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# Cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo in late-onset Pompe disease: PROPEL study subgroup analyses


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## OBJECTIVE

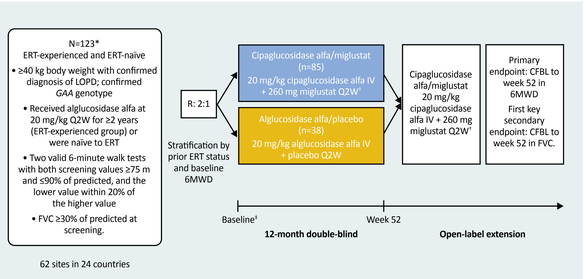
- PROPEL (NCT03729362) is a Phase III, randomised, double-blind, active-controlled trial to assess the efficacy and safety of cipaglucosidase alfa/miglustat in adults with late-onset Pompe disease (LOPD) compared with alglucosidase alfa/placebo.
- We report prespecified and *post hoc* subgroup analyses based on enzyme-replacement therapy (ERT) status, baseline 6-minute walk distance (6MWD), and baseline percent predicted sitting forced vital capacity (FVC).

## INTRODUCTION

- Pompe disease is a rare, autosomal recessive lysosomal disorder caused by pathogenic variants of the acid alpha-glucosidase (GAA) gene.[1,2]
- ERT with the recombinant human GAA (rhGAA), alglucosidase alfa, is the only approved treatment shown to improve prognosis in patients with infantile-onset Pompe disease (IOPD) and LOPD.[3,4]
- Cipaglucosidase alfa/miglustat is an investigational, two-component therapy comprising cipaglucosidase alfa administered in conjunction with miglustat[5]
  - Cipaglucosidase alfa is an rhGAA with enhanced glycosylation designed for improved uptake and processing
  - Miglustat is a small molecule that stabilises cipaglucosidase alfa in blood and enhances delivery of the active enzyme to tissues.

## METHODS

### Figure 1. PROPEL study design[6]




*Two patients were randomised but not dosed; †195 mg for patients weighing 40–<50 kg; ‡Baseline values were measured during screening (up to 30 days before dosing). For 6MWD and FVC, the baseline value was the average of the last two measurements obtained on or prior to first dose date. CFBL, change from baseline; IV, intravenous; Q2W, every 2 weeks; R, randomisation.

### Statistical methodology

- One ERT-naïve patient (algucosidase alfa/placebo group), deemed clinically implausible by the principal investigator based on baseline assessments, was excluded from all efficacy analyses.
- Additional statistical methodology is available in the Supplement, which is accessible via the QR code.

## RESULTS

### Patients

- Of the 85 patients randomised to cipaglucosidase alfa/miglustat, 80 completed the study; of the 38 patients randomised to alglucosidase alfa/placebo, 37 completed the study.
- Patient demographics at baseline were representative of the population and generally similar in the two treatment arms (**Table 1**).

### Primary endpoint and first key secondary endpoint

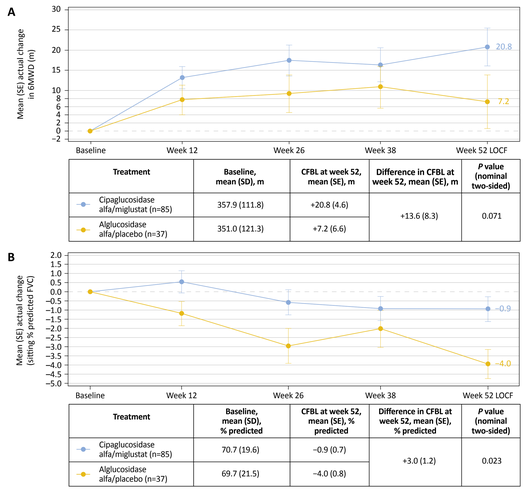
- Overall, patients treated with cipaglucosidase alfa/miglustat showed improvement over time in 6MWD and stabilisation over time in FVC in comparison with those treated with alglucosidase alfa/placebo (**Figure 2**)
  - 6MWD showed greater improvement with cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo but did not reach statistical superiority ($P$=0.071; **Figure 2A**)
  - FVC demonstrated a nominally statistically significant and clinically meaningful improvement with cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo (nominal $P$=0.023; **Figure 2B**).

### Table 1. Baseline characteristics

| | Cipaglucosidase alfa/miglustat n=85 | Alglucosidase alfa/placebo n=38 | Total N=123 |
|---|---|---|---|
| **Median (range) age, years** | 48.0 (19, 74) | 46.0 (22, 66) | 47.0 (19, 74) |
| **Male** | 36 (42.4) | 20 (52.6) | 56 (45.5) |
| **Female** | 49 (57.6) | 18 (47.4) | 67 (54.5) |
| **ERT-naïve** | 20 (23.5) | 8 (21.1) | 28 (22.8) |
| **ERT-experienced** | 65 (76.5) | 30 (78.9) | 95 (77.2) |
| **Median (range) previous ERT duration, years, ERT experienced only** | 7.6 (2.0, 13.7) | 7.1 (2.1, 13.2) | 7.4 (2.0, 13.7) |
| **Prespecified baseline 6MWD, n (%)** | | | |
| **≥75–<150 m** | 4 (4.7) | 4 (10.5) | 8 (6.5) |
| **≥150–<400 m** | 55 (64.7) | 22 (57.9) | 77 (62.6) |
| **≥400 m** | 26 (30.6) | 12 (31.6) | 38 (30.9) |

Data are n (%) unless indicated.

### Figure 2. Change from baseline in (A) 6MWD and (B) 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 (nominal two-sided) |
|---|---|---|---|---|
| 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 (nominal two-sided) |
|---|---|---|---|---|
| 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) | | |

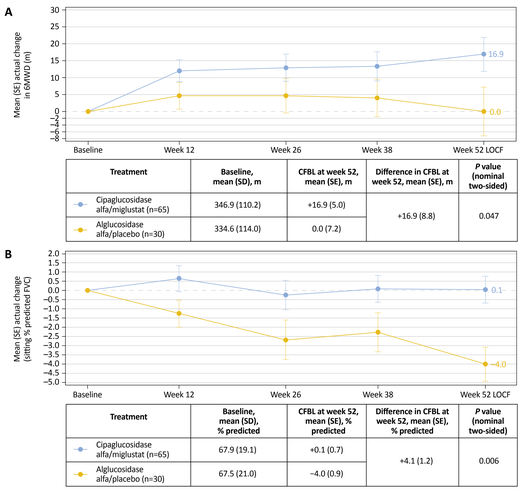
CFBL is mean (SE) LOCF. 6MWD data were not normally distributed and the 6MWD *P* value is from non-parametric ANCOVA; 6MWD parametric MMRM $P$=0.097. FVC data were normally distributed and the *P* value is from ANCOVA. Since the primary endpoint did not meet statistical significance, subsequent analyses of key secondary endpoints that were tested according to the hierarchy of the statistical analysis plan are interpreted as nominal statistical assessments of superiority. ANCOVA, analysis of covariance; LOCF, last observation carried forward; MMRM, mixed-effect model for repeated measures; SE, standard error.

### Prespecified subgroup analyses

**1. ERT status**

- In the ERT-experienced population, 6MWD and FVC showed a nominally statistically significant and clinically meaningful improvement at week 52 with cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo (nominal $P$<0.05 for both; **Figure 3**).
- In the smaller ERT-naïve population (n=27), variability was greater and 6MWD and FVC both numerically favoured alglucosidase alfa/placebo
  - 6MWD: both the cipaglucosidase alfa/miglustat (n=20) and alglucosidase alfa/placebo (n=7) groups had similar improvements over time (mean [SE] CFBL to week 52: +33.4 [10.9] m and +38.3 [11.1] m, respectively; nominal two-sided $P$=0.60)
  - FVC: both the cipaglucosidase alfa/miglustat (n=20) and alglucosidase alfa/placebo (n=7) groups declined over time (mean [SE] CFBL to week 52: −4.1 [1.5] % and −3.6 [1.8] %, respectively; nominal two-sided $P$=0.57).

### Figure 3. Change from baseline in (A) 6MWD and (B) 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 (nominal two-sided) |
|---|---|---|---|---|
| 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) | | |

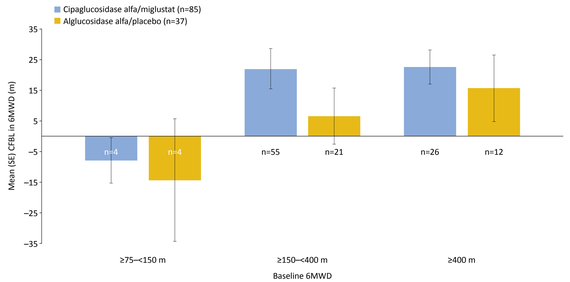
| Treatment | Baseline, mean (SD), % predicted | CFBL at week 52, mean (SE), % predicted | Difference in CFBL at week 52, mean (SE), % predicted | *P* value (nominal two-sided) |
|---|---|---|---|---|
| Cipaglucosidase alfa/miglustat (n=65) | 67.9 (19.1) | +0.1 (0.7) | +4.1 (1.2) | 0.006 |
| Alglucosidase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

6MWD data were not normally distributed and the 6MWD *P* value is from non-parametric ANCOVA; 6MWD parametric MMRM $P$=0.078. FVC data were normally distributed and the FVC *P* value is from ANCOVA.

**2. Baseline 6MWD categories**

- Cipaglucosidase alfa/miglustat was favoured across prespecified baseline 6MWD categories versus alglucosidase alfa/placebo (**Figure 4**).

### Figure 4. Change from baseline in 6MWD by prespecified baseline 6MWD categories in the overall population (n=122)



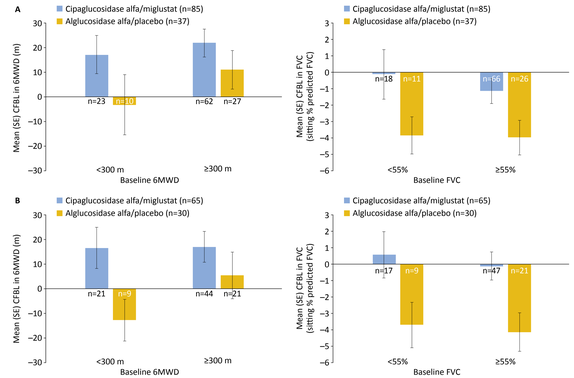

CFBL is mean LOCF (SE) to week 52.

### *Post hoc* subgroup analyses

**Baseline 6MWD and FVC categories**

- Outcomes consistently favoured cipaglucosidase alfa/miglustat in the overall and ERT-experienced populations in patients with baseline 6MWD of <300 m and ≥300 m, and FVC of <55% and ≥55% (**Figure 5**).
- ERT-naïve population (n=27): three patients had a baseline 6MWD of <300 m and three had a baseline FVC of <55%; analyses of CFBL were not performed in these subgroups owing to the small patient numbers
  - Baseline 6MWD ≥300 m: both the cipaglucosidase alfa/miglustat (n=18) and alglucosidase alfa/placebo (n=6) groups had similar improvements over time (mean [SE] CFBL to week 52: +34.4 [12.1] m and +30.8 [9.6] m, respectively)
  - Baseline FVC ≥55%: both the cipaglucosidase alfa/miglustat (n=19) and alglucosidase alfa/placebo (n=5) groups declined over time (mean [SE] CFBL to week 52: −3.7 [1.5] % and −3.3 [2.6] %, respectively).

### Figure 5. Change from baseline in 6MWD and FVC by baseline status in (A) the overall population (n=122) and (B) ERT-experienced patients (n=95)




CFBL is mean LOCF (SE) to week 52.

### Safety summary

- The safety profile was similar for cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo (**Table 2**); further characterisation of the safety profile is available in **Supplementary Table 1**.

### Table 2. Safety summary

| | Cipaglucosidase alfa/miglustat n=85 | Alglucosidase alfa/placebo n=38 |
|---|---|---|
| **TEAEs, n (%)** | 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** | 3 (3.5)† | 1 (2.6)‡ |
| **TEAEs leading to death** | 0 | 0 |
| **IARs** | 21 (24.7) | 10 (26.3) |

*IAR of anaphylactic reaction; †COVID-19-related pneumonia and IARs of anaphylactic reaction and chills; ‡Stroke, unrelated to treatment. IAR, infusion-associated reaction; TEAE, treatment-emergent adverse event.

## CONCLUSIONS

- In the overall study population including ERT-naïve and ERT-experienced patients, cipaglucosidase alfa/miglustat showed positive trends or clinically meaningful improvements on motor and respiratory functions compared with approved ERT, regardless of baseline 6MWD and % FVC assessments, and across both prespecified and *post hoc* subgroup analyses.
- 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, Dr Mark Roberts, has no conflicts of interest to declare.


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