Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised, multicentre trial

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Summary

Background Pompe disease is a rare, progressive neuromuscular disorder caused by deficiency of acid α-glucosidase (GAA) and accumulation of lysosomal glycogen. We assessed the safety and efficacy of avalglucosidase alfa, a recombinant human GAA enzyme replacement therapy specifically designed for enhanced mannose-6-phosphate-receptor targeting and enzyme uptake aimed at increased glycogen clearance, compared with the current approved standard of care, alglucosidase alfa, in patients with late-onset Pompe disease.

Methods We did a randomised, double-blind, phase 3 trial at 55 sites in 20 countries. We enrolled individuals (aged ≥3 years) with enzymatically confirmed late-onset Pompe disease who had never received treatment. We used a centralised treatment allocation system to randomly allocate participants to either avalglucosidase alfa or alglucosidase alfa. Participants and investigators were unaware of their treatment allocation. The primary outcome measure was change from baseline to week 49 in upright forced vital capacity percent (FVC%) predicted. We used a hierarchical fixed sequential testing strategy, whereby non-inferiority of avalglucosidase alfa compared with alglucosidase alfa was assessed first, with a non-inferiority margin of 1·1. If non-inferiority was seen, then superiority was tested with a 5% significance level. The key secondary objective was effect on functional endurance, measured by the 6-minute walk test (6MWT). Safety was assessed, including treatment-emergent adverse events and infusion-associated reactions. The modified intent-to-treat population was the primary analysis population for all efficacy analyses. The safety population was the analysis population for safety analyses. This trial is registered with ClinicalTrials.gov, NCT02782741. We report results of the 49-week primary analysis period.

Findings Between Nov 2, 2016, and March 29, 2019, 100 participants were randomly allocated avalglucosidase alfa (n=51) or alglucosidase alfa (n=49). Treatment with avalglucosidase alfa resulted in a least-squares mean improvement in upright FVC% predicted of 2·89% (SE 0·88) compared with 0·46% (0·93) with alglucosidase alfa at week 49 (difference 2·43% [95% CI –0·13 to 4·99]). Non-inferiority was shown because the lower bound of the 95% CI for the difference far exceeded the predefined non-inferiority margin but did not exclude 0 (p=0·0074). Superiority was not reached (p=0·063), so formal testing was stopped, as per the testing hierarchy. Improvements were also seen in the 6MWT with avalglucosidase alfa compared with alglucosidase alfa, with greater increases in distance covered (difference 30·01 m [95% CI 1·33 to 58·69]) and percent predicted (4·71% [0·25 to 9·17]). Treatment-emergent adverse events potentially related to treatment were reported in 23 (45%) of 51 participants in the avalglucosidase alfa group and in 24 (49%) of 49 in the alglucosidase alfa group, and infusion-associated reactions were reported in 13 (26%) participants in the avalglucosidase alfa group and 16 (33%) in the alglucosidase alfa group. Of the five trial withdrawals, all in the alglucosidase alfa group, four were due to adverse events, including two infusion-associated reactions. Serious treatment-emergent adverse events were reported in eight (16%) participants who received avalglucosidase alfa and in 12 (25%) who received alglucosidase alfa. One participant treated with alglucosidase alfa died because of acute myocardial infarction determined to be unrelated to treatment. Antidrug antibody responses were similar in both groups. High and persistent titres (≥12 800) and neutralising antibodies were more common with alglucosidase alfa (in 16 [33%] participants) than with avalglucosidase alfa (ten [20%]).

Interpretation We consider that this study provides evidence of clinically meaningful improvement with avalglucosidase alfa therapy over alglucosidase alfa in respiratory function, ambulation, and functional endurance, with no new safety signals reported. An open-label extended-treatment period is ongoing to confirm the long-term safety and efficacy of avalglucosidase alfa, with the aim for this therapy to become the new standard treatment in late-onset Pompe disease.

Funding Sanofi Genzyme.

Introduction

Pompe disease is a rare, progressive neuromuscular disorder caused by deficiency of acid α-glucosidase (GAA), an enzyme that breaks down glycogen. Deficient enzymatic activity causes lysosomal glycogen accumulation leading to cellular dysfunction, progressive muscle damage, and functional disabilities. Pompe disease has a broad clinical presentation, with considerable variation in age at onset and rates of progression. In patients with late-onset Pompe disease, symptoms can occur at any age, without cardiomyopathy in the first year of life, which is characteristic of infantile-onset Pompe disease.[1–5]

Although multiple systems are affected,[6] respiratory muscle dysfunction and failure lead to substantial morbidity and mortality in patients with late-onset Pompe disease. When untreated, progressive muscle damage causes respiratory and mobility problems that manifest at variable rates and, for many, ultimately leads to respiratory support and wheelchair use. Enzyme replacement therapy with alglucosidase alfa, which was approved by the US Food and Drug Administration and European Medicines Agency, has been the standard of care for patients with Pompe disease since 2006.[7,8] Avalglucosidase alfa is a recombinant human GAA enzyme replacement therapy specifically designed for enhanced targeting of mannose-6-phosphate (M6P) receptor-mediated uptake, the essential pathway for cellular uptake and lysosomal trafficking,[9,10] aimed at increasing the clinical efficacy achieved with alglucosidase alfa. Increased bis-M6P concentrations can overcome known limitations of natural phosphorylation of GAA, optimise glycan phosphorylation, and increase enzyme uptake through greater affinity for M6P receptors on the cells of target tissues. Avalglucosidase alfa is produced by chemical conjugation of an oligosaccharide harbouring bis-M6P residues onto recombinant human GAA via oxime chemistry. Avalglucosidase alfa has an approximately 15-times increase in levels of M6P compared wih alglucosidase alfa.[11,12]

In preclinical models, avalglucosidase alfa achieved five-times greater glycogen clearance from cardiac, respiratory, and skeletal muscle and greater motor function improvements compared with alglucosidase alfa at an equivalent dose.[12] In the phase 1 NEO1 trial[13] of avalglucosidase alfa in treatment-naive and previously treated patients with late-onset Pompe disease, and the extension study NEO-EXT,[14] stabilisation in respiratory and motor function was observed after up to 6 years of treatment, indicating a sustained benefit compared with the progressive natural history of untreated Pompe disease.[2,15–18]

Research in context

Evidence before this study

We searched PubMed using the search terms "late-onset Pompe disease", "treatment", "enzyme replacement therapy", "efficacy", and "outcomes", with no language or article type restrictions, for papers published from Jan 1, 2010, to Jan 1, 2021, to identify publications describing the outcomes associated with enzyme replacement therapy in patients with late-onset Pompe disease. Articles published before 2010, the year enzyme replacement therapy with alglucosidase alfa was first approved as a treatment for late-onset Pompe disease, were not considered. Our search resulted in identification of 22 relevant articles. We found that although treatment with alglucosidase alfa, the first approved treatment for patients with Pompe disease, results in stabilisation or improvement of outcomes for many patients, there are variable response patterns among patients with late-onset Pompe disease. In some patients, declines in health continue during treatment despite no identifiable modifying factors that can be altered, including the development of antidrug antibodies, which could be treated with immune tolerance therapy. Because of this variable response and disease progression in some patients during treatment with alglucosidase alfa, there is an unmet need for patients with late-onset Pompe disease. Avalglucosidase alfa is a recombinant human enzyme replacement therapy that has been designed specifically for increased enzyme uptake in the cells of target tissues, with the aim to increase the clinical efficacy achieved with alglucosidase alfa. In preclinical Pompe disease models, treatment with avalglucosidase alfa resulted in greater improvements in glycogen clearance and motor function compared with alglucosidase alfa. Improvement of outcomes with avalglucosidase alfa in treatment-naive patients and patients previously treated with long-term alglucosidase alfa has been shown and reported in the NEO1 and NEO-EXT studies.

Added value of this study

The phase 3 COMET trial was the first study designed to directly compare the safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease, which has previously only been evaluated in an open-label trial (NEO1/NEO-EXT). Undertaken at 55 sites across 20 countries, COMET is the first direct comparison of avalglucosidase alfa and alglucosidase alfa in a large cohort (n=100) of patients with late-onset Pompe disease representing a broad geographical population.

Implications of all the available evidence

Improvements in respiratory function and functional endurance was seen with avalglucosidase alfa compared with alglucosidase alfa. Avalglucosidase alfa has a more favourable safety profile compared with alglucosidase alfa, which is consistent with long-term experience in the NEO1 and NEO-EXT studies, without new or unexpected safety signals.

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Avalglucosidase alfa is approved in the USA for patients aged 1 year and older with late-onset Pompe disease and in Japan for all patients with Pompe disease (Nexviazyme, Sanofi Genzyme, Cambridge, MA, USA). Avalglucosidase alfa is being studied in the phase 3 COMET trial in patients with late-onset Pompe disease and the Mini-COMET trial (NCT03019406) in patients with infantile-onset Pompe disease. Reported here are safety and efficacy results of the 49-week, blinded treatment, primary analysis period of the COMET trial.

Methods

Study design and participants

COMET is a phase 3, randomised double-blind trial at 55 study sites in 20 countries. This study includes two treatment periods: a double-blind, 49-week primary analysis period and an open-label extended treatment period. Eligible participants were aged at least 3 years; had a diagnosis of Pompe disease confirmed by GAA enzyme deficiency from any tissue source or two confirmed pathogenic *GAA* variants, or both; were naive to Pompe-specific treatment; and were able to successfully perform repeated forced vital capacity (FVC) measurements in the upright position of 30–85% predicted and walk at least 40 m without stopping and without using an ambulation-assistance device. Participants with known Pompe-specific cardiac hypertrophy (reported in their medical history), who required invasive ventilation (non-invasive ventilation was allowed), and who were wheelchair-dependent were excluded. Other exclusion criteria included clinically significant organic disease (apart from Pompe-disease-related symptoms), previous or current use of immune tolerance induction therapy, pregnancy or breastfeeding, and being a female of childbearing potential not protected by highly effective contraception or unwilling or unable to test for pregnancy (complete exclusion criteria given in the appendix p 2).

The study protocol was reviewed and approved by appropriate ethics committees or institutional review boards and done in accordance with the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. Written informed consent was obtained from patients before any study-related procedures.

Randomisation and masking

During the primary analysis period, participants were randomly assigned (1:1) to either avalglucosidase alfa or alglucosidase alfa. Randomisation was stratified by baseline upright FVC percent (FVC%) predicted (<55% or ≥55%), sex, age (<18 years or ≥18 years), and region among participants aged at least 18 years (Japan or outside Japan [regional regulatory requirements]). The random treatment assignments for eligible patients were done using a centralised treatment allocation system (interactive response technology). This system generated the patient randomisation list and allocated the patient identification number and corresponding treatment kits to patients accordingly. Participants, investigators, and study site personnel (except for the unmasked pharmacist or the unmasked designee) remained unaware of study treatment assignments and did not have access to the randomisation schedule. To control the number of participants with high baseline FVC, the percentage of participants with baseline upright FVC greater than or equal to 80–85% predicted was held at 15% of the total population. All treatments were intravenous infusions that were administered during the same time frame.

In the open-label extended-treatment period, participants randomly assigned to alglucosidase alfa during the primary analysis period were switched to avalglucosidase alfa after week 49, while remaining masked to their initial treatment allocation.

Procedures

The COMET trial comprised up to 76 study visits: the screening visit (visit 1, day –14 to day –1); visit 2 (day 1 or day 2) to visit 27 (week 49), occurring every 1–2 weeks for infusion of the assigned study drug, pharmacokinetic assessments, safety assessments, and efficacy evaluations in the double-blind treatment period; and visit 28 (week 51) to visit 76 (week 145) for infusion of avalglucosidase alfa, safety assessments, and efficacy assessments in the open-label extended treatment period. An additional extended open-label period of up to 144 weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first) is ongoing, which will comprise visits every 2 weeks (study drug infusion, adverse events check, and vital signs) as well as less frequent visits for other assessments (eg, every 4 weeks, 12 weeks, 24 weeks, and 48 weeks). At the end of this period, the end of study visit or contact will be done.

Clinical study data (coded by patient identification number) were stored in a clinical data management system, which is a distinct database in a separate environment from the database containing pharmacogenetic data. This blood sample, and the DNA that was extracted from it, was assigned a second number, a genetic identification (deidentification code), that was different from the patient indentification. This double coding was done to separate a patient's medical information and DNA data. The key linking the patient treatment number to the genetic identification was maintained by a third party, under appropriate control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, was possible only by using this key. All data were reported only in coded form to maintain confidentiality.

Participants received intravenous infusions of avalglucosidase alfa (Sanofi Genzyme, Cambridge, MA, USA) 20 mg/kg every 2 weeks or the recommended labelled dose of alglucosidase alfa (Sanofi Genzyme) 20 mg/kg every 2 weeks.[7,8] The dose for avalglucosidase alfa was supported by results from non-clinical studies and the

NEO1 trial[13] and was chosen as most likely to result in greater glycogen clearance in skeletal muscle and clinical efficacy compared with alglucosidase alfa without new safety concerns after treatment for 6 months.

Pulmonary function testing was done locally at each study centre and assessed by a central laboratory (E-Research Technology, Maryland Heights, MO, USA). The administration protocol for pulmonary function testing was standardised across study sites in accordance with the American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines.[19]

Immunogenicity was assessed by measuring antidrug antibodies using a direct ELISA (anti-avalglucosidase alfa assay; anti-alglucosidase alfa assay) and neutralising antibodies using both an inhibition of enzymatic activity assay and a cell-based inhibition of enzyme uptake assay. All testing was done at Sanofi US, Biomarkers and Clinical Bioanalyses-Boston, Framingham, MA, using validated methods. The anti-avalglucosidase alfa assay used an anti-human IgG and IgM detection reagent whereas the anti-alglucosidase alfa assay used an anti-human IgG detection reagent.

Clinical laboratory parameters and biomarkers for Pompe disease (ie, urinary hexose tetrasaccharide, serum creatine kinase, alanine aminotransferase, and aspartate aminotransferase) were measured per protocol, sampled at predefined timepoints, more frequently during the first year of the study and less frequently thereafter. Genotypes of patients (to assess study eligibility) were obtained from historical records. If historical results were not available, genotyping of the human acid GAA was done by molecular sequencing to identify variants and genetic variation (polymorphisms and associated haplotypes) within the *GAA* gene.

Outcomes

The primary objective for efficacy was to assess respiratory muscle function during the primary analysis period, which was measured by change from baseline to week 49 in upright FVC% predicted. FVC is widely used to assess respiratory function in patients with late-onset Pompe disease and is considered a primary endpoint for measurement of disease progression and has been used as a co-primary endpoint in other studies of late-onset Pompe disease.[17,20] Additionally, FVC is mechanistically linked to disease morbidity and mortality.[21,22]

The key secondary objective for efficacy was to assess functional endurance during the primary analysis period, which was measured by change from baseline to week 49 in the 6-minute walk test (6MWT) for the total distance walked in metres per ATS guidelines.[23] The 6MWT percent predicted was calculated based on normal reference equations covering the age range of trial participants.[24,25] Additional secondary objectives for efficacy were to assess change from baseline to week 49 in inspiratory muscle strength (measured by upright maximum inspiratory pressure [MIP] percent predicted) and expiratory muscle strength (measured by maximum expiratory pressure [MEP] percent predicted), lower extremity muscle strength (measured by hand-held dynamometry [HHD]), motor function (measured by the quick motor function test [QMFT], which is based on the gross motor function measure-88 [GMFM-88]),[26] and health-related quality of life (measured by the 12-item short-form [SF-12] health survey, using the physical component summary [PCS] and mental component summary [MCS] scales).

A secondary objective was to assess safety. Safety assessments were based on the number of participants with adverse events that developed, worsened, or became serious from the first administration of the study drug to the time just before the first administration of the study drug in the open-label extended treatment period or up to 28 days after the last infusion date if the participant did not enter the open-label extended treatment period. Treatment-emergent adverse events, including infusion-associated reactions, were recorded. Treatment-emergent adverse events were reported by local investigators by seriousness, severity, relatedness, and frequency (complete criteria are given in the appendix p 3). Safety data were reviewed twice a year by an independent data monitoring committee and on an ad hoc basis as necessary.

Additional protocol-defined objectives included assessment of motor function (measured by the Gait, Stair, Gower's Maneuver, and Chair composite score[27] and by GMFM-88), upper extremity muscle strength (measured by HHD), health-related quality of life (measured by the five-level EQ-5D and the Pediatric Quality of Life Inventory [per protocol, this was only assessed in patients aged <18 years and data were only available for one patient]), and patient-reported outcomes assessing Pompe disease symptoms (including the Rasch-built Pompe-specific activity scale,[28] the patient global impression of change,[29] the Pompe disease symptom scale, and the Pompe disease impact scale.

Statistical analysis

COMET was designed to show non-inferiority of the primary objective for efficacy (ie, change from baseline to week 49 in upright FVC% predicted). A hierarchical testing strategy—to test for non-inferiority first, followed by superiority—was selected for this study because of the rarity of Pompe disease and because recruiting sufficient patients would be challenging. As suggested and agreed by regulatory bodies, we lowered the percentage for the determination of the non-inferiority margin from 95% to 80%. Thus, rather than using the 95%-95% rule, the non-inferiority margin was based on the lower bound of the 80% CI for the difference between alglucosidase alfa and placebo in Late-Onset Treatment Study (LOTS) (80% CI 2·14–5·15).[17] The chosen non-inferiority margin of 1·1% predicted retained approximately 50% of the treatment effect of alglucosidase alfa versus placebo based

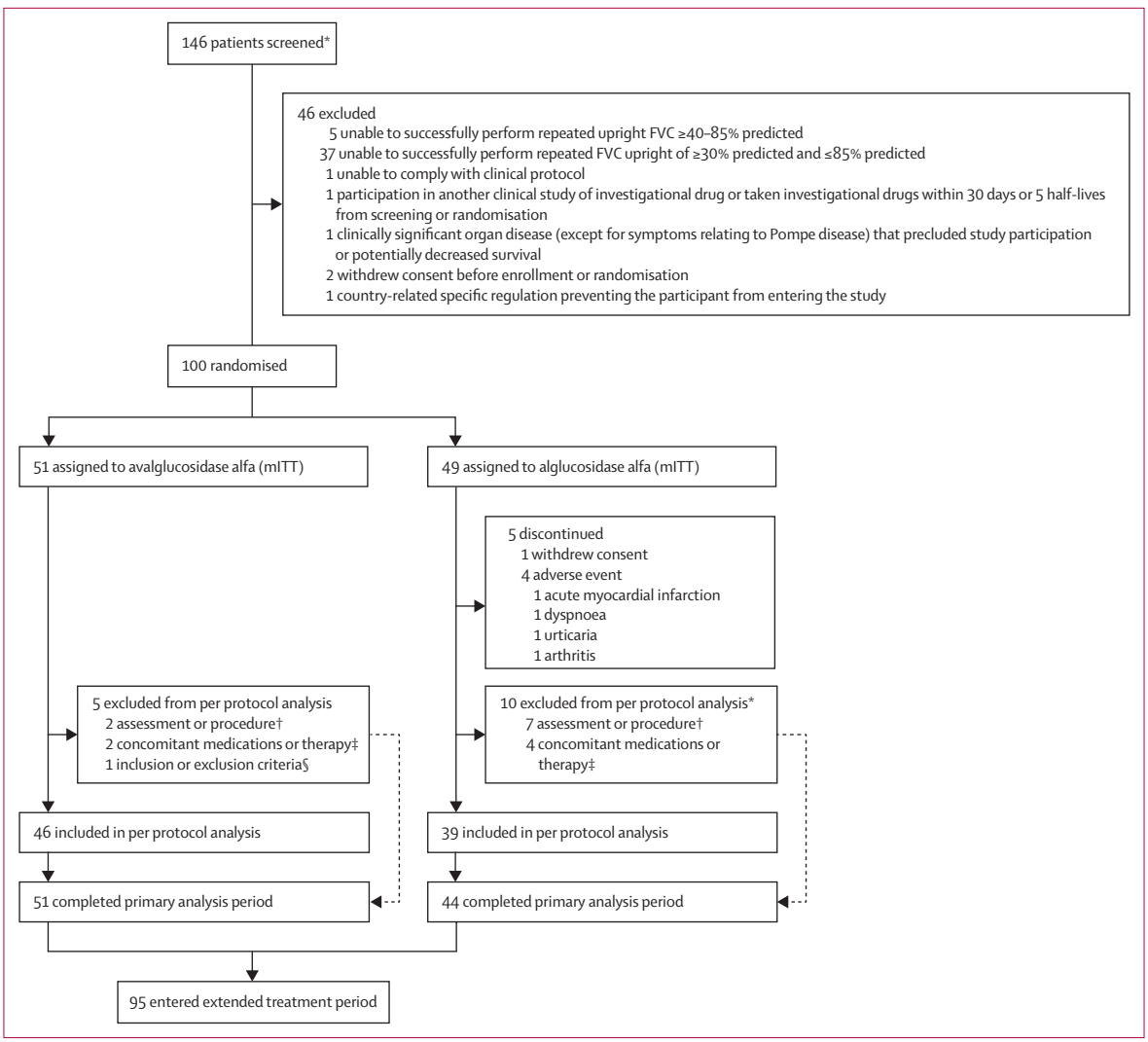


Figure 1: **Trial profile**
FVC=forced vital capacity. IMP=investigational medicinal product. mITT=modified intention to treat. *A participant in the mITT population could have multiple reasons resulting in exclusion from the per protocol analysis and might be included in each reason. †Did not undergo assessment or week-49 assessment during the extended treatment period. ‡Received prohibited medication (immunomodulator); one discontinued participant in the alglucosidase alfa group was also excluded for that reason and is included twice. §Inclusion criterion not confirmed at time of randomisation.

on the lower bound of the 80% CI. A literature review on the clinical relevance of outcome measures used in late-onset Pompe disease[30] showed that in six (67%) of nine studies in which patients were treated with alglucosidase alfa, the changes from baseline in upright FVC% predicted were above or within the minimal clinically important difference established for another restrictive respiratory disease. The current proposed non-inferiority margin of 1·1% predicted is smaller than this reference range.

The sample size calculation was based on the non-inferiority test of the change from baseline to week 49 in upright FVC% predicted, with the following assumptions: (1) the primary endpoint is normally distributed with a common SD of 5·1%; (2) mean treatment difference between groups of 2·0% predicted; (3) two-sided 5% significance level; and (4) expected percentage of missing data of up to 10%.[17,31] The SD of 5·1% was assumed based on data from the LOTS trial.[17] In this phase 3 placebo-controlled trial, the mean change from baseline at week 52 was 1·651% for alglucosidase alfa and –1·865% for placebo. The mean treatment difference (avalglucosidase alfa–alglucosidase alfa) of 2·0% was assumed on the basis of a conservative estimate when comparing the LOTS trial[17] with the open-label NEO1 study of avalglucosidase alfa.[13] A total sample size of 96 would provide approximately 80% power to show non-inferiority of avalglucosidase alfa versus alglucosidase alfa, when the true treatment difference (avalglucosidase alfa–alglucosidase alfa) is 2·0% predicted.

For multiplicity issues, a hierarchical fixed sequential testing strategy for the primary and secondary objectives was used. If non-inferiority was met, superiority testing was done. If the true treatment difference was 3·5% predicted, the study would have greater than 85% power to show superiority of avalglucosidase alfa to alglucosidase alfa. If superiority was shown for upright FVC% predicted, then superiority would be tested for secondary objectives for efficacy in the following order: 6MWT distance, MIP percent (MIP%) predicted, MEP percent (MEP%) predicted, and hand-held dynamometry summary score for the lower extremities. The estimand was defined as the difference between avalglucosidase alfa and alglucosidase alfa in the mean change from baseline to week 49 in upright FVC% predicted, regardless of whether intercurrent events have occurred.

As prespecified, a constancy assumption that the effect of alglucosidase alfa relative to placebo in the current trial is similar to the effect observed in the LOTS trial was assessed. An exploratory analysis using the covariate-adjustment regression model approach proposed by Nie and colleagues[32] was done to investigate the effect of population differences between the LOTS and COMET trials on the degree of constancy assumption violation. An ANCOVA model was fitted to LOTS data to generate a predictive model for the outcome of change from baseline in upright FVC% predicted at week 49 as a function of the following covariates: treatment, age, sex, race, duration of disease, baseline FVC, baseline 6MWT, and respiratory support device use at baseline on the basis of LOTS trial results.

For efficacy analyses, participants were analysed by modified intention to treat (mITT). This population (referred to as the primary analysis population) consisted of participants who received at least one infusion (partial or full) of the assigned treatment. The per-protocol population consisted of participants in the primary analysis population who received at least 80% of planned doses, had a valid FVC assessment at week 49, and had no major protocol deviations that potentially affected the primary endpoint. The per-protocol population was used for a sensitivity analysis of the primary endpoint during the primary analysis period. The safety population, defined as all participants who received at least one infusion (partial or total) in the primary analysis period, was used for safety analyses. Participants in all populations were summarised according to the treatment received.

The analysis method was based on a mixed model for repeated measures, assuming data were missing at random. Changes from baseline were analysed using a repeated measures approach based on restricted maximum likelihood in combination with the Newton-Raphson algorithm. Analyses included the fixed categorical effects of sex, treatment, visit, and treatment-by-visit interaction as well as the continuous fixed covariates of baseline score and age. A common

	Avalglucosidase alfa (n=51)	Alglucosidase alfa (n=49)	Total (n=100)
Age, years			
Mean (SD)	46·0 (14·5)	50·3 (13·7)	48·1 (14·2)
Range	16–78	20–78	16–78
<18	1 (2%)	0	1 (1%)
≥18 to ≤44	23 (45%)	19 (39%)	42 (42%)
≥45	27 (53%)	30 (61%)	57 (57%)
Sex			
Male	27 (53%)	25 (51%)	52 (52%)
Female	24 (47%)	24 (49%)	48 (48%)
Race			
Asian	3 (6%)	0	3 (3%)
Black or African American	1 (2%)	2 (4%)	3 (3%)
White	47 (92%)	47 (96%)	94 (94%)
Ethnicity			
Hispanic or Latino	3 (6%)	12 (24%)	15 (15%)
Not Hispanic or Latino	44 (86%)	32 (65%)	76 (76%)
Not reported	4 (8%)	5 (10%)	9 (9%)
Region			
Europe	31 (61%)	21 (43%)	52 (52%)
North America	14 (28%)	20 (41%)	34 (34%)
Latin America	2 (4%)	7 (14%)	9 (9%)
Asia-Pacific	4 (8%)	1 (2%)	5 (5%)
Age at onset of first symptom of Pompe disease, years			
Mean (SD)	32·9 (16·6); n=50	37·7 (15·7); n=49	35·3 (16·3); n=99
Range	3·8–66·3	6·1–73·2	3·8–73·2
Time from first symptom to first infusion of study drug, years			
Mean (SD)	13·36 (10·98); n=50	12·65 (10·08); n=49	13·01 (10·49); n=99
Range	0·88–58·24	0·42–38·20	0·42–58·24
Age at diagnosis, years			
Mean (SD)	44·7 (14·7)	48·2 (14·6)	46·4 (14·7)
Range	10·8–77·7	17·1–76·7	10·8–77·7
Time from diagnosis to first infusion of study drug, years			
Mean (SD)	1·30 (2·67)	2·21 (4·99)	1·75 (3·99)
Range	0·04–12·93	0·03–27·37	0·03–27·37
Upright FVC, % predicted			
Mean (SD)	62·5 (14·4)	61·6 (12·4)	62·1 (13·4)
Range	32·1–84·8	39·3–84·5	32·1–84·8
6MWT, m			
Mean (SD)	399·3 (110·9)	378·1 (116·2)	388·9 (113·5)
Range	118·0–630·0	138·0–592·0	118·0–630·0
6MWT, % predicted			
Mean (SD)	57·3 (15·0)	55·3 (16·6)	56·3 (15·8)
Range	18·5–85·9	22·6–101·9	18·5–101·9
Upright MIP, % predicted*			
Mean (SD)	51·74 (24·85); n=48	53·71 (23·47); n=47	..
Range	9·0–116·5	17·7–106·5	..
Upright MEP, % predicted*			
Mean (SD)	59·17 (21·60); n=48	70·21 (27·32); n=47	..
Range	28·7–117·9	19·7–136·2	..

(Table 1 continues on next page)

	Avalglucosidase alfa (n=51)	Alglucosidase alfa (n=49)	Total (n=100)
(Continued from previous page)			
HHD (lower extremity), composite			
Mean (SD)	1330·45 (625·44); n=50	1466·16 (604·91); n=46	1395·48 (616·23); n=96
Range	323·00–3522·00	329·00–3218·00	323·00–3522·00
HHD (upper extremity), composite			
Mean (SD)	1535·95 (673·60); n=46	1608·56 (633·95); n=47	136·88 (62·42); n=93
Range	350·50–3869·00	347·00–3102·00	347·00–3869·00
QMFT score			
Mean (SD)	41·29 (10·15); n=51	42·30 (10·58); n=46	41·77 (10·32); n=97
Min, Max	41·00 (17·00–63·00)	43·50 (19·00–63·00)	17·00–63·00
SF-12 (PCS) score			
Mean (SD)	35·95 (7·82); n=50	36·76 (9·40); n=48	36·35 (8·60); n=98
Range	17·75–55·85	16·30–57·30	16·29–57·34
SF-12 (MCS) score			
Mean (SD)	48·31 (10·11); n=50	50·58 (8·69); n=48	49·42 (9·46); n=98
Range	24·21–70·82	30·39–64·98	24·21–70·82
Urinary Hex_4, mmol/mol creatinine)			
Mean (SD)	12·71 (10·10); n=51	8·74 (5·04); n=49	
Range	2·95–47·98	2·02–25·27	
Alanine aminotransferase, IU/L			
Mean (SD)	81·30 (56·51); n=50	60·76 (30·28); n=49	..
Range	24·00–319·00	12·00–186·00	..
Aspartate aminotransferase, IU/L			
Mean (SD)	79·64 (55·58); n=50	57·73 (25·49); n=49	..
Range	27·00–285·00	16·00–141·00	..
Creatine kinase, IU/L			
Mean (SD)	739·9 (577·62); n=50	566·35 (431·46); n=48	..
Range	158·00–3128·00	66·00–2545·00	..

Data are n (%), unless otherwise indicated. Normal ranges are urinary Hex_4 0·19–3·36 mmol/mol creatinine (males and females, aged 13–18 years) or 0·14–1·92 (males and females, aged >18 years); alanine aminotransferase 6–34 IU/L (females, aged <69 years), 6–32 IU/L (females, aged ≥69 years), 6–43 IU/L (males, aged 10–68 years), or 6–35 IU/L (males, aged ≥69 years); aspartate aminotransferase 10–40 IU/L (males and females, aged 7–17 years), 9–34 IU/L (females, aged ≥18 years), or 11–36 IU/L (males, aged ≥18 years); and creatine kinase 18–169 IU/L (females, aged 16–17 years), 26–192 IU/L (females, aged ≥18 years), 18–408 IU/L (males, aged 16–17 years), or 39–308 IU/L (males, aged ≥18 years). 6MWT=6-minute walk test. FVC=forced vital capacity. Hex_4=hexose tetrasaccharide. HHD=hand-held dynamometry. MCS=mental component summary. MEP=maximum expiratory pressure. MIP=maximum inspiratory pressure. mITT=modified intention to treat. PCS=physical component summary. QMFT=quick motor function test. SF-12=health-related quality of life 12-item short-form health survey. *Four participants (two in each group) with implausibly high MIP % predicted and MEP % predicted values at baseline were excluded from all MIP and MIP analyses.

Table 1: **Baseline demographics and characteristics for the mITT population**

unstructured covariance matrix was used to model within-patient errors. If this analysis failed to converge, the following covariance structures were tested in a subsequent order until model convergence was achieved: heterogeneous Toeplitz (heterogeneous variance, an extension of homogeneous Toeplitz), homogeneous Toeplitz (equal variance and a separate correlation for each level of separation between the timepoints), heterogeneous AR(1; heterogeneous variance, an extension of AR[1]), AR(1; first-order autoregressive, equal variances, and exponentially decreasing correlations). The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Significance tests were based on least-squares means using a one-sided 2·5% significance level for non-inferiority and two-sided α of 0·05 for superiority (two-sided 95% CIs). Analyses were done using SAS (version 9.4).

To further understand the difference between avalglucosidase alfa and alglucosidase alfa, categorical responder analyses for change from baseline in upright FVC% predicted and 6MWT distance were done according to the statistical analysis plan and based on predefined responder thresholds.[23,33,34] The change from baseline in 6MWT distance was analysed separately using the mixed model for repeated measures.

This study is registered with ClinicalTrials.gov, NCT02782741.

Role of the funding source

The design and conduct of the study, data collection, management, analysis, and interpretation were done by the funder in collaboration with the academic authors. Preparation, review, and approval of the manuscript were done by all authors, with the assistance of a professional medical writer employed by the funder.

Results

Between Nov 2, 2016, and March 29, 2019, 146 individuals were screened for the study, of whom 46 were excluded (figure 1). 100 participants were randomly assigned to avalglucosidase alfa (n=51) or alglucosidase alfa (n=49). Five (5%) people permanently discontinued during the primary analysis period (all in the alglucosidase alfa group) and 95 (95%) completed the primary analysis period. Protocol deviations were balanced across treatment groups, with no apparent distribution pattern, and these were, therefore, unlikely to affect the outcome of the study.

Baseline demographics and characteristics were representative of the general population with late-onset Pompe disease and were generally similar between treatment groups (table 1). Most participants were aged at least 45 years old, although individuals in the avalglucosidase alfa group had a slightly younger mean age. More participants in the alglucosidase alfa group than in the avalglucosidase alfa group were of Hispanic or Latino ethnicity and were enrolled in Latin America, whereas more participants in the avalglucosidase alfa group than in the alglucosidase alfa group were enrolled in Europe. Baseline upright FVC% predicted and 6MWT distance were similar between the two treatment groups overall.

The most frequent variant in the *GAA* gene in patients in this study, c.-32-13T>G, was found in at least one allele in 89 participants, of whom 43 (84%) were assigned avalglucosidase alfa and 46 (94%) were allocated alglucosidase alfa. A list of the most common variants reported in at least five participants is given in the appendix (p 4).

Creatine kinase, alanine aminotransferase, and aspartate aminotransferase levels were increased at baseline from normal ranges in both groups, which is not unexpected for individuals with late-onset Pompe disease who have never received treatment. Urinary hexose tetrasaccharide was also increased at baseline in all participants. Amounts of these enzymes were higher in the avalglucosidase alfa group than in the alglucosidase alfa group (table 1).

Treatment compliance rates were high during the primary analysis period, with 100% (n=51) of individuals assigned avalglucosidase alfa and 92% (n=45) of those allocated alglucosidase alfa achieving compliance. Non-compliance was defined as missing two or more consecutive infusions or missing 20% or more total doses in the 49 week primary analysis period or percentage of compliance less than 80% in the primary analysis period.

Avalglucosidase alfa treatment resulted in an improvement from baseline to week 49 in the least-squares mean upright FVC% predicted of 2·89% (SE 0·88) compared with improvements of 0·46% (0·93) with alglucosidase alfa treatment (table 2). Improvement relative to baseline was observed in participants treated with avalglucosidase alfa as early as week 13 and maintained throughout the study period (figure 2A). A smaller initial improvement remained stable with alglucosidase alfa after week 13 (figure 2A). A decrease was seen at week 37 compared with week 25 (from 3·21% to 2·21%) with avalglucosidase alfa; however, overall improvements continued to week 49. At week 49, participants treated with avalglucosidase alfa showed a 2·43% greater increase in FVC% predicted compared with those treated with alglucosidase alfa (95% CI –0·13 to 4·99; figure 3A). The lower bound of the 95% CI for the difference far exceeded –1·1% predicted (the predefined non-inferiority margin) and was statistically non-inferior (p=0·0074; figure 3). Superiority testing resulted in a p value of 0·063. Because superiority was not reached, formal testing was stopped per the testing hierarchy and p values for secondary endpoints are provided at the nominal level (without multiplicity adjustment). A sensitivity analysis in the per-protocol population was similar to results in the mITT population (appendix p 5).

The findings of the prespecified constancy assumption showed that the estimates of the effect of alglucosidase alfa compared with placebo from the predictive model were 2·87 for COMET and 3·02 for LOTS. The difference in the effect of alglucosidase alfa calibrated to the LOTS and COMET trials was small (–0·15) compared with the non-inferiority margin (1·1% predicted). Based on this result, the constancy assumption was considered to hold.

A responder analysis for upright FVC% predicted showed that more participants treated with avalglucosidase alfa reported a relative increase from baseline of at least 15% at week 49 (n=10 [20%]) compared with alglucosidase alfa (n=3 [6%]) with an odds ratio (OR) from logistic regression of 3·47 (95% CI 0·86–13·98).

	Avalglucosidase alfa (n=51)	Alglucosidase alfa (n=49)	Least-squares mean difference between treatments (95% CI)
Upright FVC% predicted	2·89 (0·88)	0·46 (0·93)	2·43 (–0·13 to 4·99)
6MWT, m	32·21 (9·93)	2·19 (10·40)	30·01 (1·33 to 58·69)
6MWT% predicted	5·02 (1·54)	0·31 (1·62)	4·71 (0·25 to 9·17)
MIP% predicted*	8·70 (2·09)	4·29 (2·19)	4·4 (–1·63 to 10·44)
MEP% predicted*	10·89 (2·84)	8·38 (2·96)	2·51 (–5·7 to 10·73)
HHD, lower extremity	260·69 (46·07)	153·72 (48·54)	106·97 (–26·56 to 240·5)
HHD, upper extremity	173·54 (38·04)	109·67 (38·98)	63·87 (–44·76 to 172·51)
QMFT total score	3·98 (0·63)	1·89 (0·69)	2·08 (0·22 to 3·95)
SF-12 PCS score	2·37 (0·99)	1·60 (1·07)	0·77 (–2·13 to 3·67)
SF-12 MCS score	2·88 (1·22)	0·76 (1·32)	2·12 (–1·46 to 5·69)

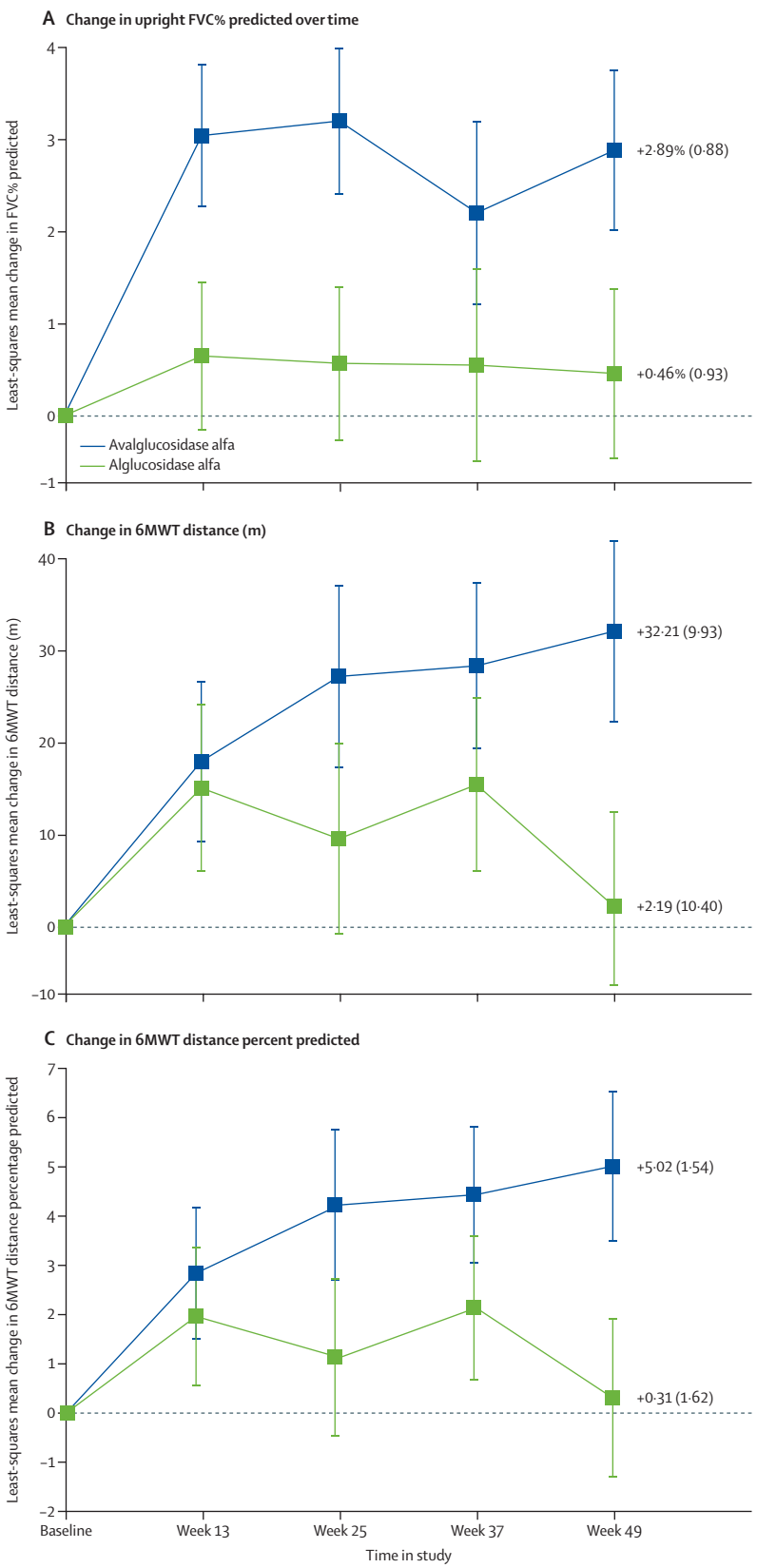
Data are least-squares mean (SE), unless otherwise indicated. All efficacy analyses were done in the modified intention-to-treat population. 6MWT=6-minute walk test. FVC=forced vital capacity. HHD=hand-held dynamometry; MCS=mental component summary. MEP=maximum expiratory pressure. MIP=maximum inspiratory pressure. PCS=physical component summary. QMFT=quick motor function test. SF-12=health-related quality of life 12-item short-form health survey. *Four participants (two in each group) with implausibly high MIP% predicted and MEP% predicted values at baseline were excluded from all MIP and MIP analyses.

Table 2: **Changes from baseline to week 49 in predefined primary and secondary objectives for efficacy**

At week 49, participants treated with avalglucosidase alfa showed a greater increase in 6MWT distance compared with those treated with alglucosidase alfa (least-squares mean 32·21 m [SE 9·93] *vs* 2·19 m [10·40]; difference 30·01 m [95% CI 1·33–58·69]; p=0·040, statistically significant at the nominal level of 5%; table 2; figure 3A). Progressive improvements relative to baseline were seen throughout the 49-week double-blind treatment period in the 6MWT distance (both in metres and as percent predicted) with avalglucosidase alfa. Improvements were not as consistent or as large with alglucosidase alfa (figure 2B, C; table 2).

See Online for appendix

A responder analysis for 6MWT distance showed more participants treated with avalglucosidase alfa reported an increase from baseline at week 49 of at least 54 m (n=12 [24%]) compared with alglucosidase alfa (n=6 [12%]) with an OR from logistic regression of 2·09 (95% CI 0·70–6·25). Results of prespecified subgroup analyses for upright FVC% predicted and 6MWT distance were similar to the results of the main analyses in the mITT population (appendix pp 6–7).



Four participants (two in each group) had physiologically implausible MIP and MEP baseline values (both entered as 200 cm H_20). Values at subsequent study visits were vastly different from baseline yet consistent with one another throughout the rest of the study. Baseline values for these participants probably reflect a data entry error. Data from these four participants were excluded from MIP and MEP analyses.

Greater numerical improvements in mean changes from baseline to week 49 were observed (although the 95% CIs crossed 0) with avalglucosidase alfa compared with alglucosidase alfa in the prespecified secondary endpoints of respiratory muscle strength (MIP% predicted and MEP% predicted), lower extremity muscle strength (HHD), motor function (quick motor function test), and health-related quality of life (SF-12 PCS and SF-12 MCS; table 2, figure 3A, B; appendix pp 8–11).

Decreases relative to baseline were seen over time in all biomarkers and key laboratory parameters assessed (appendix pp 12–15). Seemingly larger decreases were seen at week 49 with avalglucosidase alfa versus alglucosidase alfa, with some values approaching normal ranges at week 49 (appendix pp 12–15).

44 (86%) of 51 patients who received avalglucosidase alfa and 45 (92%) of 49 who received alglucosidase alfa reported a treatment-emergent adverse event. Treatment-emergent adverse events potentially related to treatment were reported in 23 (45%) of 51 participants in the avalglucosidase alfa group and in 24 (49%) of 49 in the alglucosidase alfa group. The most common treatment-emergent adverse events reported are presented in the appendix (p 16). For avalglucosidase alfa, nasopharyngitis and back pain were each reported in 12 (24%) participants, and headache in 11 (22%) participants; for alglucosidase alfa, headache was reported in 16 (33%) participants and nasopharyngitis in 12 (25%) participants.

Serious treatment-emergent adverse events were reported in eight (16%) participants who received avalglucosidase alfa and in 12 (25%) who received alglucosidase alfa (table 3). One (2%) participant treated with alglucosidase alfa died because of a serious adverse event of acute myocardial infarction determined to be unrelated to treatment. Five (10%) participants withdrew from the study, all in the alglucosidase alfa group. Of these, four (8%) were due to adverse events (including two participants with infusion-associated reactions). No participant in the avalglucosidase alfa group withdrew. Dyspnoea (n=1) was the only serious adverse event reported as related to avalglucosidase alfa. Six serious

Figure 2: **Change from baseline to week 49 in primary and key secondary objectives, per treatment group**
(A) Change in upright FVC percentage predicted over time (primary objective). (B) Change in 6MWT distance (m) over time. (C) Change in 6MWT distance percent predicted over time. Datapoints denote least-squares mean. Error bars indicate SE. FVC=forced vital capacity. 6MWT=6-minute walk test

adverse events (dizziness, visual impairment, hypotension, dyspnoea, cold sweat, and chills) were reported in three (6%) participants as related to alglucosidase alfa. Treatment-emergent hypersensitivity reactions were observed in 12 (24%) participants in the avalglucosidase alfa group and 15 (31%) participants in the alglucosidase alfa group. One (2%) participant in the alglucosidase alfa group and none in the avalglucosidase alfa group had anaphylaxis. No participants in either treatment group had immune-mediated reactions.

Protocol-defined adverse events of special interest included pregnancy, symptomatic overdose, predefined increases of aminotransferases, bilirubin, and creatinine, and infusion-associated reactions. During the primary analysis period, adverse events of special interest were reported in 13 (26%) participants in the avalglucosidase alfa group and 18 (37%) participants in the alglucosidase alfa group (appendix pp 17–18). In the avalglucosidase alfa group, 13 (26%) patients had infusion-associated reactions and one (2%) had an increase in alanine aminotransferase. In the alglucosidase alfa group, there were 16 (33%) infusion-associated reactions, two (4%) pregnancies, and three (6%) increases in aspartate aminotransferase, alanine aminotransferase, or hepatic enzyme. Most infusion-associated reactions were mild or moderate. Protocol-defined severe infusion-associated reactions were reported in no participants in the avalglucosidase alfa group and in two (4%) participants in the alglucosidase alfa group. The most frequently reported adverse events of special interest (in two or more participants) were pruritus (n=4 [8%]), urticaria (n=3 [6%]), rash (n=2 [4%]), headache (n=2 [4%]), and diarrhoea (n=2 [4%]) in the avalglucosidase alfa group; and nausea (n=4 [8%]), pruritus (n=4 [8%]), increased alanine aminotransferase (n=3 [6%]), flushing (n=3 [6%]), chills (n=2 [4%]), dizziness (n=2 [4%]), dyspnoea (n=2 [4%]), erythema (n=2 [4%]), feeling hot (n=2 [4%]), and rash (n=2 [4%]) in the alglucosidase alfa group.

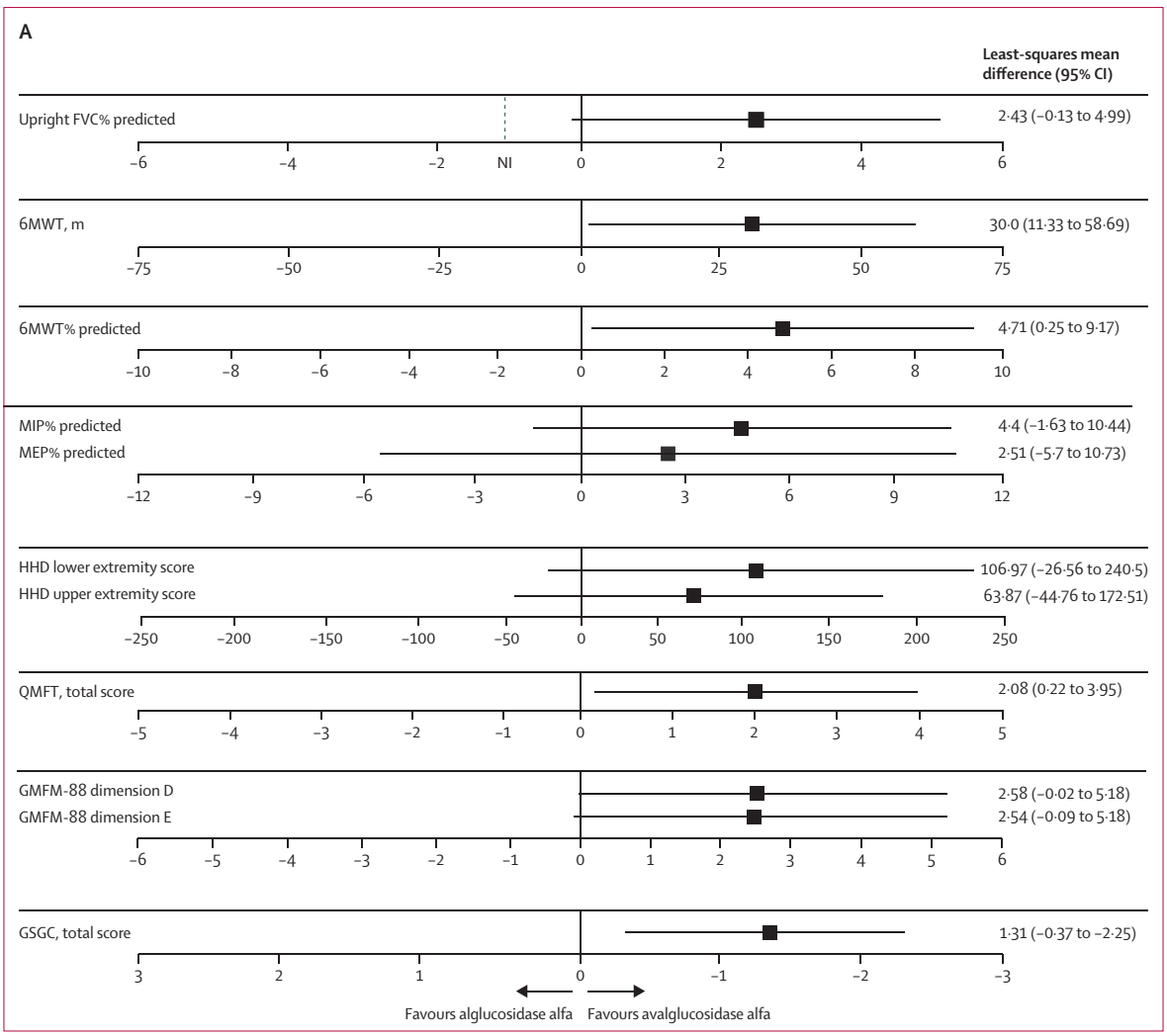
Immunogenicity results during the primary analysis period are summarised in table 3. Antidrug antibody responses were similar in both treatment groups (table 3). Two participants in each group were reported to be positive for antidrug antibodies at baseline (table 3). Treatment-induced antidrug antibodies (ie, antidrug antibodies that developed during the study in participants who were negative at baseline) were reported in 96% of participants in each group (table 3). Fewer participants in the avalglucosidase group (ten [20%]) had antidrug antibody peak titres 12 800 or greater than participants in the alglucosidase alfa group (16 [33%]; table 3). We found a lower proportion of participants with persistent high titres with avalglucosidase alfa (ten [24%]) versus alglucosidase alfa (16 [35%]). Among participants with persistent antidrug antibodies, high peak titre levels remained high, whereas moderate and low titres were reduced and patients tolerised. Three (6%) participants in the avalglucosidase alfa group tolerised compared with four (9%) in the alglucosidase alfa group (table 3). Neutralising antibody responses based on either enzyme activity inhibition or enzyme activity uptake were more commonly reported for alglucosidase alfa than for avalglucosidase alfa (table 3).

Discussion

We consider that the findings of the COMET trial show clinically meaningful improvements with avalglucosidase alfa compared with alglucosidase alfa in patients with late-onset Pompe disease. The primary objective for efficacy, of non-inferiority in respiratory function (as measured by upright FVC% predicted) was met, far exceeding the predefined margin. The test for superiority did not reach the prespecified 5% statistical significance level and, therefore, secondary objectives for efficacy could not be formally tested according to the predefined hierarchical testing strategy. However, greater numerical improvements were seen with avalglucosidase alfa compared with alglucosidase alfa in measures of functional endurance (6MWT), respiratory and extremity muscle strength, and health-related quality of life outcomes. Results are reported for 100 participants with late-onset Pompe disease enrolled at 55 study sites in 20 countries, representing a large population of patients for a rare disease.

The statistical approach taken in this study was conservative to account for variability in the patient population and control any false-positive study outcomes, reflecting robust testing. The chosen primary objective (upright FVC) is positively associated with other outcome measures in late-onset Pompe disease, including measures of endurance (eg, 6MWT), skeletal muscle strength, and patient-reported outcomes, and improvements in FVC correspond to improvements in other functional measures.[15] Upright FVC% predicted is also a reliable measure of respiratory function and often difficult to improve in patients with late-onset Pompe disease.

The observed improvement in upright FVC is clinically meaningful for several reasons. Respiratory morbidity and mortality, including respiratory failure and requirement for ventilatory support, is associated with severity of respiratory muscle weakness as assessed by upright FVC.[2,16,35] A minimal clinical difference of 2–6% was established for a restrictive respiratory disease and has been applied to other studies in late-onset Pompe disease.[30] The difference of 2·43% reported for upright FVC% predicted between the avalglucosidase alfa treatment group versus the alglucosidase alfa group is within this range and is clinically meaningful for patients with late-onset Pompe disease. Moreover, initiation of respiratory support results in reduced physical function with adverse effects on quality of life.[2] Given the progressive nature of late-onset Pompe disease, improvement in respiratory muscle strength (MIP or MEP) and upright FVC would delay onset of respiratory failure and potentially decrease reliance on mechanical ventilatory support. Lastly, the observed correlation



(Figure 3 continues on next page)

between improvements in upright FVC with several domains, including endurance, muscle strength, quality of life, and biomarkers (eg, hexose tetrasaccharide, a breakdown product of glycogen), further reinforces the clinical meaningfulness for the observed increase in upright FVC with avalglucosidase alfa.

Late-onset Pompe disease is a multisystemic disorder with considerable variation in disease manifestations and progression among patients, not only between but also within phenotypes. Because of the high variability in how patients are affected by the disease, secondary and exploratory outcomes are important and provide clinical insight into patient responses and effects of treatment.[1–6] Greater improvements were observed in the key secondary objective of 6MWT, with a greater increase in distance walked and percent predicted with avalglucosidase alfa compared with alglucosidase alfa. Responder analyses based on predefined meaningful thresholds for upright FVC[33,36] and 6MWT[23] further showed greater benefits for respiratory and musculoskeletal health with avalglucosidase alfa compared with alglucosidase alfa. Although differences in improvements in primary and secondary outcomes might appear small in absolute terms, in a progressive disease these differences can be meaningful because they offset the natural course of the disease more potently with avalglucosidase alfa than with alglucosidase alfa, here shown within a 49-week period. Preliminary long-term data indicate that this effect is likely to translate to a longer stabilisation period and potentially prolonged avoidance of respiratory and motor impairment with avalglucosidase alfa treatment.[14] Participants will continue to be followed up in the open-label extended-treatment phase of the COMET study to confirm the long-term effects of avalglucosidase alfa.

Some evidence for improvements with avalglucosidase alfa compared with alglucosidase alfa was seen across measures of respiratory and muscle strength, motor function, and health-related quality of life, reinforcing the

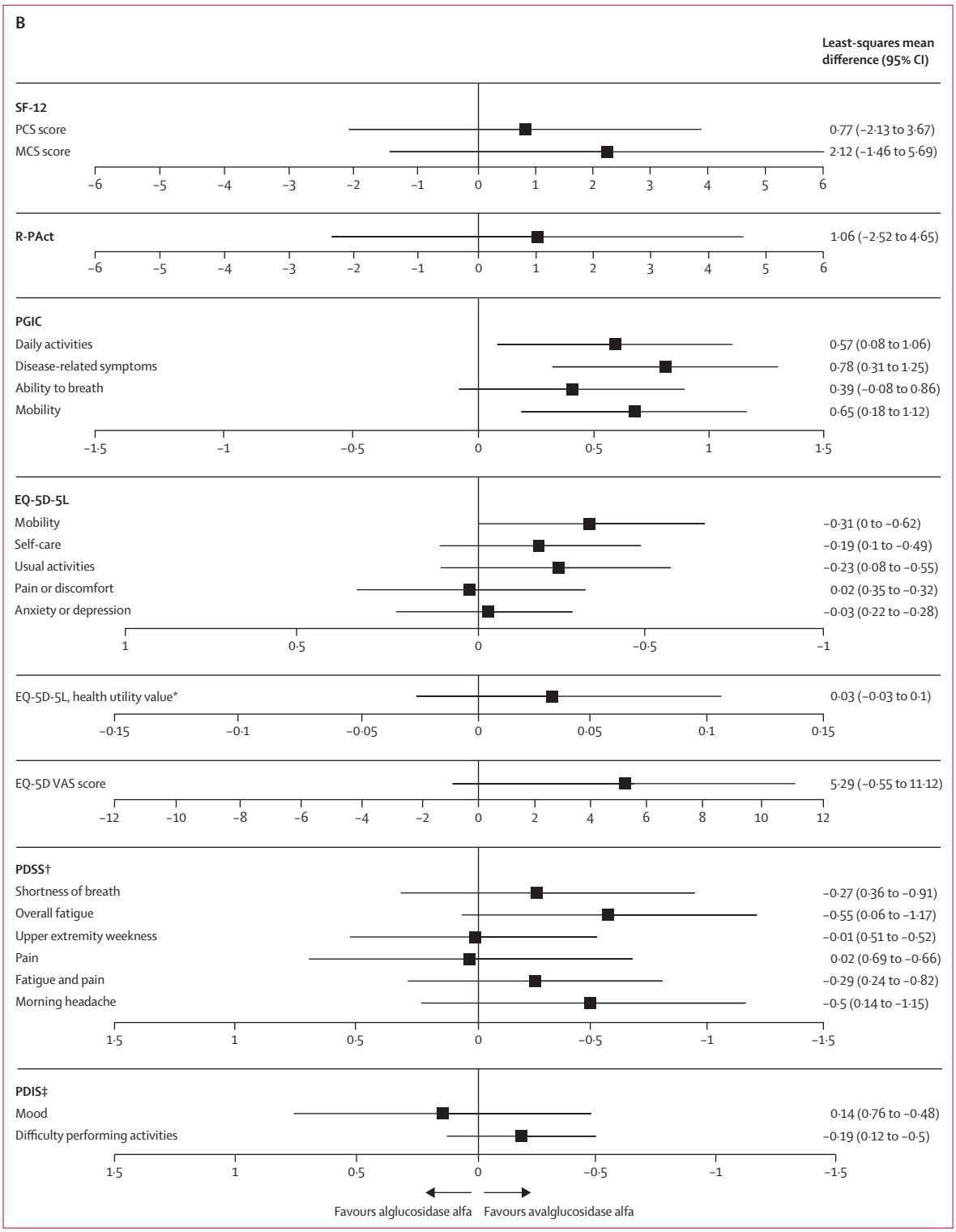


Figure 3: **Differences between treatment groups in changes from baseline to week 49 in predefined study objectives**
(A) Least-squares mean (95% CI) differences for predefined objectives for efficacy, measuring respiratory muscle function, functional endurance, muscle strength, and motor function. (B) Least-squares mean (95% CI) differences for predefined objectives measuring health-related quality of life. 6MWT=6-min walk test. EQ-5D-5L=five-level EQ-5D. EQ-5D-VAS=EQ-5D visual analogue scale. FVC=forced vital capacity. HHD=hand-held dynamometry. GMFM-88=gross motor function measure-88. GSGC=Gait, Stair, Gower's Maneuver, and Chair. MCS=mental component summary. MEP=maximum expiratory pressure. MIP=minimum expiratory pressure. PCS=physical component summary. PDIS=Pompe disease impact scale. PDSS=Pompe disease symptom scale. PGIC=patient global impression of change. QMFT=quick motor function test. R-Pact=Rasch-built Pompe-specific activity. SF-12=health-related quality of life 12-item short-form health survey. *Health-State Utility Values (5L) using UK tariff by treatment (crosswalk method). †Shortness of breath score included breathing and breathing while lying down; overall fatigue score included tiredness, fatigue, muscle weakness anywhere, muscle weakness in the lower body, and muscle weakness in the upper body; upper extremity weakness score included muscle weakness in the arms and muscle weakness in the hands; pain score included muscle aches and pain; and fatigue and pain score included the overall fatigue score, upper extremity weakness score, and pain score. ‡Mood score included anxiety, worry, and depression; difficulty performing activities score included walking difficulty, climbing difficulty, rising difficulty, bending over difficulty, and squatting down difficulty.

results with the upright FVC and 6MWT objectives. Importantly, in this double-blinded study, patient-reported outcomes also showed some evidence of potential benefit with avalglucosidase alfa compared with alglucosidase alfa. Thus, the cumulative response to treatment with avalglucosidase alfa across clinically relevant outcome measures of respiratory and musculoskeletal health and health-related quality of life was shown.

	Avalglucosidase alfa (n=51)	Alglucosidase alfa (n=49)
TEAEs	44 (86%)	45 (92%)
TEAEs potentially related to treatment	23 (45%)	24 (49%)
Serious TEAEs	8 (16%)	12 (25%)
Serious TEAEs potentially related to treatment	1 (2%)	3 (6%)
Severe TEAEs	6 (12%)	7 (14%)
TEAEs leading to study withdrawal	0	4 (8%)
TEAEs leading to death	0	1 (2%)
AESIs	13 (26%)	18 (37%)
IARs (protocol defined)*	13 (26%)	16 (33%)
Antidrug antibody status		
Always negative	2 (4%)	2 (4%)
Ever positive with negative baseline	47 (92%)	44 (92%)
Positive at baseline	2 (4%)	2 (4%)
Treatment-emergent ADA†	49 (96%)	46 (96%)
Treatment-induced ADA‡	47 (96%)	44 (96%)
Transient ADA	1 (2%)	1 (2%)
Persistent ADA	43 (88%)	39 (85%)
High response	10 (20%)	16 (35%)
Intermediate response	20 (41%)	19 (41%)
Low response	13 (27%)	4 (9%)
Tolerised ADA	3 (6%)	4 (9%)
Treatment-boosted ADA§	2 (100%)	2 (100%)
ADA peak titre¶||**		
100–800	17 (33%)	8 (17%)
1600–6400	20 (39%)	20 (42%)
≥12 800	10 (20%)	16 (33%)
ADA last titre¶**††		
100–800	26 (55%)	13 (30%)
1600–6400	11 (23%)	17 (39%)
≥12 800	10 (21%)	14 (32%)
Neutralising antibody response type based on enzyme activity inhibition		
Always negative	49 (96%)	44 (92%)
Positive at baseline	0	0
Positive post baseline	2 (4%)	4 (8%)
Neutralising antibody response type based on enzyme uptake inhibition		
Always negative	38 (75%)	28 (58%)
Positive at baseline	1 (2%)	1 (2%)
Positive post baseline	12 (24%)	19 (40%)

Data are n (%). Numbers for TEAEs reported are n (%) of participants with at least one TEAE in each category. All ADAs are either anti-avalglucosidase alfa antibodies or anti-alglucosidase alfa antibodies. ADAs were assessed monthly during the study. Immunogenicity was assessed on the basis of ADAs using a direct ELISA and neutralising antibodies using an inhibition of enzymatic activity assay and a cell-based inhibition of enzyme uptake assay. The anti-avalglucosidase alfa ADA ELISA used an anti-human IgG and IgM detection reagent and the anti-alglucosidase alfa ADA ELISA used an anti-human IgG detection reagent. AESI=adverse event of special interest. IAR=infusion-associated reactions. TEAE=treatment-emergent adverse event. *Defined as an adverse event that occurred during either the infusion or observation period following the infusion, related or possible related to the investigational treatment. †100 × (treatment-boosted + treatment-induced ADA positive participants)/(number of evaluable participants). ‡100 × (treatment-induced ADA positive participants)/(number of evaluable participants with ADA negative at baseline). §100 × (treatment-boosted ADA positive participants)/(number of evaluable participants with ADA positive at baseline). ¶For participants with evaluable ADA: avalglucosidase alfa, n=47; alglucosidase alfa, n=44. ||Peak titre ranges: were 100–51 200 for avalglucosidase alfa and 100–409 600 for alglucosidase alfa. **Two participants in the avalglucosidase alfa group had peak and last titres of 51 200. One participant in the alglucosidase alfa group had peak titre of 409 600 and last titre of 204 800. ††Last titre ranges were 100–51 200 for avalglucosidase alfa and 100–204 800 for alglucosidase alfa.

Table 3: **Safety and immunogenicity summary during the primary analysis period**

Inherent difficulties in standardising outcomes measures across study sites, based on regional practices and experience, needs to be considered when evaluating data overall. For example, considerable variability exists in the administration of MIP and MEP assessments by individual practitioners and by regional practices, and normative values vary among studies.[36] These differences contributed to the variability in MIP and MEP values at baseline seen in this study.

Treatment with avalglucosidase alfa was associated with a more favourable safety profile compared with that of alglucosidase alfa, as shown by lower frequencies of treatment-emergent adverse events thought to be treatment related, serious adverse events, and infusion-associated reactions with avalglucosidase alfa. Immunogenicity results are in line with the findings relating to treatment-emergent adverse events and serious adverse events. Although five participants treated with alglucosidase alfa withdrew from the study, all avalglucosidase alfa-treated participants completed the primary analysis period. Additionally, antidrug antibody data indicate that avalglucosidase alfa is not more immunogenic than alglucosidase alfa. Importantly, no emerging risks from treatment with avalglucosidase alfa were identified during this study.

Direct comparison of these results to those of the LOTS[17] trial is constrained by multiple differences. First, the COMET trial did not include a placebo group, precluding comparisons with untreated patients, which was the objective of LOTS. Second, participants randomly assigned to alglucosidase alfa in both trials differed across baseline characteristics. Baseline mean upright FVC% predicted and 6MWT were higher in COMET compared with in LOTS. Participants in COMET also had an older mean age at symptom onset, longer mean disease duration, and shorter median time from diagnosis to treatment compared with those in LOTS. Third, COMET included a broad geographical population from 55 sites across 20 countries compared with LOTS, which enrolled participants at seven sites in France, the Netherlands, and the USA. Although the number of participants with the most common *GAA* variants, particularly with at least one IVS1 variant, was similar across both studies, COMET included more participants of Hispanic and Asian backgrounds enrolled at sites in Latin America and Asia-Pacific regions than did LOTS. The primary analysis period duration also differed between the trials (49 weeks in COMET *vs* 78 weeks in LOTS). Finally, in the 10 years between these trials, the standard of care for patients with late-onset Pompe disease, including physical therapy, pulmonary care, and nutrition, has substantially changed.

In conclusion, on the basis of our collective clinical experience, we consider the improvements in respiratory function, functional endurance, muscle strength, motor function, health-related quality of life, and disease-specific biomarkers seen with avalglucosidase alfa

compared with alglucosidase alfa in the COMET trial to be clinically meaningful. Although superiority testing did not reach statistical significance, improvements were seen for other study objectives with avalglucosidase alfa compared with alglucosidase alfa. It is unlikely that any one result favours avalglucosidase alfa at random. Therefore, these improvements are meaningful for patients. Additionally, the safety and tolerability profile of avalglucosidase alfa appeared to be more favourable than that of alglucosidase alfa. These data offer clinical evidence of substantial improvement with avalglucosidase alfa over alglucosidase alfa for patients with late-onset Pompe disease in respiratory function, ambulation, and functional endurance, as well as improved safety and health-related quality of life.

Contributors

All authors provided substantial contributions to the interpretation of data and drafting and critical revision of the manuscript. JD-M, PSK, MMD, and BS provided equal contributions. JD-M, KAH, CH, OH-B, JJ, NT, and TZ were responsible for verification of the data. All authors had full access to the underlying data and had final responsibility for the decision to submit the manuscript for publication. The contents of this Article do not reflect the views of the US Department of Veterans Affairs or the US Government.

Declaration of interests

SA received reimbursement for attending symposia and other expenses. KB has served on advisory boards for Sanofi Genzyme, AskBio, Spark Therapeutics, and Takeda; and received consultant fees from Sanofi Genzyme, Amicus Therapeutics, AskBio, Spark Therapeutics, Takeda and Valerion. Y-HC has received research support, consulting fees, reimbursement for attending symposium and other expenses, and fees for non-continuing medical education or continuing education services from Sanofi Genzyme. PRC has served as a member of the Pompe Registry North American Advisory Board and undertaken contracted research for Amicus, Sanofi Genzyme, Spark, ReveraGen Biopharma, and NS Pharma. She has been a consultant for Roche and Epirium. She has received travel funding from Roche, Spark, and NS Pharma. JWD has received consulting fees from Audentes, Biogen;, Ionis Pharmaceuticals, Cytokinetics, Pfizer, AveXis, Roche/Genentech Pharmaceuticals, AMO Pharmaceuticals, and Sarepta Therapeutics; and has undertaken contracted research for Biogen, Ionis Pharmaceuticals, Cytokinetics, Roche Pharmaceuticals, AveXis, Sanofi- Genzyme, Sarepta Therapeutics, and Scholar Rock. JD-M has served as a consultant or speaker for Sanofi Genzyme, Lupin, Sarepta, and PTC Therapeutics; and received research support from Boehringer Ingelheim and Sanofi Genzyme. MMD has served as a consultant forArgenX, Catalyst, Cello, CSL Behring, EcoR1, Kezar, Momenta, NuFactor, Octapharma, RaPharma/UCB, RMS Medical, Sanofi Genzyme, Shire Takeda, Spark Therapeutics, and UCB Biopharma; and has received grants from Alexion, Alnylam Pharmaceuticals, Amicus, BioMarin, Bristol-Myers Squibb, Catalyst, Corbus, CSL Behring, US Food and Drug Administration/Office of Orphan Products Development, Genentech, GlaxoSmithKline, Grifols, Kezar, Mitsubishi Tanabe Pharma, Muscular Dystrophy Association, US National Institutes of Health (NIH), Novartis, Octapharma, Orphazyme, Ra Pharma/UCB, Sanofi Genzyme, Sarepta Therapeutics, Shire Takeda, Spark Therapeutics, UCB Biopharma, Viromed/Healixmith, and TMA. SE-O has served on advisory boards for Sanofi Genzyme. OG-A has served on advisory boards for Amicus, BioMarin, Sanofi, and Takeda; served on speaker's bureau for Sanofi and Takeda; received consulting fees from Amicus, BioMarin, Sanofi Genzyme, Shire Human Genetics Therapies, and Takeda; and undertaken contracted research for Amicus, Freeline, Genentech, Protalix, Sangamo, Sanofi, and Takeda. SI has received honoraria from Actelion, Boehringher Ingelheim, Ever Pharma, Merz Pharma, Servier, Takeda, and Teva. PSK has served on advisory boards for Amicus, Baebies, and Sanofi Genzyme; received consulting fees from Amicus, AskBio, Sanofi Genzyme, and Vertex; undertaken contracted research for Amicus, Sanofi Genzyme, and Valerion; received honoraria from Amicus, AskBio, Sanofi Genzyme, and Vertex; received travel expenses from Amicus and Sanofi Genzyme; and has ownership interests in AskBio and Baebies. HK has served on advisory boards for Alexion, Catalyst Pharmaceuticals, PTC therapeutics, and Sanofi Genzyme; and is on the speaker's bureau of Akcea, Catalyst Pharmaceuticals, and Sanofi Genzyme. SL has served on advisory boards and speaker's bureau, received consulting fees, and undertaken contracted research for Sanofi Genzyme. TM has served on advisory boards for Amicus, Biomarin, Idera, Novartis, Sanofi Genzyme, Ultragenyx, and received travel subsidies and honoraria for related activities; has served as a consultant to NuFactor, Sarepta Therapeutics, and Walgreens, and received travel subsidies and honoraria; served on the speaker's bureau for Sanofi Genzyme and Grifols and received travel subsidies and honoraria for these; and received research funding from Alexion, Alnylam, Amicus, Baxter, Bio-Blast, Biogen, Biomarin, CSL Behring, Sanofi Genzyme, Grifols, GlaxoSmithKline, Idera, ISIS Pharmaceuticals, NIH, Novartis, and Ultragenyx. MR has received research support from Amicus; received consulting fees, honoraria, and travel reimbursement from Sanofi Genzyme, BioMarin, and Amicus; has received royalties from NIH; is a member of a speaker's bureau for NIH; and is a member of the Pompe Registry Scientific Advisory Board. BS has served within the last 3 years on advisory boards for Amicus Therapeutics, Audentes Therapeutics, Dyne, Lupin, Nexien, Sanofi Genzyme, Spark, and UCB; undertaken contracted research for Amicus, Greenovation Biopharm, and Sanofi Genzyme; received honoraria from Alexion and Kedrion; and travel expenses from Kedrion and Sanofi Genzyme. VS has received consulting fees from AveXis, Exonics Therapeutic, Roche, Sanofi Genzyme, and Sarepta Therapeutics; received honoraria from Sanofi Genzyme; and undertaken contracted research from Sanofi Genzyme and Ultragenyx. AT has received reimbursement for participation either as a speaker for lectures and symposia or as a Pompe Registry board member from Sanofi Genzyme. ATvdP provided consulting services, participated in advisory board meetings, and received grants for pre-marketing studies and research from industries (eg, Sanofi Genzyme, Biomarin, and Amicus, etc) via agreements between Erasmus MC and the industries. KAH and her spouse, CH, OH-B, JJ, NT, and TZ are employees of Sanofi Genzyme. All other authors declare no competing interests.

Data sharing

Qualified researchers may request access to patient-level data and related study documents. Patient-level data will be anonymised and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.clinicalstudydatarequest.com.

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