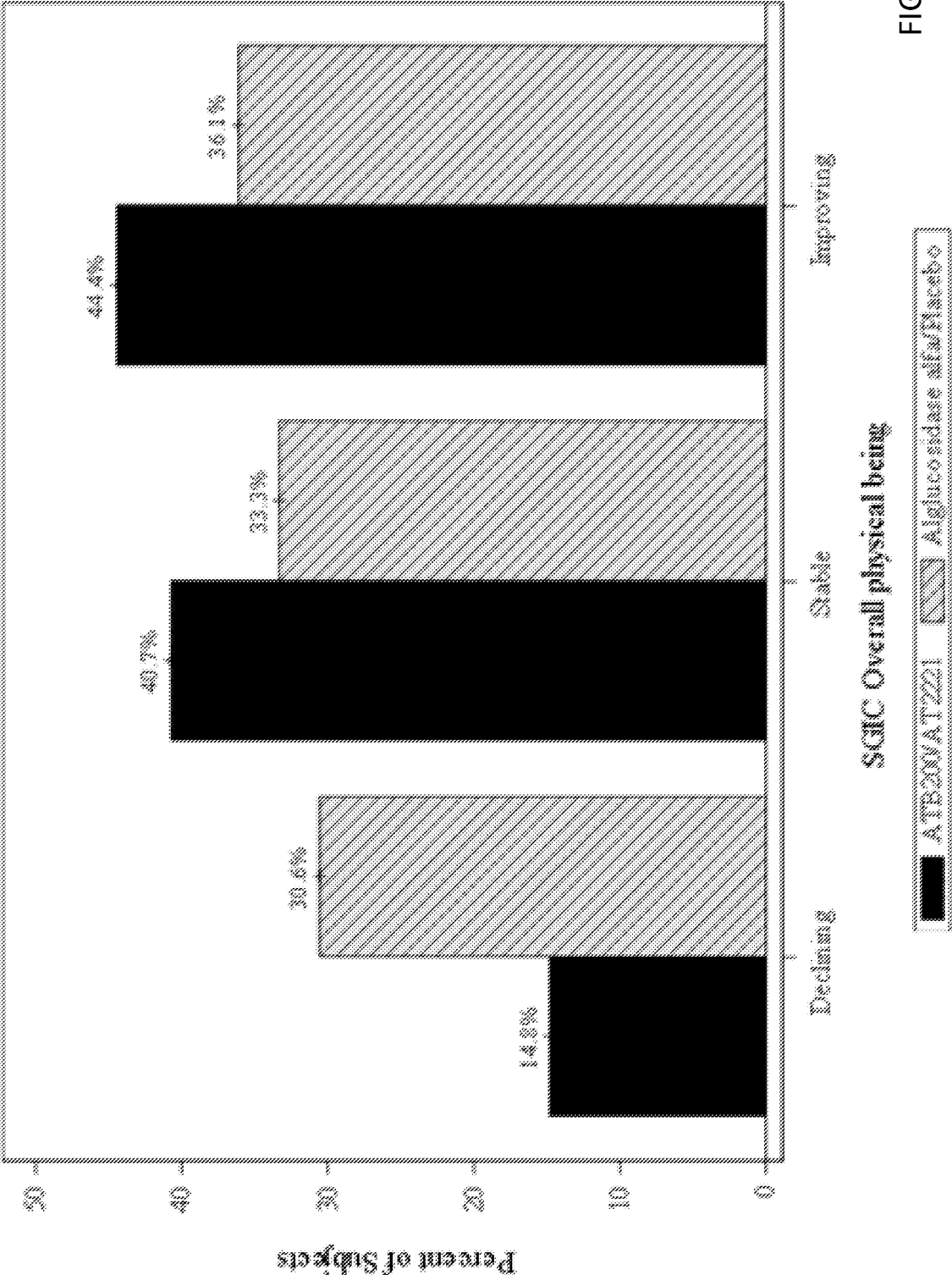


FIG. 86

Abbreviations: AT2221 = miglustat; ATB200 = cipaglucosidase alfa; SGIC = Subject's Global Impression of Change

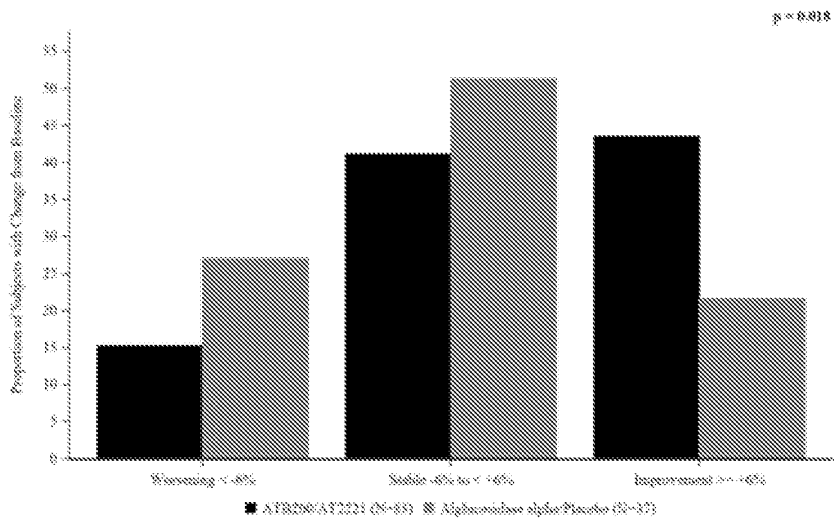


FIG. 87A

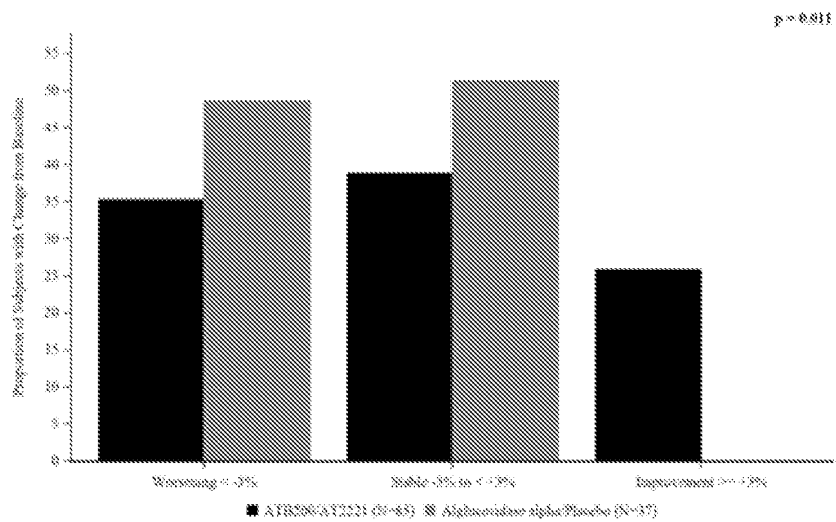


FIG. 87B

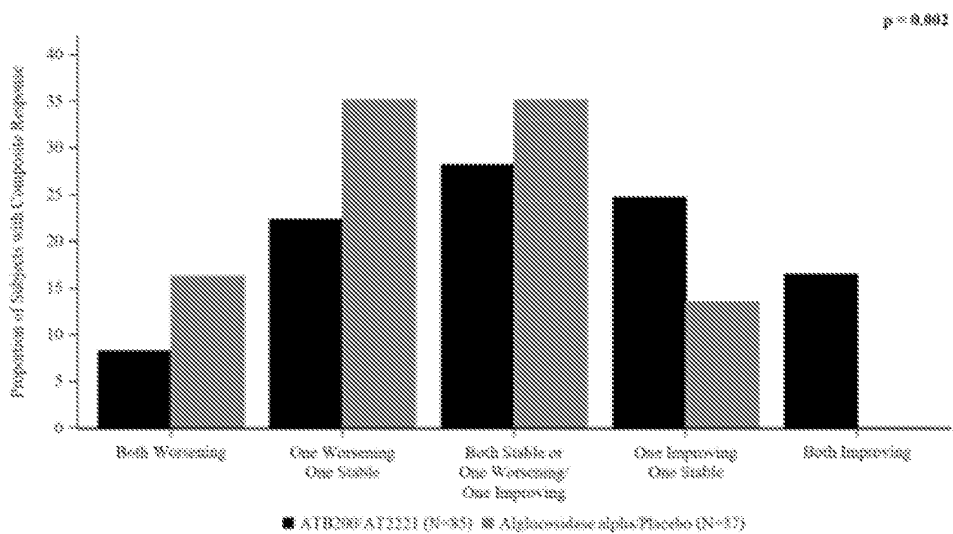
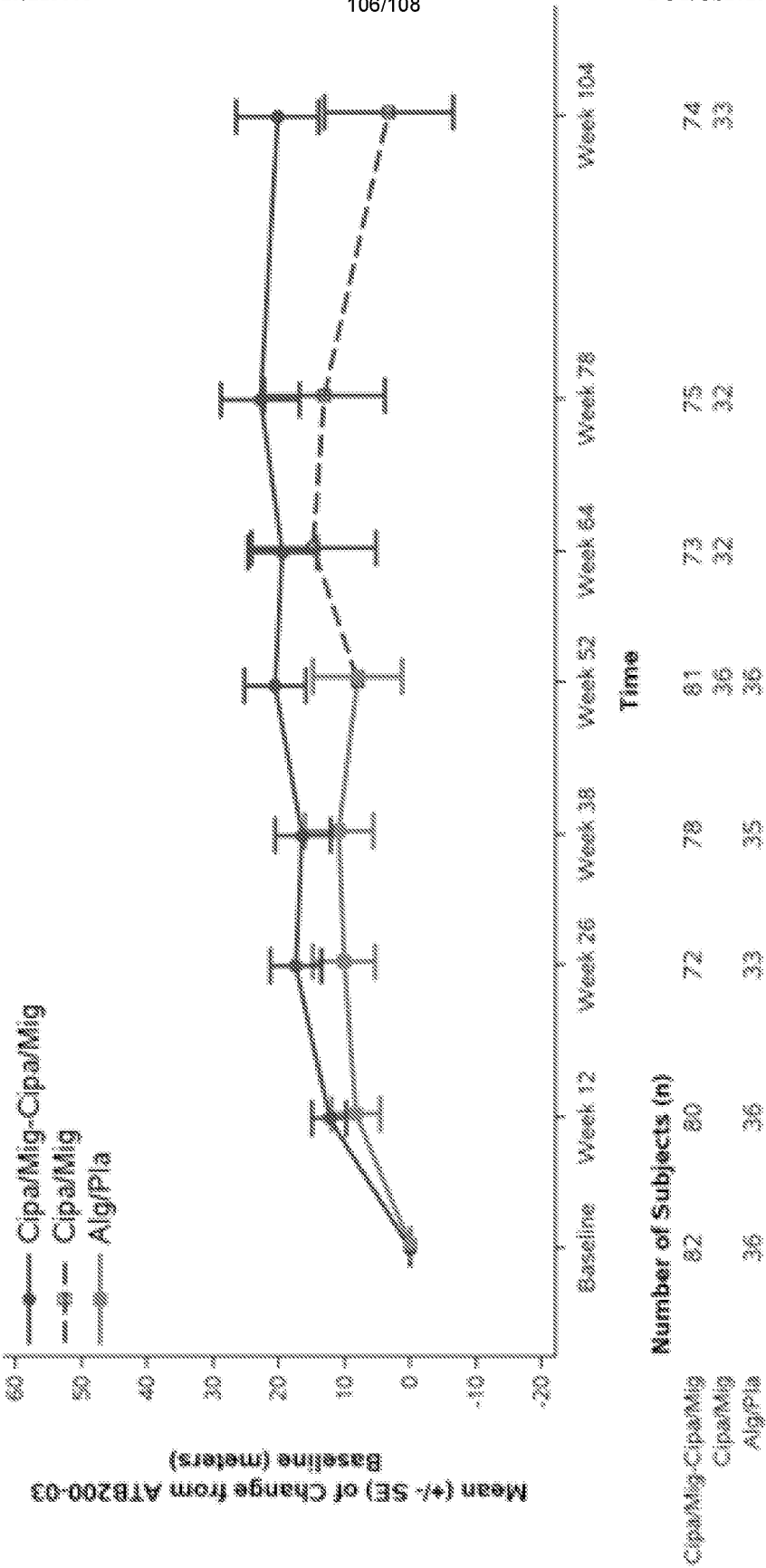


FIG. 87C

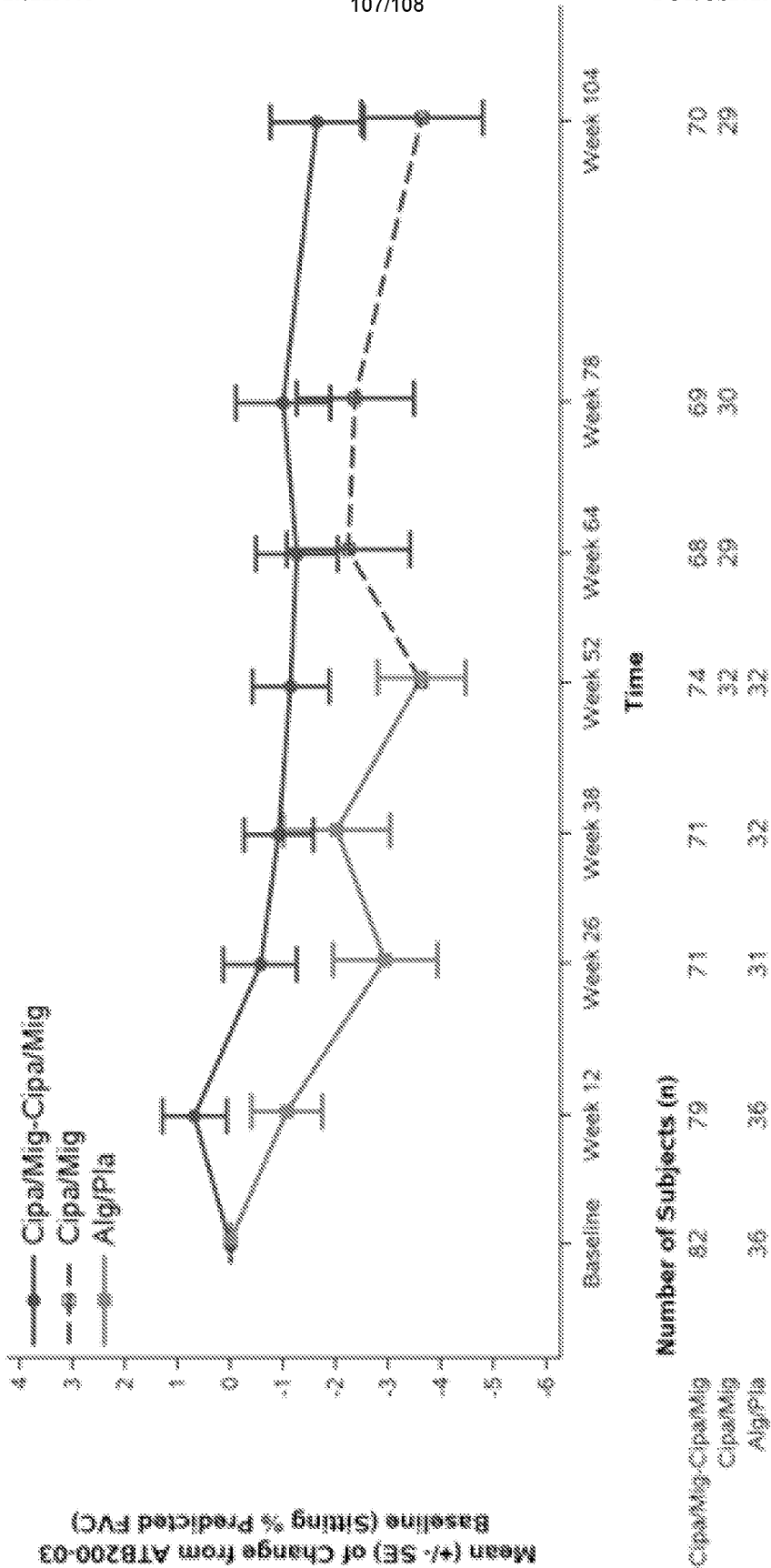
Line Chart for Mean ($\pm$ SE) of Change from Study ATB200-03 Baseline over Time in 6MWD (meters) (OLE-ES Population Excluding Subject 4005 2511) – Study ATB200-07



Abbreviations: 6MWD = 6-minute walk distance; Alg/Pla = Alglucosidase alfa/Placebo; Cipa/Mig = Cipaglucosidase alfa/Miglustat; OLE ES = open-label extension-enrolled subjects; SE = standard error

FIG. 88

Line Chart for Mean ($\pm$ SE) of Change from Study ATB200-03 Baseline over Time in Sitting % Predicted FVC (OLE-ES Population Excluding Subject 4005 2511) – Study ATB200-07



Abbreviations: Alg/Pla = Alglucosidase alfa/Placebo; Cipa/Mig = Cipaglucosidase alfa/Miglustat; FVC = forced vital capacity; OLE ES = open-label extension-enrolled subjects; SE = standard error

FIG. 89

Line Chart for Mean ($\pm$ SE) of Change from Study ATB200-03 Baseline over Time in CK (U/L) (OLE-ES Population Excluding Subject 4005-2511) – Study ATB200-07

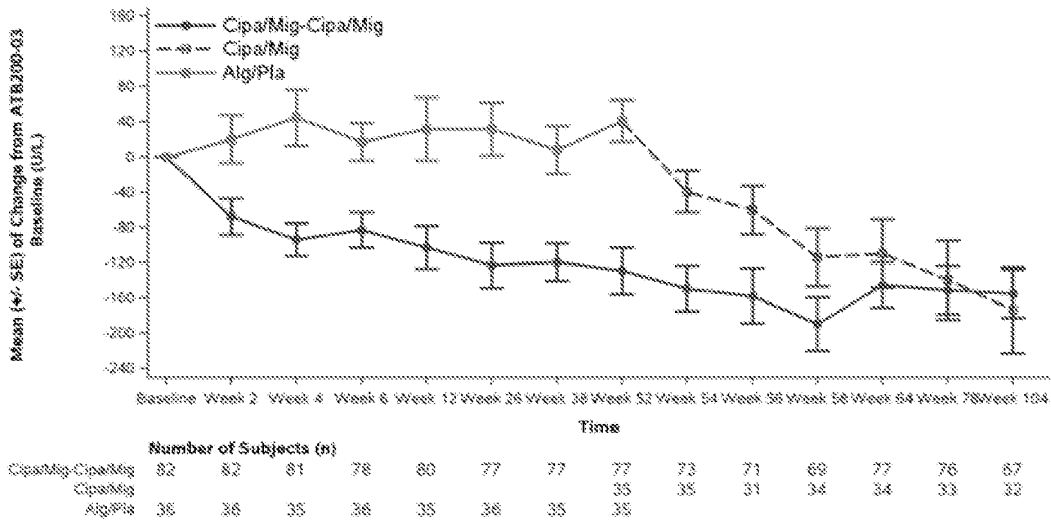


FIG. 90A

Line Chart for Mean ($\pm$ SE) of Change from Study ATB200-03 Baseline over Time in Hex4 (mmol/mol creatinine) (OLE-ES Population Excluding Subject 4005 2511) – Study ATB200-07

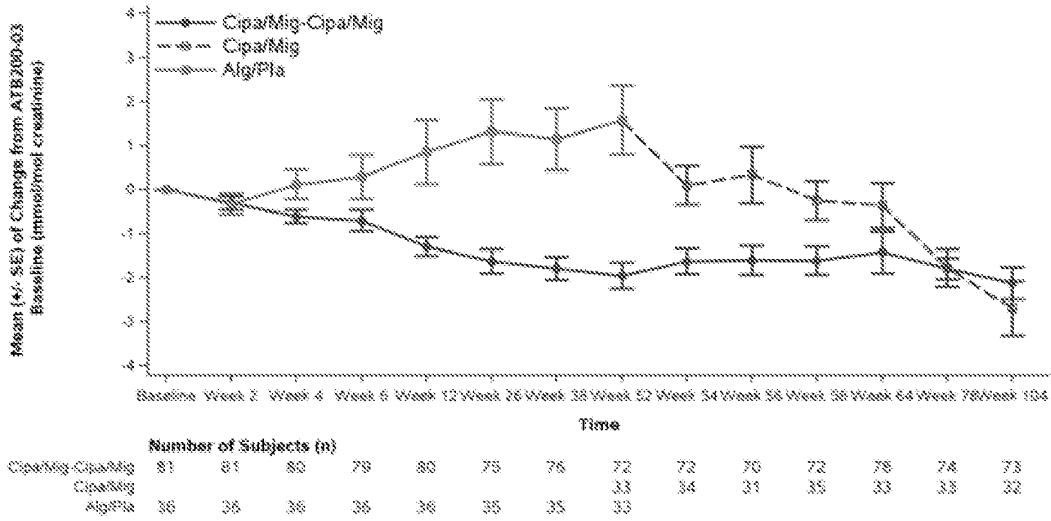


FIG. 90B