Efficacy and safety of cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo in late-onset Pompe disease: PROPEL study

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INTRODUCTION

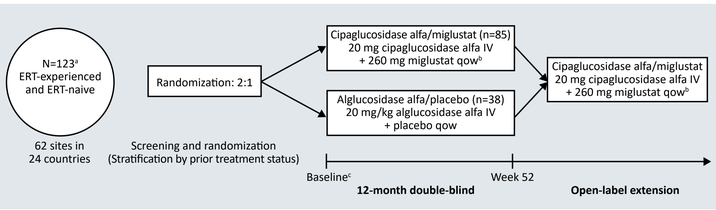
- Pompe disease is a rare, autosomal recessive lysosomal disorder caused by pathogenic variants of the acid alpha-glucosidase (GAA) gene.[1,2]
- Functional deficiency of GAA leads to lysosomal accumulation of glycogen in all tissues, especially skeletal, cardiac, and smooth muscles.[1,3]
- The clinical presentation of Pompe disease includes two phenotypes: infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD).[3]
- LOPD is primarily characterized by progressive weakness in the limb-girdle and respiratory muscles, leading to motor and respiratory difficulties.[2]
- Alglucosidase alfa, a recombinant human GAA (rhGAA), is the only approved treatment that has been shown to improve prognosis in patients with IOPD and LOPD.[4,5]
- Cipaglucosidase alfa/miglustat is an investigational, two-component therapy comprising cipaglucosidase alfa administered in conjunction with miglustat:[6]
  - Cipaglucosidase alfa is an rhGAA with enhanced glycosylation designed for improved uptake and processing.
  - Miglustat is a small molecule that stabilizes cipaglucosidase alfa in blood and enhances delivery of the active enzyme to tissues.

METHODS

PROPEL Study Design

- PROPEL is a Phase III, randomized, double-blind, active-controlled trial to assess the efficacy and safety of cipaglucosidase alfa/miglustat in adult patients with LOPD compared with alglucosidase alfa/placebo (NCT03729362; **Figure 1**).[7]

Figure 1. PROPEL study design



[a]Two patients were randomized but not dosed; [b]195 mg for patients weighing 40–<50 kg; [c]baseline values were measured during screening (up to 30 days before dosing). For 6MWD and FVC: the baseline value is the average of last two measurements obtained on or prior to first dose date

- Key enrollment criteria were:
  - ≥18 years old, weighing ≥40 kg at screening with confirmed diagnosis of LOPD; GAA genotype was confirmed for all enrolled patients.
  - Stratified by prior enzyme-replacement therapy (ERT) status: those who received ERT (alglucosidase alfa) at the recommended dose and regimen of 20 mg/kg qow for ≥2 years (experienced group) or who were naive to ERT (naive group).
  - Must have performed two valid 6-minute walk tests with the following criteria: both screening values were ≥75 m and ≤90% of the predicted value for healthy adults, and the lower value was within 20% of the higher value.
  - Sitting forced vital capacity (FVC) ≥30% of the predicted value for healthy adults at screening.

Randomization and Study Endpoints

- Patients were randomized 2:1 to receive cipaglucosidase alfa/miglustat or alglucosidase alfa/placebo.
- The primary endpoint was change from baseline to week 52 in 6-minute walk distance (6MWD).
- The first key secondary endpoint was change from baseline to week 52 in % predicted sitting FVC.
- The other key secondary endpoints were change from baseline to week 52 in the following parameters, assessed in a prespecified statistical hierarchy:
  - Manual muscle test (MMT) score for lower extremities.
  - Patient-Reported Outcomes Measurement Information System (PROMIS®) – Physical Function domain score.
  - PROMIS® – Fatigue domain score.
  - Gait, Stairs, Gowers, Chair (GSGC) total score.
- Additional secondary endpoints that were relevant to both pulmonary and motor functions as well as muscle strength included:
  - Maximal inspiratory pressure and maximal expiratory pressure (pulmonary).
  - Timed 10-meter walk and 4-stair climb.
  - Gowers' maneuver and chair test as components of the GSGC assessment (motor); and MMT scores for total and upper extremities (muscle strength).
- Biomarker assessments included serum creatine kinase (CK) and urinary hexose tetrasaccharide 4 (Hex4) levels.

Statistical Methodology

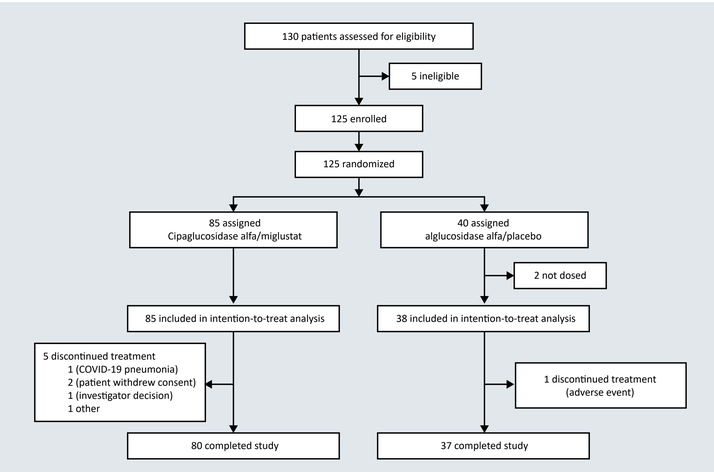
- The primary endpoint (6MWD) was analyzed using a mixed-effects model for repeated measures to assess the superiority of cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo.
- Tests of data normality and non-parametric analysis of covariance (ANCOVA) were prespecified if normality assumptions were violated.
- All key secondary endpoints, including FVC and the other secondary endpoints, were analyzed by ANCOVA.
- The primary and key secondary endpoints were tested at the one-sided 0.025 significance level.

RESULTS

Patients

- Patient disposition is presented in **Figure 2**.

Figure 2. Patient disposition



- Patient demographics at baseline were representative of the population and generally similar in the two treatment arms (**Table 1**).

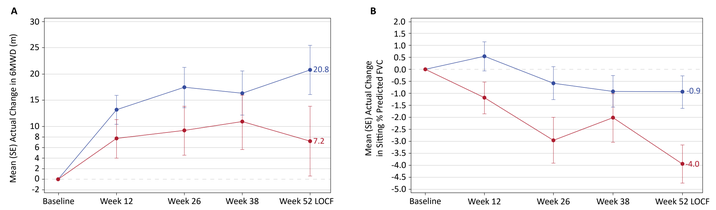
Table 1. Baseline demographics

	Cipaglucosidase alfa/miglustat n=85	Alglucosidase alfa/placebo 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)
Sex, n (%)			
Male	36 (42.4)	20 (52.6)	56 (45.5)
Female	49 (57.6)	18 (47.4)	67 (54.5)
Previous ERT Duration (years, ERT-experienced only)			
Mean (SD)	7.5 (3.4)	7.1 (3.6)	7.4 (3.4)
Median (min, max)	7.6 (2.0, 13.7)	7.1 (2.1, 13.2)	7.4 (2.0, 13.7)
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)

Primary Endpoint and First Key Secondary Endpoint

- Overall patients treated with cipaglucosidase alfa/miglustat showed improvement over time in 6MWD and stabilization over time in FVC in comparison with those treated with alglucosidase alfa/placebo (**Figure 3**).
- 6MWD showed greater improvement with cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo but did not reach statistical superiority (*P*=0.071; **Figure 3A**).
- FVC demonstrated a nominally statistically significant and clinically meaningful improvement with cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo (nominal *P*=0.023; **Figure 3B**).

Figure 3. Change from baseline in (A) 6MWD and (B) % predicted FVC in the overall population (N=122)



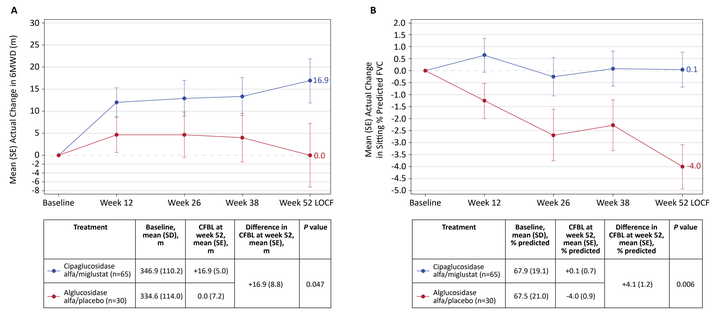
Treatment	Baseline, mean (SD), m	CFBL at week 52, mean (SE), m	Difference in CFBL at week 52, mean (SE), m	*P* value
Cipaglucosidase alfa/miglustat (n=85)	357.9 (111.8)	+20.8 (4.6)	+13.6 (8.3)	0.071
Alglucosidase alfa/placebo (n=37)	351.0 (121.3)	+7.2 (6.6)		

Treatment	Baseline, mean (SD), % predicted	CFBL at week 52, mean (SE), % predicted	Difference in CFBL at week 52, mean (SE), % predicted	*P* value
Cipaglucosidase alfa/miglustat (n=85)	70.7 (19.6)	-0.9 (0.7)	+3.0 (1.2)	0.023
Alglucosidase alfa/placebo (n=37)	69.7 (21.5)	-4.0 (0.8)		

CFBL is mean LOCF (SE); *P* values are nominal two-sided. 6MWD data were not normally distributed and 6MWD *P* value is for non-parametric ANCOVA; 6MWD parametric MMRM *P*=0.097. FVC data were normally distributed and *P* values are from ANCOVA. Results exclude one clinically implausible patient for deliberate underperformance at baseline to gain entry into the study. Since the primary endpoint did not meet statistical significance, subsequent analyses of key secondary endpoints that were tested according to the hierarchy of statistical analysis plan are interpreted as nominal statistical assessments of superiority

- ERT-experienced patients treated with cipaglucosidase alfa/miglustat demonstrated improvements over time in 6MWD and FVC compared with those treated with alglucosidase alfa/placebo (**Figure 4**).
- In the ERT-experienced population, 6MWD and FVC demonstrated a nominally statistically significant and clinically meaningful improvement with cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo (nominal *P*<0.05 for both; **Figure 4**).

Figure 4. Change from baseline in (A) 6MWD and (B) % predicted FVC in ERT-experienced patients (n=95)



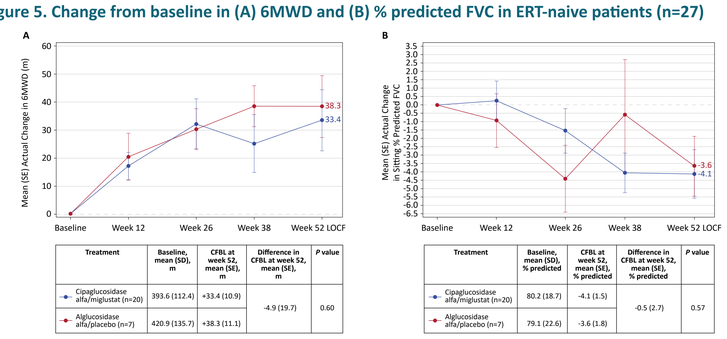
Treatment	Baseline, mean (SD), m	CFBL at week 52, mean (SE), m	Difference in CFBL at week 52, mean (SE), m	*P* value
Cipaglucosidase alfa/miglustat (n=65)	346.9 (110.2)	+16.9 (5.0)	+16.9 (8.8)	0.047
Alglucosidase alfa/placebo (n=30)	334.6 (114.0)	0.0 (7.2)		

Treatment	Baseline, mean (SD), % predicted	CFBL at week 52, mean (SE), % predicted	Difference in CFBL at week 52, mean (SE), % predicted	*P* value
Cipaglucosidase alfa/miglustat (n=65)	67.9 (19.1)	+0.1 (0.7)	+4.1 (1.2)	0.006
Alglucosidase alfa/placebo (n=30)	67.5 (21.0)	-4.0 (0.9)		

P values are nominal two-sided. 6MWD data were not normally distributed and 6MWD *P* value is for non-parametric ANCOVA; 6MWD parametric MMRM *P*=0.078. FVC data were normally distributed and *P* values are from ANCOVA

- In the smaller ERT-naive population, variability was greater and 6MWD and FVC both numerically favored alglucosidase alfa/placebo (**Figure 5**).
- ERT-naive patients in both the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo treatment groups had similar improvements over time in 6MWD, and both declined over time in FVC (**Figure 5**).

Figure 5. Change from baseline in (A) 6MWD and (B) % predicted FVC in ERT-naive patients (n=27)



Treatment	Baseline, mean (SD), m	CFBL at week 52, mean (SE), m	Difference in CFBL at week 52, mean (SE), m	*P* value
Cipaglucosidase alfa/miglustat (n=20)	393.6 (112.4)	+33.4 (10.9)	-4.9 (19.7)	0.60
Alglucosidase alfa/placebo (n=7)	420.9 (135.7)	+38.3 (11.1)		

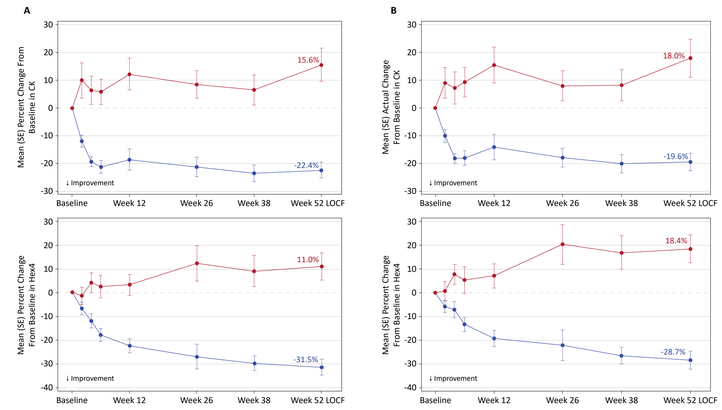
Treatment	Baseline, mean (SD), % predicted	CFBL at week 52, mean (SE), % predicted	Difference in CFBL at week 52, mean (SE), % predicted	*P* value
Cipaglucosidase alfa/miglustat (n=20)	80.2 (18.7)	-4.1 (1.5)	-0.5 (2.7)	0.57
Alglucosidase alfa/placebo (n=7)	79.1 (22.6)	-3.6 (1.8)		

P values are nominal two-sided. FVC data normally distributed and *P* values are from ANCOVA; 6MWD data not normally distributed and 6MWD *P* value is for Wilcoxon test; 6MWD parametric MMRM *P*=0.75. Results exclude one clinically implausible patient who used an investigational anabolic steroid ostarine (selective androgen receptor modulator) just prior to study start

Other Key Secondary Endpoints and Biomarkers

- In the overall and ERT-experienced populations, lower extremities MMT, PROMIS® – Physical Function and PROMIS® – Fatigue numerically favored cipaglucosidase alfa/miglustat.
- A clinically and nominally statistically significant improvement in GSGC total score was observed with cipaglucosidase alfa/miglustat compared with alglucosidase alfa/placebo in both the overall and ERT-experienced populations.
- In the overall and ERT-experienced populations, reductions in both CK and Hex4 were greater with cipaglucosidase alfa/miglustat (nominal *P*<0.001 for both; **Figure 6**).

Figure 6. Change from baseline in CK and Hex4 in (A) the overall population (N=122) and (B) ERT-experienced patients (n=95)



	Treatment	Baseline, mean (SD)	CFBL at week 52, mean (SE)	Difference in CFBL at week 52, mean (SE)	*P* value
CK, U/L	Cipaglucosidase alfa/miglustat (n=85)	447.0 (399.5)	-130.5 (25.1)	-190.7 (29.4)	<0.001
	Alglucosidase alfa/placebo (n=37)	527.8 (426.6)	60.2 (26.2)		
Hex4, mmol/mol creatinine	Cipaglucosidase alfa/miglustat (n=85)	4.6 (3.4)	-1.9 (0.3)	-3.1 (0.4)	<0.001
	Alglucosidase alfa/placebo (n=37)	6.9 (6.9)	1.2 (0.7)		

	Treatment	Baseline, mean (SD)	CFBL at week 52, mean (SE)	Difference in CFBL at week 52, mean (SE)	*P* value
CK, U/L	Cipaglucosidase alfa/miglustat (n=65)	441.8 (402.9)	-118.0 (28.4)	-197.6 (32.1)	<0.001
	Alglucosidase alfa/placebo (n=30)	492.3 (442.7)	79.6 (26.9)		
Hex4, mmol/mol creatinine	Cipaglucosidase alfa/miglustat (n=65)	4.6 (3.5)	-1.7 (0.3)	-3.6 (0.5)	<0.001
	Alglucosidase alfa/placebo (n=30)	7.2 (7.6)	1.9 (0.8)		

P values are nominal two-sided. Results exclude one clinically implausible patient who used an investigational anabolic steroid ostarine (selective androgen receptor modulator) just prior to study start

Summary of Assessed Endpoints

- Endpoints across motor function, pulmonary function, muscle strength, patient-reported outcomes, and biomarkers favored cipaglucosidase alfa/miglustat over alglucosidase alfa/placebo in both the overall and ERT-experienced populations, and those endpoints also improved from baseline (**Figure 7**).
- In the ERT-naive population, these endpoints demonstrated improvements in both arms with some parameters numerically favoring cipaglucosidase alfa/miglustat and others favoring alglucosidase alfa/placebo. Biomarkers both showed greater reductions with cipaglucosidase alfa/miglustat.

Figure 7. Summary of assessed endpoints: overall population and ERT-experienced patients

		Overall population				ERT-experienced			
	Endpoints	Cipaglucosidase alfa/miglustat n=85		Alglucosidase alfa/placebo n=37		Cipaglucosidase alfa/miglustat n=65		Alglucosidase alfa/placebo n=30	
		Baseline, mean	CFBL at week 52, mean (SE)	Baseline, mean	CFBL at week 52, mean (SE)	Baseline, mean	CFBL at week 52, mean (SE)	Baseline, mean	CFBL at week 52, mean (SE)
Motor function	6MWD, m	357.9	20.8 (4.6)	351.0	7.2 (6.6)	346.9	16.9 (5.0)	334.6	0.0 (7.2)
	GSGC total score	14.5	-0.5 (0.3)	14.5	0.8 (0.3)	15.6	-0.5 (0.3)	15.5	0.6 (0.4)
	10-meter walk, s	9.7	-0.5 (0.6)	9.6	1.9 (1.0)	10.4	-0.6 (0.9)	10.2	2.5 (1.2)
	4-stair climb, s	14.1	-8.5 (7.9)	8.2	0.3 (1.0)	17.3	-11.1 (10.5)	9.3	0.6 (1.2)
	Gower's maneuver, s	10.8	-0.3 (0.7)	19.8	-2.2 (1.4)	11.5	-0.4 (0.8)	23.9	-2.6 (1.9)
	Rising from chair, s	13.6	-10.2 (9.7)	4.5	-0.5 (0.7)	17.6	-13.7 (13.0)	5.2	-0.4 (0.9)
Pulmonary function	FVC, % predicted	70.7	-0.9 (0.7)	69.7	-4.0 (0.8)	67.9	0.1 (0.7)	67.5	-4.0 (0.9)
	MIP, % predicted	61.8	2.1 (2.1)	59.9	-2.7 (2.8)	61.3	1.0 (2.5)	55.0	-1.7 (1.5)
	MEP, % predicted	70.7	0.6 (2.4)	65.1	-1.6 (2.1)	70.7	-2.7 (2.7)	62.2	-3.9 (1.8)
Muscle strength	Lower MMT score	28.0	1.6 (0.4)	27.7	0.9 (0.4)	26.4	1.6 (0.5)	26.1	0.9 (0.5)
	Upper MMT score	34.3	1.5 (0.4)	34.7	0.7 (0.6)	33.7	1.8 (0.4)	34.2	0.4 (0.7)
	Total MMT score	62.3	3.1 (0.7)	62.4	1.4 (0.8)	60.1	3.4 (0.9)	60.3	1.1 (0.9)
PROs	PROMIS®-Physical Function	66.9	1.9 (0.8)	68.0	0.2 (1.8)	64.4	1.8 (0.9)	66.9	-1.0 (2.0)
	PROMIS®-Fatigue	22.3	-2.0 (0.6)	21.1	-1.7 (1.1)	22.0	-1.9 (0.7)	20.4	-0.3 (1.0)
Biomarkers	Urine Hex4, mmol/mol	4.6	-1.9 (0.3)	6.9	1.2 (0.7)	4.6	-1.7 (0.3)	7.2	1.9 (0.8)
	Serum CK, U/L	447.0	-130.5 (25.1)	527.8	60.2 (26.2)	441.8	-118.0 (28.4)	492.3	79.6 (26.9)

Based on LOCF means

Treatment group favored | Nominal statistical significance (*P*<0.05)

Safety Summary

- The safety profile was similar for cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo (**Table 2**).
- Treatment-emergent adverse events (TEAEs) leading to withdrawal in the cipaglucosidase alfa/miglustat arm were two infusion-associated reactions, one of which was a serious adverse event.
- The TEAE leading to withdrawal in the alglucosidase/placebo arm was stroke (unrelated to study drug).

Table 2. Safety summary

Treatment	Cipaglucosidase alfa/miglustat n=85	Alglucosidase alfa/placebo 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%)

CONCLUSIONS

- In the overall study population of ERT-naive and ERT-experienced patients, cipaglucosidase alfa/miglustat showed clinically meaningful improvements on motor and respiratory functions and biomarkers compared with alglucosidase alfa/placebo.
- Among the ERT-experienced patients (mean ERT duration of 7.4 years), those randomized to cipaglucosidase alfa/miglustat showed clinically meaningful improvements in motor and respiratory functions and biomarkers when compared with patients randomized to alglucosidase alfa/placebo.
- Of the 17 efficacy and biomarker endpoints assessed, 16 favored cipaglucosidase alfa/miglustat compared with alglucosidase alfa/placebo in both the overall study population and ERT-experienced patients.
- Cipaglucosidase alfa/miglustat demonstrated a similar safety profile to that of alglucosidase alfa/placebo.

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This presentation shares information about Amicus Therapeutics' investigational therapy, cipaglucosidase alfa/miglustat, which is in development for the treatment of Pompe disease. This investigational therapy is not approved by any regulatory agency at this time.

The presenter, Benedikt Schoser, has received grant funding to his institution and consulting fees from Amicus Therapeutics. He has served as an advisory board member for Sanofi Genzyme, Lupin, Spark Therapeutics, and Audentes Therapeutics. He has served as a consultant for Alexion and as a speaker for Kedrion and UCB Pharma.

Abbreviations

6MWD, 6-minute walk distance; ANCOVA, analysis of covariance; CFBL, change from baseline; CK, creatine kinase; ERT, enzyme-replacement therapy; FVC, forced vital capacity; GAA, acid alpha-glucosidase; GSGC, Gait, Stairs, Gowers, Chair; Hex4, hexose tetrasaccharide 4; IAR, infusion-associated reaction; IOPD, infantile-onset Pompe disease; LOCF, last observation carried forward; LOPD, late-onset Pompe disease; MEP, maximum expiratory pressure; MIP, maximal inspiratory pressure; MMRM, mixed-effect model for repeated measures; MMT, manual muscle test; PRO, patient-reported outcome; PROMIS®, Patient-Reported Outcomes Measurement Information System; qow, every other week; rhGAA, recombinant human GAA; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event.

References

1. Hers HG. *Biochem J.* 1963;86:11–16.
2. Kishnani PS *et al. J Pediatr.* 2004;144:S35–43.
3. Kishnani PS *et al. Genet Med.* 2006;8:267–88.
4. Lumizyme [prescribing information]. Sanofi Genzyme; 2020.
5. Do HV *et al. Ann Transl Med.* 2019;7:291.
6. Xu S *et al. JCI Insight.* 2019;4.
7. ClinicalTrials.gov NCT03729362. Available at: https://clinicaltrials.gov/ct2/show/NCT037293629.

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