Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial

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Summary

Background Pompe disease is a rare disorder characterised by progressive loss of muscle and respiratory function due to acid α-glucosidase deficiency. Enzyme replacement therapy with recombinant human acid α-glucosidase, alglucosidase alfa, is the first approved treatment for the disease, but some patients do not respond, and many do not show a sustained benefit. We aimed to assess the safety and efficacy of an investigational two-component therapy (cipaglucosidase alfa, a novel recombinant human acid α-glucosidase, plus miglustat, an enzyme stabiliser) for late-onset Pompe disease.

Methods We did a randomised, double-blind, parallel-group, phase 3 trial at 62 neuromuscular and metabolic medical centres in 24 countries in the Americas, Asia-Pacific, and Europe. Eligible participants were aged 18 years or older with late-onset Pompe disease, and had either been receiving alglucosidase alfa for at least 2 years or were enzyme replacement therapy-naive. Participants were randomly assigned (2:1) using interactive response technology software, stratified by 6-min walk distance and previous enzyme replacement therapy status, to intravenous cipaglucosidase alfa (20 mg/kg) plus oral miglustat or to intravenous alglucosidase alfa (20 mg/kg) plus oral placebo once every 2 weeks for 52 weeks. Patients, investigators, and outcome assessors were masked to treatment assignment. The primary endpoint was change from baseline to week 52 in 6-min walk distance, assessed using a mixed-effect model for repeated measures analysis for comparison of superiority in the intention-to-treat population (all patients who received at least one dose of study drug). This study is now complete and is registered with ClinicalTrials.gov, NCT03729362.

Findings Between Dec 3, 2018, and Nov 26, 2019, 130 patients were screened for eligibility and 125 were enrolled and randomly assigned to receive cipaglucosidase alfa plus miglustat (n=85) or alglucosidase alfa plus placebo (n=40). Two patients in the alglucosidase alfa plus placebo group did not receive any dose due to absence of genotype confirmation of late-onset Pompe disease and were excluded from analysis. Six patients discontinued (one in the alglucosidase alfa plus placebo group, five in the cipaglucosidase alfa plus miglustat group), and 117 completed the study. At week 52, mean change from baseline in 6-min walk distance was 20·8 m (SE 4·6) in the cipaglucosidase alfa plus miglustat group versus 7·2 m (6·6) in the alglucosidase alfa plus placebo group using last observation carried forward (between-group difference 13·6 m [95% CI −2·8 to 29·9]). 118 (96%) of 123 patients experienced at least one treatment-emergent adverse event during the study; the incidence was similar between the cipaglucosidase alfa plus miglustat group (n=81 [95%]) and the alglucosidase alfa plus placebo group (n=37 [97%]). The most frequently reported treatment-emergent adverse events were fall (25 [29%] patients in the cipaglucosidase alfa plus miglustat group *vs* 15 [39%] in the alglucosidase alfa plus placebo group), headache (20 [24%] *vs* 9 [24%]), nasopharyngitis (19 [22%] *vs* 3 [8%]), myalgia (14 [16%] *vs* 5 [13%]), and arthralgia (13 [15%]) *vs* 5 [13%]). 12 serious adverse events occurred in eight patients in the cipaglucosidase alfa plus miglustat group; only one event (anaphylaxis) was deemed related to study drug. One serious adverse event (stroke) occurred in the alglucosidase alfa plus placebo group, which was deemed unrelated to study drug. There were no deaths.

Interpretation Cipaglucosidase alfa plus miglustat did not achieve statistical superiority to alglucosidase alfa plus placebo for improving 6-min walk distance in our overall population of patients with late-onset Pompe disease. Further studies should investigate the longer-term safety and efficacy of cipaglucosidase alfa plus miglustat and whether this investigational two-component therapy might provide benefits, particularly in respiratory function and in patients who have been receiving enzyme replacement therapy for more than 2 years, as suggested by our secondary and subgroup analyses.

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See **Comment** page 973

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Research in context

Evidence before this study

We searched MEDLINE and Embase for clinical trials published in English from Jan 1, 2010, to March 1, 2021, using the terms "enzyme replacement therapy" OR "alglucosidase alfa" AND "Pompe". Results from the LOTS trial (NCT00158600) showed the safety and efficacy of alglucosidase alfa compared with placebo in late-onset Pompe disease, as evidenced by improved 6-min walk distance (6MWD) and pulmonary function (as assessed using forced vital capacity [FVC]) over 78 weeks. A systematic review published in 2017 reported that, although many adult patients with Pompe disease showed initial improvement on approved enzyme replacement therapy, a subgroup of patients did not show any initial benefit in 6MWD (up to 24% of patients) or FVC (up to 30% of patients). Poor skeletal muscle response to alglucosidase alfa is due in part to poor phosphorylation of recombinant human acid α-glucosidase (rhGAA), instability of rhGAA in the bloodstream, and immunogenicity. A two-component therapy comprising cipaglucosidase alfa and miglustat, an enzyme stabilizer designed to overcome these key challenges, significantly improved the Pompe disease pathogenic cascade compared with alglucosidase alfa in a murine model of Pompe disease. Functional benefits of cipaglucosidase alfa plus miglustat were shown in ATB200-02 (NCT02675465), an open-label phase 1/2 trial that included adults with Pompe disease.

Added value of this study

To our knowledge, this phase 3 study of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo is the largest randomised controlled trial in any lysosomal disorder, and is the only study in late-onset Pompe disease to include patients who have previously been treated with an approved therapy at the licenced standard dose.

Implications of all the available evidence

Despite the availability of an approved treatment, substantial unmet needs remain, and additional treatment options are needed for patients with late-onset Pompe disease. In this study, cipaglucosidase alfa plus miglustat resulted in clinically meaningful improvements in key motor and respiratory outcomes compared with approved enzyme replacement therapy in patients with late-onset Pompe disease, even among those who had been receiving approved therapy for at least 2 years, a population subgroup whose response has been shown to plateau or decline after several years on treatment.

Introduction

Pompe disease is a rare, autosomal recessive disorder caused by pathogenic variants in the *GAA* gene that result in complete or partial loss of endogenous acid α-glucosidase (GAA) activity, which is normally responsible for the breakdown of lysosomal glycogen.[1] The enzyme deficiency leads to accumulation of glycogen in all tissues, especially skeletal, cardiac, and smooth muscle.[1–3] A cascade of events stemming from lysosomal dysfunction, including autophagy dysregulation and disruption of signalling pathways and protein homoeostasis, predominantly leads to muscle dysfunction and damage, although multisystemic dysregulation is evident.[4]

Pompe disease is a spectrum of phenotypes broadly classified into two clinical subtypes: infantile-onset Pompe disease and late-onset Pompe disease.[1,2] Late-onset Pompe disease is characterised by progressive weakness in the axial, limb-girdle, and respiratory muscles, leading to motor and respiratory difficulties.[3] As the disease progresses, people living with Pompe disease often require wheelchairs for mobility and ventilators for breathing assistance, and respiratory failure is the most common cause of death.[2,3,5]

Alglucosidase alfa, the first approved treatment for patients with Pompe disease,[6,7] has been shown to improve prognosis.[8,9] Alglucosidase alfa has provided clinical benefits, particularly in increasing ventilator-free survival, in infantile-onset Pompe disease.[2] Although alglucosidase alfa enzyme replacement therapy (ERT) can slow disease progression, it has not been shown to halt or reverse disease progression. Thus, a substantial unmet medical need remains.[8,10,11] Patients with late-onset Pompe disease have generally been shown to improve initially or stabilise with alglucosidase alfa during the first 2–3 years on treatment; however, this is followed by a plateau or steady decline in many patients.[11–14]

We evaluated an investigational two-component therapy comprising intravenous cipaglucosidase alfa, a novel recombinant human acid α-glucosidase (rhGAA) with enhanced glycosylation for improved cellular uptake and processing, administered in conjunction with miglustat, an orally administered small molecule stabiliser of cipaglucosidase alfa.[15] Cipaglucosidase alfa is enriched with cellularly derived bis-phosphorylated N-glycans to improve its cation-independent cellular uptake through mannose-6-phosphate receptors and ensure that it can be fully processed into the most active form of the enzyme.[15] Miglustat binds to and stabilises cipaglucosidase alfa and prolongs its distribution half-life, thereby increasing levels of active enzyme available for targeting to lysosomes in muscles.[15]

In *GAA*-knockout mice,[16] cipaglucosidase alfa plus miglustat completely reversed the primary defect of GAA deficiency and glycogen accumulation in skeletal muscles, restored muscle strength, and corrected or improved several aspects of the pathogenesis, including lysosomal damage, autophagic build-up, dysregulated signalling in the AMP-activated kinase and mechanistic target of rapamycin (AMPK/mTOR) pathway, proteostasis, and metabolic dysfunction.[4,15]

Safety and efficacy of cipaglucosidase alfa plus miglustat were previously evaluated in adult patients with Pompe disease in an open-label, phase 1/2 study that showed cipaglucosidase alfa plus miglustat was well tolerated and provided durable functional benefits (up to 24 months) in patients who had or had not previously received ERT.[17] We aimed to assess the safety and efficacy of cipaglucosidase alfa plus miglustat compared with alglucosidase alfa plus placebo in the treatment of late-onset Pompe disease.

Methods

Study design and participants

We did a randomised, double-blind, parallel-group, phase 3 trial at 62 neuromuscular and metabolic medical centres in 24 countries (Argentina, Austria, Australia, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Denmark, France, Germany, Greece, Hungary, Italy, Japan, the Netherlands, New Zealand, Poland, Slovenia, Spain, South Korea, Sweden, Taiwan, the UK, and the USA; PROPEL). Eligible patients were aged 18 years or older with body weight of at least 40 kg and a diagnosis of late-onset Pompe disease based on documentation of GAA enzyme deficiency or *GAA* genotyping; genotype information was confirmed for all participants at Emory Genetics Laboratory, Atlanta, GA, USA. Patients had either received alglucosidase alfa at the recommended dose and regimen of 20 mg/kg once every 2 weeks for at least 2 years (ERT-experienced) or had not received previous treatment with alglucosidase alfa or investigational ERT (ERT-naive). Patients were required to have a sitting forced vital capacity (FVC) of at least 30% of the predicted value for healthy adults and to have performed two valid 6-min walk tests (both 6-min walk test screening values had to be ≥75 m and ≤90% of the predicted value for healthy adults, and the lower value had to be ≥80% of the higher value). Exclusion criteria were receiving any investigational therapy or pharmacological treatment for Pompe disease within 30 days or five half-lives of the therapy before day 1 of the study; receiving gene therapy for Pompe disease; use of ventilation support for more than 6 h per day while awake; taking any prohibited medications (miglitol, miglustat, acarbose, or voglibose) within 30 days before day 1; hypersensitivity to any of the excipients in cipaglucosidase alfa, alglucosidase alfa, or miglustat; or any medical condition or any other extenuating circumstance that might, in the opinion of the investigator or medical monitor, pose an undue safety risk to the patient or might compromise their ability to comply with the study.

This study was designed and monitored in accordance with the ethical principles of Good Clinical Practice guidelines and the Declaration of Helsinki. The clinical study protocol was reviewed and approved by the appropriate independent ethics committee or institutional review board at each study site. All participants provided written informed consent before participating in the study.

Randomisation and masking

Patients were recruited by treating physicians (neuromuscular and metabolic disease specialists) and media advertisements. Eligible patients were randomly assigned (2:1) using proprietary and validated interactive response technology software (Almac Clinical Technologies, Craigavon, UK) to receive cipaglucosidase alfa plus miglustat or alglucosidase alfa plus placebo (appendix p 2). Randomisation was stratified by 6-min walk distance (6MWD) at baseline (75 to <150 m, 150 to <400 m, or ≥400 m) and previous ERT status (ERT-naive or ERT-experienced). Patients, the study sponsor, investigators, site personnel, and contracted research organisations involved in monitoring, data management, data analysis, or other aspects of the study were masked to treatment assignment. Study drug codes were available for data analysis after completion of the study, verification of data files, determination of protocol violations (appendix p 2), and locking of the database.

See Online for appendix

Procedures

Participants received cipaglucosidase alfa (Amicus Therapeutics, Philadelphia, PA, USA) plus miglustat (Amicus Therapeutics) or alglucosidase alfa (Genzyme Corporation, Cambridge, MA, USA) plus placebo (Alcami, Wilmington, NC, USA) once every 2 weeks for 52 weeks. Cipaglucosidase alfa (20 mg/kg) and alglucosidase alfa (20 mg/kg) were administered by intravenous infusion. Miglustat (195 mg for patients with body weight of 40 to <50 kg, and 260 mg for patients with body weight of ≥50 kg) and placebo were administered orally approximately 1 h before infusion of cipaglucosidase alfa or alglucosidase alfa, respectively. The timing of miglustat administration was selected to optimise binding and stabilisation of cipaglucosidase alfa while in circulation. Cipaglucosidase alfa and alglucosidase alfa appeared identical, as both were white to off-white lyophilised cake or powder supplied in single-use, clear, 20 mL glass vials. Miglustat was supplied as white, hard capsules in 40 mL high-density polyethylene bottles and placebo was matched to miglustat. Miglustat dosing was dependent on the body weight and comprised three or four capsules of 65 mg miglustat. Potential study participants were screened within a 30-day period (with visits occurring over ≥2 days). During the screening period, ERT-experienced patients continued to take alglucosidase alfa, which was replaced by study drug on the same schedule as alglucosidase alfa (every 2 weeks), without interruption after randomisation. Participants who missed study visits due to COVID-19 pandemic-related reasons were allowed to participate in the study beyond 52 weeks (appendix p 2).

Efficacy assessments were done at baseline and at weeks 12, 26, 38, and 52 (or end of study). After completion of 52 weeks, participants had the option of enrolling in an open-label extension study; those who did not enrol were followed-up for 30 days after their last dose.

Serum creatine kinase levels were measured using the standard laboratory test. Urinary glucose tetrasaccharide (Hex4) levels were quantified at the Duke Biochemical Genetics Laboratory, Durham, NC, USA, by stable isotope dilution following ultraperformance liquid chromatography. Clinical laboratory tests and physical examinations were done at weeks 2, 4, 6, 12, 26, 38, and 52. Immunogenicity testing was performed on day 1 and at weeks 2, 4, 6, 12, 26, 38, and 52, and 30 days or longer after the last dose. Adverse events were assessed at all infusion visits (every 2 weeks) and follow-up visits. The site investigator determined whether an adverse event was deemed related to study drug.

Outcomes

The primary efficacy endpoint was change from baseline to week 52 in 6MWD (measured on a flat surface with walking shoes; walking aids, such as a cane, walker, or rollator, were permitted and were used consistently throughout the study, when required). The first key secondary efficacy endpoint was change from baseline to week 52 in sitting FVC (% predicted). The other key secondary endpoints assessed in a prespecified statistical hierarchy were change from baseline at week 52 in the manual muscle test score for lower extremities (sum of hip and knee scores); change from baseline to week 26 in 6MWD; change from baseline to week 52 in the total score for the Patient-Reported Outcomes Measurement Information System (PROMIS) physical function and fatigue measures; and change from baseline to week 52 in the total Gait, Stairs, Gower's manoeuvre, Chair (GSGC) score. Additional secondary efficacy endpoints were: change from baseline to week 52 in measures of respiratory function (maximal inspiratory pressure, maximal expiratory pressure, sniff nasal inspiratory pressure, slow vital capacity [SVC; % predicted], and maximum vital capacity [% predicted]); change from baseline to week 52 in time to complete GSGC component tests (10-m walk, four-stair climb, Gower's manoeuvre, and rising from chair) and timed up-and-go test for motor function; change from baseline to week 52 in manual muscle test scores for total and upper body extremities, and quantitative muscle test scores for muscle strength (appendix pp 2–4). Other secondary efficacy outcomes were participants' functional status at week 52, as measured by the Subject's Global Impression of Change and Physician's Global Impression of Change, and change from baseline to week 52 in patient-reported outcome measures (PROMIS—dyspnoea, PROMIS—upper extremities, Rasch-built Pompe-specific activity scale, and EQ-5D-5L). Pharmacodynamic endpoints were change from baseline to week 52 in serum creatine kinase level and change from baseline to week 52 in urinary Hex4 level.

The safety profile of the study drugs was characterised by incidence of treatment-emergent adverse events, serious adverse events, and adverse events leading to discontinuation of study drugs, infusion-associated reactions, and abnormalities in vital signs, clinical laboratory values, and physical examinations. Adverse event intensity was assessed by the site investigator as mild, moderate, or severe.

Statistical analysis

99 participants were required to achieve an overall 90% power to detect the effect size of 0·7 at a one-sided significance level of 0·025 between the two treatment groups at the 2:1 randomisation ratio (appendix p 4). Therefore, enrolment of at least 110 patients was planned, assuming a 10% dropout rate.

Efficacy analyses were performed in the intention-to-treat population (all randomised patients who received at least one dose of study drug). For most measures, baseline was defined as the last non-missing measurement before the administration of the first dose of study drug. For 6MWD and FVC, the baseline value was the mean of the last two values obtained on or before the day of the first dose. For the multi-item endpoints (eg, manual muscle test and GSGC), if a patient had missing baseline values for individual items, the mean value for those items from all patients with non-missing values across the two treatment groups was imputed.

The primary efficacy endpoint (change in 6MWD) was analysed using a mixed-effect model for repeated measures to compare for superiority of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo with observed values (appendix p 4). Key secondary endpoints were analysed using an analysis of covariance (ANCOVA) model adjusting for treatment, previous ERT status, sex, baseline endpoint value, age, weight, and height, on the intention-to-treat, last-observation-carried-forward population, and compared between treatment groups in a hierarchical order using a fixed sequence testing procedure to account for multiplicity. The primary and key secondary endpoints were tested at the one-sided significance level of 0·025. Additional secondary endpoints were analysed by means of ANCOVA. Two-sided p values are presented for ease of interpretation.

Prespecified analyses were performed on subgroups randomised by previous ERT status (ERT-experienced or ERT-naive). The subgroups were compared for the primary and key secondary endpoints, SVC (% predicted), and biomarkers, as well as for treatment-emergent adverse events.

Post-hoc analyses were performed to compare the treatment groups by previous ERT status for other secondary endpoints, excluding SVC (% predicted). To examine whether baseline ambulatory and respiratory performance might have affected the treatment outcomes, additional post-hoc analyses were performed by baseline 6MWD (<300 m *vs* ≥300 m) and baseline FVC (% predicted; <55% *vs* ≥55%), consistent with published baseline assessments.[18]

Safety assessments were performed in the safety population, which included all patients who received at least one dose of cipaglucosidase alfa plus miglustat or alglucosidase alfa plus placebo. Missing attributes for treatment-emergent adverse events were imputed with the worst possible outcome (ie, severe for missing intensity, and related for missing relationship to study drug) for summary purposes.

Study conduct was monitored by an independent data monitoring committee. All statistical analyses were done using SAS version 9.4. This trial is registered with ClinicalTrials.gov, NCT03729362.

Role of the funding source

The funder of the study designed the study in collaboration with the authors; was responsible for trial monitoring, data collection, and statistical analysis; and funded third-party medical writing assistance for the manuscript, which was written under the direction of the authors.

Results

Between Dec 3, 2018, and Nov 26, 2019, 130 patients were screened for eligibility and 125 were enrolled and randomly assigned to receive cipaglucosidase alfa plus miglustat (n=85) or alglucosidase alfa plus placebo (n=40; figure 1). Two patients in the alglucosidase alfa plus placebo group did not receive any dose due to absence of genotype confirmation and were excluded from the intention-to-treat population. One ERT-naive patient in the alglucosidase alfa plus placebo group was deemed by the principal investigator as likely to have deliberately underperformed at baseline; this patient was excluded from all efficacy analyses and this exclusion did not alter the statistical outcome of the analyses (appendix pp 4–5). Six patients discontinued overall (one in the alglucosidase alfa plus placebo group, five in the cipaglucosidase alfa plus miglustat group), and 117 completed the study. Database lock occurred on Jan 20, 2021. The dropout rate was 4·9%, and all patients who completed the study were subsequently enrolled in the open-label extension study.

Patient demographics at baseline were representative of the population with late-onset Pompe disease and generally similar between the treatment groups (table 1). The proportion of patients with the common intervening sequence splice site mutation c.-32-13T>G was similar between treatment groups (76 [89%] of 85 in the cipaglucosidase alfa plus miglustat group versus 32 [84%] of 38 in the alglucosidase alfa plus placebo group). Approximately two-thirds of the patients enrolled were ERT-experienced and the mean duration of previous treatment with alglucosidase alfa was 7·5 years (SD 3·4; range 2·0–13·7) in the cipaglucosidase alfa plus miglustat group and 7·1 years (3·6; 2·1–13·2) in the alglucosidase alfa plus placebo group. 6MWD and FVC measures at baseline were representative of the population with late-onset Pompe disease and were generally similar between the treatment groups (table 1). However, within each treatment group, baseline values for both 6MWD and FVC were lower in the patients who had previously received ERT than in those who had not.

In the overall population, at week 52, mean change from baseline in 6MWD was 20·8 m (SE 4·6) in the cipaglucosidase alfa plus miglustat group versus 7·2 m (6·6) in the alglucosidase alfa plus placebo group using last observation carried forward (between-group difference 13·6 m [95% CI –2·8 to 29·9]); however, the difference did not reach statistical superiority in the primary analysis using a mixed-effect model for repeated measures (p=0·097). Because the 6MWD data were not normally distributed, a prespecified non-parametric ANCOVA analysis was employed to compare the two treatment groups (p=0·071; figure 2A).

As the primary endpoint did not meet statistical significance, subsequent analyses of key secondary endpoints were interpreted as nominal statistical assessments of superiority. FVC, the first key secondary endpoint, was normally distributed and analysed by prespecified ANCOVA. In the overall population, at week 52, the cipaglucosidase alfa plus miglustat group showed a nominally significant and clinically meaningful improvement in sitting FVC (% predicted) over the alglucosidase alfa plus placebo group using last

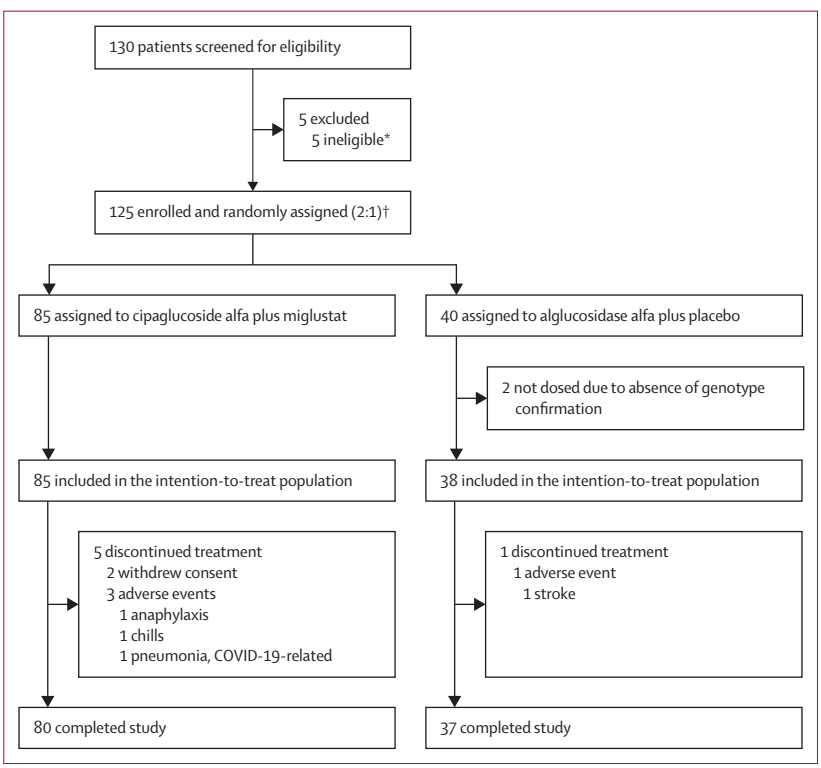


Figure 1: **Trial profile**

One patient in the alglucosidase alfa plus placebo group who completed the study was deemed to have deliberately underperformed in eligibility assessments at baseline, and was excluded from the efficacy analyses. *Five patients signed an informed consent form but did not meet study inclusion criteria and were therefore not randomly assigned. †Randomisation was stratified by previous enzyme replacement therapy status and 6-min walk distance at baseline.

	Cipaglucosidase alfa plus miglustat group (n=85)	Alglucosidase alfa plus placebo group (n=38)
Overall		
Age, years		
Mean (SD)	47·6 (13·3)	45·1 (13·3)
Median (range)	48·0 (19·0–74·0)	46·0 (22·0–66·0)
Age at diagnosis, mean (SD)	39·9 (13·8)	36·9 (15·3)
Sex		
Female	49 (58%)	18 (47%)
Male	36 (42%)	20 (53%)
Race		
White	74 (87%)	30 (79%)
Asian	5 (6%)	5 (13%)
Other	6 (7%)	3 (8%)
Region		
North America or South America	26 (31%)	15 (39%)
Europe	43 (51%)	12 (32%)
Asia-Pacific	16 (19%)	11 (29%)
Use of walking aid	17 (20%)	11 (29%)
6MWD, m*		
Mean (SD)	357·9 (111·8)	351 (121·3)†
Median (range)	359·5 (79·0–575·0)	365·5 (112·5–623·0)†
Sitting FVC, % predicted		
Mean (SD)	70·7% (19·6)	69·7% (21·5)†
Median (range)	70·0% (30·5–132·5)	71·0% (31·5–122·0)†
ERT-experienced patients		
Patients	65 (76%)	30 (79%)
ERT duration in years, mean (SD)	7·5 (3·4)	7·1 (3·6)
Age at first ERT dose in years, mean (SD)	40·8 (12·7)	38·7 (15·1)
6MWD, m*		
Mean (SD)	346·9 (110·2)	334·6 (114·0)
Median (range)	352·5 (79·0–557·5)	343·5 (112·5–532·3)
Sitting FVC, % predicted		
Mean (SD)	67·9 (19·1)	67·5 (21·0)
Median (range)	68·0 (30·5–132·5)	69·0 (31·5–122·0)
ERT-naive patients		
Patients	20 (24%)	8 (21%)
6MWD, m		
Mean (SD)	393·6 (112·4)	420·9 (135·7)†
Median (range)	375·2 (154·0–575·0)	385·5 (201·0–623·0)†
Sitting FVC, % predicted		
Mean (SD)	80·2 (18·7)	79·1 (22·6)†
Median (range)	82·3 (48·0–111·0)	93·5 (46·5–98·0)†

Data are n (%) unless otherwise stated. ERT=enzyme replacement therapy. 6MWD=6-min walk distance. FVC=forced vital capacity. *Mean of two screening values. †Results exclude one patient suspected of deliberate underperformance at baseline.

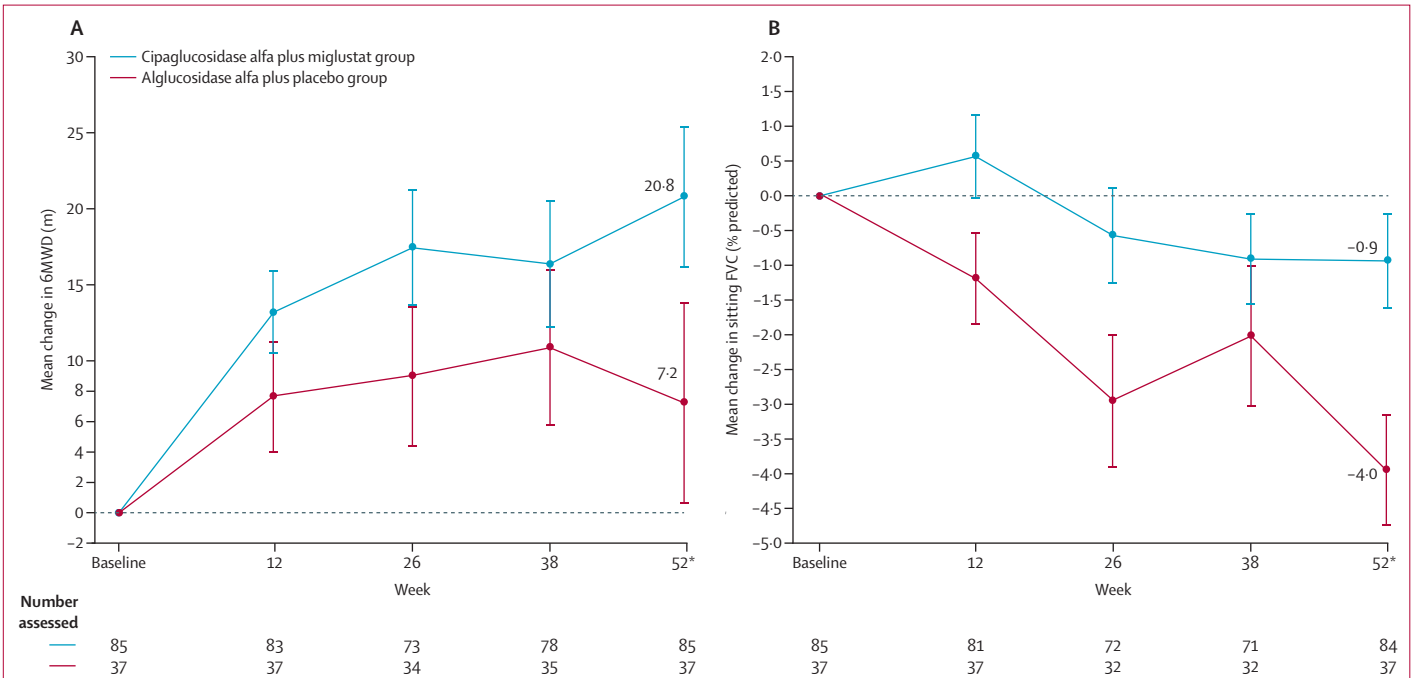
Table 1: **Baseline characteristics**

observation carried forward (mean change –0·9% [SE 0·7] *vs* –4·0% [0·8]; between-group difference 3·0% [95% CI 0·7–5·3]; p=0·023; figure 2B).

ERT-experienced patients in the cipaglucosidase alfa plus miglustat group (n=65) showed an overall improvement in 6MWD from baseline to week 52, with a period of stabilisation between week 12 and week 38 (appendix p 5). By comparison, ERT-experienced patients in the alglucosidase alfa plus placebo group (n=30) showed an initial small improvement at week 12 followed by a stabilisation through week 38 and returned to baseline levels by week 52 (mean change 16·9 m [SE 5·0] *vs* 0·0 m [7·2]; between-group difference 16·9 m [SE 8·8]; nominal p=0·047). As the 6MWD data were not normally distributed, a prespecified non-parametric ANCOVA analysis was used for comparison (appendix p 5). ERT-experienced patients in the cipaglucosidase alfa plus miglustat group showed a stabilisation in sitting FVC (% predicted), compared with worsening in ERT-experienced patients in the alglucosidase alfa plus placebo group (mean change 0·1% [SE 0·7] *vs* –4·0% [0·9]; between-group difference 4·1% [SE 1·2]; nominal p=0·0061]; appendix p 6). In the exploratory subgroup analysis stratified by baseline 6MWD and FVC, patients in the cipaglucosidase alfa plus miglustat group in the overall and ERT-experienced populations showed benefit over those in the alglucosidase alfa plus placebo group in the respective populations for both 6MWD and FVC, regardless of baseline performance (appendix p 7). However, interpretation of the subgroup analyses from the ERT-naive cohort was confounded by the small sample size (appendix p 7).

The treatment effects observed in the primary analyses were supported by the relevant secondary endpoints as nearly all the assessed outcomes numerically favoured cipaglucosidase alfa plus miglustat over alglucosidase alfa plus placebo in both the overall and ERT-experienced populations (table 2; appendix pp 8–10). A significant reduction in creatine kinase levels at week 52 was found with cipaglucosidase alfa plus miglustat compared with alglucosidase alfa plus placebo in both the overall population (mean change –130·5 U/L [SE 25·1] *vs* 60·2 U/L [26·2]; nominal p<0·0001) and the ERT-experienced cohort (–118·0 U/L [28·4] *vs* 79·6 U/L [26·9]; nominal p<0·0001; appendix p 12). Hex4 levels (mmol/mol creatinine) were substantially reduced at week 52 in the cipaglucosidase alfa plus miglustat group compared with the alglucosidase alfa plus placebo group in both the overall population (mean change –1·9 [SE 0·3] *vs* 1·2 [0·7]; nominal p<0·0001) and the ERT-experienced cohort (–1·7 [0·3] *vs* +1·9 [0·8]; nominal p=0·0001; appendix p 12).

In ERT-naive patients (n=27), alglucosidase alfa plus placebo had a numerical benefit over cipaglucosidase alfa plus miglustat for the primary and first key secondary endpoints; however, the differences were not significant (mean change in 6MWD 38·3 m [SE 11·1] *vs* 33·4 m [10·9], p=0·60 from the Wilcoxon rank-sum test, due to violation of normality assumption and instability of ANCOVA analysis caused by sparseness of data; mean change in FVC –3·6% [SE 1·8] *vs* –4·1% [1·5], p=0·57; appendix p 13). Most of the key secondary and other secondary endpoints showed improvement in



Number assessed					
Cipaglucosidase alfa plus miglustat group	85	83	73	78	85
Alglucosidase alfa plus placebo group	37	37	34	35	37

Number assessed					
Cipaglucosidase alfa plus miglustat group	85	81	72	71	84
Alglucosidase alfa plus placebo group	37	37	32	32	37

	Cipaglucosidase alfa plus miglustat group (n=85)	Alglucosidase alfa plus placebo group (n=37)	Between-group difference, mean (SE)	p value
Baseline 6MWD in m, mean (SD)	357·9 (111·8)	351·0 (121·3)	..	..
Change from baseline at week 52 in m, mean (SE)	20·8 (4·6)	7·2 (6·6)	13·6 (8·3)	0·071

	Cipaglucosidase alfa plus miglustat group (n=85)	Alglucosidase alfa plus placebo group (n=37)	Between-group difference, mean (SE)	p value
Baseline FVC (% predicted), mean (SD)	70·7% (19·6)	69·7 (21·5)	..	..
Change from baseline at week 52 in % predicted, mean (SE)	−0·9% (0·7)	−4·0% (0·8)	3·0% (1·2)	0·023

Figure 2: **Change from baseline in 6MWD and FVC (% predicted) in the overall population**
Change from baseline in 6MWD (A) and FVC (% predicted; B). Change from baseline at week 52 values were based on last observation carried forward data. p values are nominal two-sided. The primary analysis for 6MWD used mixed-effect model for repeated measures; however, the 6MWD data were not normally distributed and the p value for 6MWD was from non-parametric ANCOVA as prespecified. For FVC, the p value was from ANCOVA as prespecified. Results exclude one patient judged likely to have deliberately underperformed at baseline. Error bars indicate SE. 6MWD=6-min walk distance. FVC=forced vital capacity. ANCOVA=analysis of covariance. *Last observation carried forward.

both ERT-naive treatment groups, with some parameters numerically favouring cipaglucosidase alfa plus miglustat and others favouring alglucosidase alfa plus placebo (appendix pp 8–10). Creatine kinase and Hex4 both showed greater reductions with cipaglucosidase alfa plus miglustat than with alglucosidase alfa plus placebo ($p<0·0001$ for both comparisons).

Clinical laboratory assessments were generally similar between treatment groups and did not change notably during the study. In the ERT-experienced cohort, the proportion of patients with positive specific anti-rhGAA antibodies and detectable titres remained stable in the cipaglucosidase alfa plus miglustat group (54 [83%] of 65 at baseline to 43 [74%] of 58 at last study visit) and the alglucosidase alfa plus placebo group (22 [73%] of 30 at baseline to 19 [70%] of 27 at last study visit). In the ERT-naive cohort, the proportion of patients who tested positive for specific anti-rhGAA antibodies and detectable titres increased in both the cipaglucosidase alfa plus miglustat group (none of 20 at baseline to 14 [88%] of 16 at the last study visit) and alglucosidase alfa plus placebo group (none of eight at baseline to six [100%] of six at the last visit). There was no association between the incidence of anti-rhGAA antibodies or maximum antibody titre and adverse events.

Cipaglucosidase alfa plus miglustat was generally well tolerated, and the overall safety profile was similar to that of alglucosidase alfa plus placebo (table 3). 118 (96%) of 123 patients experienced at least one treatment-emergent adverse event, and the overall incidence was similar between cipaglucosidase alfa plus miglustat (81 [95%] of 85) and alglucosidase alfa plus placebo (37 [97%] of 38) groups. The incidence of specific

	Endpoint hierarchy	Cipaglucosidase alfa plus miglustat group (n=85)		Alglucosidase alfa plus placebo group (n=37)		Least square mean difference (95% CI)
		Baseline, mean (SD); n	Change from baseline at week 52, mean (SD, SE); n	Baseline, mean (SD); n	Change from baseline at week 52, mean (SD, SE); n	
Motor function						
6MWD, m	Primary	357·9 (111·8); 85	20·8 (42·8, 4·6); 85	351·0 (121·3); 37	7·2 (40·3, 6·6); 37	13·7 (−1·2 to 28·5)
GSGC total score	Key secondary	14·5 (5·2); 74	−0·5 (2·5, 0·3); 72	14·5 (4·7); 32	0·8 (1·8, 0·3); 30	−1·4* (−2·5 to −0·4)
10-m walk, m	Other secondary	9·7 (7·6); 80	−0·5 (5·8, 0·6); 80	9·6 (5·5); 35	1·9 (6·0, 1·0); 35	−2·7* (−5·0 to −0·3)
Four-stair climb, s	Other secondary	14·1 (70·5); 79	−8·5 (70·1, 7·9); 78	8·2 (9·6); 35	0·3 (5·7, 1·0); 34	−3·1 (−6·3 to 0·0)
Gower's manoeuvre, s	Other secondary	10·8 (7·5); 61	−0·3 (5·8, 0·7); 61	19·8 (25·2); 27	−2·2 (6·9, 1·4); 25	1·6 (−1·5 to 4·7)
Rising from chair, s	Other secondary	13·6 (86·1); 77	−10·2 (84·7, 9·7); 77	4·5 (5·2); 33	−0·5 (3·9, 0·7); 33	−0·8 (−2·4 to 0·7)
Timed up and go, s	Other secondary	12·9 (10·1); 75	−0·3 (8·5, 1·0); 75	12·8 (8·9); 32	−0·1(2·7, 0·5); 31	−0·5 (−3·4 to 2·4)
6MWD, % predicted	Other secondary	57·8% (15·8); 85	4·1% (7·0, 0·8); 85	56·0% (17·3); 37	1·6% (6·0, 1·0); 37	2·4% (−0·3 to 5·0)
Pulmonary function						
Sitting FVC, % predicted	Key secondary	70·7% (19·6); 85	−0·9% (6·2, 0·7); 84	69·7% (21·5); 37	−4·0% (4·9, 0·8); 37	2·7%* (0·4 to 5·0)
Sitting SVC, % predicted	Other secondary	69·9% (17·9); 85	−2·3% (8·9, 1·0); 83	68·6% (20·7); 36	−5·9% (8·6, 1·5); 35	2·8% (−0·8 to 6·5)
Maximum vital capacity, % predicted	Other secondary	72·3% (19·1); 85	−1·2% (6·0, 0·7); 84	70·9% (20·9); 37	−3·9% (5·0, 0·8); 37	2·4%* (0·2 to 4·7)
MIP, % predicted	Other secondary	61·8% (26·2); 85	2·1% (19·2, 2·1); 84	59·9% (21·0); 37	−2·7% (16·9, 2·8); 37	4·2% (−3·4 to 11·8)
MEP, % predicted	Other secondary	70·7% (22·6); 85	0·6% (21·9, 2·4); 84	65·1% (20·5); 37	−1·6% (12·8, 2·1); 37	1·9% (−5·5 to 9·2)
SNIP, % predicted	Other secondary	46·7% (23·3); 85	2·2% (15·0, 1·6); 84	46·2% (26·6); 37	2·8% (23·8, 3·9); 37	−3·1% (−10·2 to 3·9)
Muscle strength						
Lower MMT score	Key secondary	28·0 (5·8); 84	1·6 (3·8, 0·4); 80	27·7 (6·2); 37	0·9 (2·6, 0·4); 34	1·0 (−0·5 to 2·4)
Upper MMT score	Other secondary	34·3 (3·6); 84	1·5 (3·4, 0·4); 83	34·7 (4·9); 37	0·7 (3·6, 0·6); 37	0·9 (−0·2 to 2·1)
Total MMT score	Other secondary	62·3 (8·2); 84	3·1 (6·3, 0·7); 80	62·4 (9·7); 34	1·4 (4·4, 0·8); 34	2·2 (−0·1 to 4·5)
Total QMT score, kg	Other secondary	165·8 (68·9); 82	6·9 (55·1, 6·1); 81	158·8 (80·1); 36	8·2 (31·2, 5·2); 36	3·0 (−15·7 to 21·7)
Patient-reported outcomes						
PROMIS—physical Function score	Key secondary	66·9 (12·3); 84	1·9 (7·5, 0·8); 84	68·0 (13·1); 37	0·2 (10·8, 1·8); 37	1·9 (−1·5 to 5·3)
PROMIS—fatigue score	Key secondary	22·3 (8·3); 85	−2·0 (5·8, 0·6); 85	21·1 (6·1); 37	−1·7 (6·6, 1·1); 37	0·0 (−2·1 to 2·2)
Biomarkers						
Urinary Hex4, mmol/mol creatine	Pharmacodynamic	4·6 (3·4); 84	−1·9 (2·4, 0·3); 84	6·9 (6·9); 37	1·2 (4·4, 0·7); 37	−2·5* (−3·7 to −1·3)
Serum creatine kinase, U/L	Pharmacodynamic	447·0 (399·5); 85	−130·5 (231·2, 25·1); 85	527·8 (426·6); 37	60·2 (159·5, 26·2); 37	−176·0* (−244·4 to −107·6)

Least square mean differences were based on analysis models adjusting for baseline covariates (ANCOVA for all endpoints except for 6MWD and biomarkers, which used non-parametric ANCOVA) and differed slightly from the mean differences shown in figure 2 for 6MWD and FVC (% predicted). Change from baseline at week 52 are last observation carried forward means. Functional status assessed by Subject's Global Impression of Change and Physician's Global Impression of Change and other secondary endpoints related to patient-reported outcomes (PROMIS—dyspnoea, PROMIS—upper extremities, Rasch-built Pompe-specific activity scale, and EQ-5D-5L) are not shown, as analyses are ongoing. Component muscle strength scores for MMT (proximal muscles score) and QMT values (lower and upper extremities values and proximal muscles value) are not shown, as they are reflected in the total MMT score and total QMT value. Composite secondary endpoints (proportion of participants with improvement in both 6MWD and FVC [% predicted]) and change in 6MWD from baseline to week 26 are shown in the appendix (pp 7–11). 6MWD=6-min walk distance. FVC=forced vital capacity. PROMIS=Patient-Reported Outcomes Measurement Information System. MMT=manual muscle test. QMT=quantitative muscle test. GSGC=Gait, Stairs, Gower's manoeuvre, Chair. SVC=slow vital capacity. MIP=maximal inspiratory pressure. MEP=maximal expiratory pressure. SNIP=sniff nasal inspiratory pressure. Hex4=glucose tetrasaccharide. *Indicates treatment difference nominally significant in favour of cipaglucosidase alfa plus miglustat.

Table 2: **Summary of primary, secondary, and pharmacodynamic endpoints in the overall population**

treatment-emergent adverse events was generally similar between the cipaglucosidase alfa plus miglustat and alglucosidase alfa plus placebo groups (table 3). The most frequently reported treatment-emergent adverse events were fall, headache, nasopharyngitis, myalgia, arthralgia, and nausea.

The incidence of infusion-associated reactions was similar between the cipaglucosidase alfa plus miglustat group (21 [25%] of 85 patients) and alglucosidase alfa plus placebo group (ten [26%] of 38). Three adverse events led to study withdrawal in patients who received cipaglucosidase alfa plus miglustat—one chills (severe), one anaphylaxis (severe), and one pneumonia (COVID-19-related; moderate). One adverse event led to study withdrawal in the alglucosidase alfa plus placebo group (stroke, unrelated to treatment). 12 serious adverse events occurred in eight patients in the cipaglucosidase alfa plus miglustat group (table 3); only one event (anaphylaxis) was deemed related to study drug. One serious adverse event occurred in the alglucosidase alfa plus placebo group and was deemed unrelated to treatment.

Discussion

In this study—which is, to our knowledge, the first head-to-head study in people living with late-onset Pompe disease who were previously treated with alglucosidase alfa (the first approved ERT) or who were naive to approved therapy—cipaglucosidase alfa plus miglustat did not achieve statistical superiority over alglucosidase alfa plus placebo for the primary endpoint of change in 6MWD from baseline to week 52. However, there was evidence of potentially clinically meaningful improve_ments in motor and respiratory functions at 52 weeks with cipaglucosidase alfa plus miglustat versus with alglucosidase alfa plus placebo. In the assessment of change in FVC (% predicted) from baseline to week 52, cipaglucosidase alfa plus miglustat showed a mean improvement of 3·0% (nominally significant) compared with standard of care, an outcome of crucial importance as respiratory failure is the most common cause of death in patients with late-onset Pompe disease (72% of deaths).[19]

Alglucosidase alfa has been available in the USA and Europe since 2006 and has greatly improved outcomes of infantile-onset and late-onset Pompe disease.[10,20] Long-term studies in late-onset Pompe disease have shown that many patients experience an initial improvement or stabilisation in the first 2–3 years followed by a plateau or secondary decline in muscle strength, motor function, and respiratory function.[11-14,21,22] New treatment options with sustained efficacy are urgently needed, particularly treatments capable of maximising lung function, as patients on long-term treatment often require mechanical ventilator support eventually.

Considering these unmet needs in late-onset Pompe disease, PROPEL was designed to include patients who had previously been treated with the current standard of care. In the ERT-experienced cohort, patients who continued alglucosidase alfa plus placebo had no improvement in 6MWD and showed a reduction of 4% in FVC (% predicted) at 52 weeks. By contrast, patients who were switched to cipaglucosidase alfa plus miglustat had an increase of 16·9 m in 6MWD and had stable FVC (difference 0·1%) at 52 weeks relative to baseline. The improvement in 6MWD and FVC compared with patients who continued to receive alglucosidase alfa plus placebo was evident at week 12 and greatest at week 52. 6MWD did not plateau in the cipaglucosidase alfa plus miglustat group over 52 weeks, suggesting that further improvement is possible. However, this needs to be confirmed by results from the ongoing open-label extension study. Improvements in these important domains in patients who have been on therapy for many years is particularly encouraging.

Results of post-hoc subgroup analyses showed that outcomes consistently favoured cipaglucosidase alfa plus miglustat over the standard of care, regardless of baseline 6MWD and FVC in the overall and ERT-experienced populations. The totality of evidence from additional efficacy outcomes suggests that there is a benefit of cipaglucosidase alfa plus miglustat over standard of care in both the overall and ERT-experienced populations. These efficacy outcomes were supported by biomarker data (ie, reduction of creatine kinase and Hex4) that further validate the clinical measures and support the purported mechanism of action of cipaglucosidase alfa plus miglustat; specifically, the improved uptake of a highly active form of GAA that can clear glycogen and restore muscle health.

The treatment effect was similar with cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in the ERT-naive cohort. In the LOTS study,[18] patients treated with alglucosidase alfa showed a mean improvement of 25·1 m in 6MWD at week 78 compared with baseline. When the PROPEL sample size and power calculations were determined, LOTS was the only available comparative study to inform these decisions. Thus, we did not anticipate that ERT-naive patients in the PROPEL study would show a response as large as 38·3 m

	Cipaglucosidase alfa plus miglustat group (n=85)	Alglucosidase alfa plus placebo group (n=38)
Treatment-emergent adverse events	81 (95%)	37 (97%)
Treatment-emergent adverse events potentially related to treatment	26 (31%)	14 (37%)
Serious treatment-emergent adverse events	8 (9%)	1 (3%)
Serious treatment-emergent adverse events potentially related to treatment	1 (1%)	0
Treatment-emergent adverse events leading to study withdrawal	3 (4%)	1 (3%)
Treatment-emergent adverse events leading to death	0	0
Infusion-associated reactions	21 (25%)	10 (26%)
Treatment-emergent adverse events by preferred term		
Fall	25 (29%)	15 (39%)
Headache	20 (24%)	9 (24%)
Nasopharyngitis	19 (22%)	3 (8%)
Myalgia	14 (16%)	5 (13%)
Arthralgia	13 (15%)	5 (13%)
Urinary tract infection	12 (14%)	2 (5%)
Diarrhoea	11 (13%)	4 (11%)
Pain in extremity	11 (13%)	2 (5%)
Nausea	10 (12%)	8 (21%)
Musculoskeletal pain	10 (12%)	2 (5%)
Oropharyngeal pain	10 (12%)	2 (5%)
Back pain	9 (11%)	7 (18%)
Fatigue	8 (9%)	5 (13%)

Data are n (%); n indicates number of people. Treatment-emergent adverse events by preferred term include any events that occurred in at least 10% of participants in either group; preferred terms were coded with MedDRA version 23.0.

Table 3: **Adverse events**

in 6MWD with alglucosidase alfa plus placebo, which might have led to the absence of statistical superiority in the overall population. The variability in response with standard of care is likely to be due to the inherent disease heterogeneity and changes in clinical practice since the LOTS study was conducted, such as reduced diagnostic delay. Comparisons between treatment groups in ERT-naive patients were challenging to interpret because of the small sample size, observed heterogeneity, and baseline FVC (% predicted) values that were close to normal (80%). ERT-naive patients in both treatment groups showed substantial mean increases (≥30 m) in 6MWD, but an unexpected similar decline in FVC was observed in both groups. This decline might be explained by a majority (16 [57%] of 28 patients) having baseline FVC (% predicted) values of greater than 80%.

In earlier studies, previously untreated patients generally had improved or stable FVC during the first year of ERT with alglucosidase alfa.[18,23,24] By contrast with the PROPEL study, the open-label phase 1/2 study of cipaglucosidase alfa plus miglustat showed clinically meaningful improvements in FVC (% predicted) in ERT-naive patients (mean change 6·8% [SD 6·8]) after 24 months (n=5).[25] In the PROPEL study, although the ERT-naive patients assigned to either cipaglucosidase alfa plus miglustat or alglucosidase alfa plus placebo experienced improvements in most endpoints assessing motor function, pulmonary function, muscle strength, and PROMIS scales, the benefit varied depending on the outcome tested. A notable exception was the biomarker data, which showed a significant difference between treatment groups in favour of cipaglucosidase alfa plus miglustat. Creatine kinase and Hex4 are surrogate safety markers of muscle integrity and glycogen metabolism in Pompe disease;[26,27] however, to our knowledge, there are no published reports on any associations between clinical outcomes and these safety markers. Our overall results support the therapeutic rationale for cipaglucosidase alfa plus miglustat, namely that uptake into skeletal muscle cells and reduction of accumulated glycogen is improved compared with alglucosidase alfa plus placebo.

The safety profiles of both treatments were similar over 52 weeks. The open-label phase 1/2 cipaglucosidase alfa plus miglustat study has shown efficacy and safety up to 24 months in a small number of ERT-naive and ERT-experienced patients.[27] Our results extend these earlier findings and further support the potential benefit–risk profile of this investigational therapy. Long-term safety and efficacy of cipaglucosidase alfa plus miglustat will be evaluated in the open-label extension study following PROPEL.

The smaller sample size of the ERT-naive cohort and only a single dose level of the treatments being evaluated are potential limitations of this study. Given the heterogenous nature of Pompe disease, spanning a wide spectrum of manifestations, disease severity, rates of progression, and responses to treatment, long-term follow-up studies are required to characterise the durability of the treatment effects observed here.

Although there was no significant difference in the primary endpoint, based on the totality of evidence from the secondary efficacy endpoints, cipaglucosidase alfa plus miglustat seemed to show clinically meaningful improvements on motor and pulmonary functions and biomarkers compared with alglucosidase alfa plus placebo in both the overall and the ERT-experienced populations. Cipaglucosidase alfa plus miglustat had a safety profile that was consistent with that of alglucosidase alfa plus placebo. In conclusion, the two-component therapy consists of an enhanced phosphorylated enzyme and an enzyme stabiliser, thereby providing a different mechanism of action for cipaglucosidase alfa plus miglustat compared with alglucosidase alfa, and is a potential alternative treatment option for people with late-onset Pompe disease.

Contributors

JC, PSK, TM, MR, BS, and SS contributed to study conceptualisation. BJB, JC, PSK, PL, TM, MR, BS, SS, AT, and ATvdP contributed to study design. JC, MG, HJ, and SS contributed to methodology. JC, MG, HJ, SS, and BS were responsible for data access and verification. SK, PSK, and BS contributed to study supervision. BJB, DB, PSK, PL, JD-M, TM, MR, BS, AT, and ATvdP contributed to investigation. BJB, DB, PSK, PL, JD-M, TM, MR, BS, AT, and ATvdP contributed to data collection. HJ contributed to data curation and formal analysis. JC, MG, PSK, TM, MR, BS, and SS contributed to data interpretation. SK and SS contributed to project administration and resource management. All authors participated in writing, review, and editing of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Declaration of interests

BS reports grant funding to his institution and consulting fees from Amicus Therapeutics; and has served as an advisory board member for Sanofi Genzyme, Lupin, Spark Therapeutics, and Astellas Therapeutics, as a consultant for Alexion, Argenx, and UCB Pharma, and as a speaker for Kedrion. SS, HJ, JC, MG, and SK are employees of and hold stock in Amicus Therapeutics. PL reports grant funding to his institution and consulting and travel fees from Amicus Therapeutics; has served as an advisory board member, a consultant, and a speaker at Sanofi Genzyme; and his institution received funding from Sanofi Genzyme. AT has served as a board member and as a speaker for Sanofi Genzyme, and reports fees for these activities from Sanofi Genzyme. JD-M has served

as a consultant at Sarepta, Sanofi Genzyme, and Audentes Therapeutics; has received grant funding to his institution from Sanofi Genzyme and Boehringer Ingelheim and speaker fees from Sanofi Genzyme, Sarepta, and Lupin; and has received payment for the development of educational presentations from Sanofi Genzyme. ATvdP has provided consultancy services for Amicus, Spark Therapeutics, Sanofi Genzyme, Audentes, Ultragenix, Takeda, Qiuesi, Biomarin, GlaxoSmithKline, and Alexion. DB reports funds to his institution from Amicus Therapeutics. TM has served in an advisory capacity for AbbVie, Alexion, Amicus, Argenx, Audentes, Modis, Momenta, Ra Pharmaceuticals, Sanofi Genzyme, Sarepta, Spark Therapeutics, UCB, and Ultragenyx; serves on the speaker's bureau for Sanofi Genzyme; serves on the medical advisory board for the Myositis Association, Neuromuscular Disease Foundation, Myasthenia Gravis Foundation of California, and Myasthenia Gravis Foundation of America; receives research funding from the Myositis Association, the Muscular Dystrophy Association, the National Institutes of Health, and from Alexion, Amicus, Argenx, Audentes, Bristol Myers Squibb, Cartesian Therapeutics, Grifols, Momenta, Ra Pharmaceuticals, Sanofi Genzyme, Spark Therapeutics, UCB, and Valerion; and serves on the data safety monitoring board for Acceleron, Avexis, Sarepta, and the National Institutes of Health. PSK has served as a consultant for Sanofi Genzyme, Amicus Therapeutics, Maze Therapeutics, JCR Pharmaceutical, and Asklepios Biopharmaceutical. All other authors declare no competing interests.

Data sharing

Cipaglucosidase alfa plus miglustat is an investigational therapy for which Amicus is seeking marketing licence approvals in the USA, the EU, and Japan. Data sharing proposals and requests will be reviewed on a case-by-case basis. Requests for data should be addressed to Mitchell Goldman at mgoldman@amicusrx.com. Requests will be reviewed by a medical steering committee.

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