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Efficacy and Safety of Avalglucosidase Alfa in Patients With Late-Onset Pompe Disease After 97 Weeks
A Phase 3 Randomized Clinical Trial

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IMPORTANCE In the previously reported Comparative Enzyme Replacement Trial With neoGAA Versus rhGAA (COMET) trial, avalglucosidase alfa treatment for 49 weeks showed clinically meaningful improvements in upright forced vital capacity (FVC) percent predicted and 6-minute walk test (6MWT) compared with alglucosidase alfa.

OBJECTIVE To report avalglucosidase alfa treatment outcomes during the COMET trial extension.

DESIGN, SETTING, AND PARTICIPANTS This phase 3 double-blind randomized clinical trial with crossover in the extension period enrolled patients 3 years and older with previously untreated late-onset Pompe disease (LOPD) between November 2, 2016, and February 10, 2021, with primary analysis after 49 weeks. Patients were treated at 55 referral centers in 20 countries. Efficacy outcomes were assessed at 97 weeks and safety outcomes to last follow-up, with data cutoff at February 10, 2021. Data were analyzed from May to June 2021.

INTERVENTIONS Random assignment (1:1) to receive 20 mg/kg of avalglucosidase alfa or alglucosidase alfa by intravenous infusion every other week for 49 weeks; thereafter, all patients received 20 mg/kg of avalglucosidase alfa every other week.

MAIN OUTCOMES AND MEASURES The primary outcome was the least squares (LS) mean change from baseline in FVC percent predicted. Secondary outcomes included the LS mean change from baseline in 6MWT, muscle strength, motor function, quality of life, and disease biomarkers. Safety and tolerability were also assessed.

RESULTS Of 100 participants from the double-blind treatment period, 95 entered the extension period. Of these, 51 (54%) were men, and the mean (range) age was 48.3 (10-79) years. At the start of this study, mean upright FVC percent predicted was similar between treatment arms, and 6MWT distance was greater in the avalglucosidase alfa arm. From baseline to week 97, LS mean (SE) FVC percent predicted increased by 2.65 (1.05) for those who continued avalglucosidase alfa and 0.36 (1.12) for those who switched to avalglucosidase alfa. The LS mean (SE) 6MWT distance increased by 18.60 (12.01) m and 4.56 (12.44) m, respectively. For participants who switched to avalglucosidase alfa, FVC percent predicted remained stable (LS mean [SE] change from week 49 to 97, 0.09 [0.88]) and 6MWT distance improved (LS mean [SE] change from week 49 to 97, 5.33 [10.81] m). Potentially treatment-related adverse events were reported in 29 patients (56.9%) who continued avalglucosidase alfa and in 25 patients (56.8%) who switched.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial extension, maintenance of positive clinical outcomes was demonstrated for patients continuing avalglucosidase alfa treatment and, to a lesser extent, patients who switched from alglucosidase alfa. No new safety concerns were observed.

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Visual Abstract

Supplemental content

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Group Information: A complete list of the members of the COMET Investigator Group appears in Supplement 4.

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Pompe disease is a rare autosomal-recessive neuromuscular disorder in which lysosomal buildup of glycogen results in progressive muscle weakness, respiratory dysfunction, and functional disabilities.[1] Lysosomal glycogen accumulation in Pompe disease is due to deficiency of the enzyme acid α-glucosidase (GAA), which breaks down glycogen in the lysosomes.[1] Pompe disease has a broad clinical spectrum affecting multiple body systems and considerable variation in age at symptom onset and rate of progression.[2-5] In those with late-onset Pompe disease (LOPD), symptoms may present at any age and progress more slowly than in those with infantile-onset Pompe disease (IOPD), which is characterized by cardiomyopathy in the first year of life with rapid progression and death by age 1 year.[1,3-6] In LOPD, progressive muscle damage causes respiratory and mobility dysfunction, leading to the need for respiratory support and wheelchair use for many patients.[4]

Since 2006, enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme or Lumizyme; Sanofi)[7,8] has prolonged life for patients with IOPD and improved or stabilized disease in patients with IOPD and LOPD, such that some are able to walk and breathe without assistance.[5] However, a proportion of patients with LOPD decline during long-term treatment with alglucosidase alfa, particularly in respiratory function.[9,10] Avalglucosidase alfa is a next-generation recombinant human GAA (rhGAA) ERT designed for enhanced targeting of mannose-6-phosphate (M6P) receptor-mediated uptake, the essential pathway for cellular uptake and trafficking to the lysosome,[11,12] and has approximately 15-fold higher M6P content compared with alglucosidase alfa.[13,14] Avalglucosidase alfa (Nexviazyme or Nexviadyme; Sanofi) has received marketing authorization in several countries for treatment of patients with IOPD or LOPD, including the US and the European Union.[15,16]

The phase 3 Comparative Enzyme Replacement Trial With neoGAA Versus rhGAA (COMET) trial evaluated avalglucosidase alfa vs alglucosidase alfa in treatment-naive participants with LOPD during a 49-week primary analysis period, after which all participants received avalglucosidase alfa in an open-label extension period.[17] During the primary analysis period, avalglucosidase alfa–treated participants showed clinically meaningful improvements in respiratory function (the percentage of the predicted forced vital capacity [FVC] in an upright position) and functional endurance (6-minute walk test [6MWT] distance) compared with alglucosidase alfa–treated participants.[17] These results confirmed similar findings in the phase 1 NEO1 trial[18] of avalglucosidase alfa in treatment-naive participants with LOPD participants and participants previously treated with alglucosidase alfa. Furthermore, during 6 years of avalglucosidase alfa treatment in the phase 2 NEO-EXT extension study, upright FVC percent predicted and 6MWT percent predicted remained stable in most participants, and 6MWT distance walked generally improved in participants 50 years and younger at enrollment,[19] in contrast to the progressive decline seen in the untreated natural history of Pompe disease.[4,20-23]

We evaluated the efficacy and safety of avalglucosidase alfa treatment during the COMET trial open-label extension period.

Key Points

Question What are the long-term outcomes for patients with late-onset Pompe disease (LOPD) continuing avalglucosidase alfa treatment or switching from alglucosidase alfa?

Findings In this phase 3 randomized clinical trial extension including 86 patients, from baseline to week 97, the least squares mean (SE) change in forced vital capacity percent predicted increased by 2.65 (1.05) while continuing avalglucosidase alfa and by 0.36 (1.12) after switching from alglucosidase alfa. Frequency of potentially treatment-related adverse events was similar between treatment arms.

Meaning In this trial, avalglucosidase alfa treatment, either continued or after switching from alglucosidase alfa, maintained respiratory function and functional endurance in patients with LOPD.

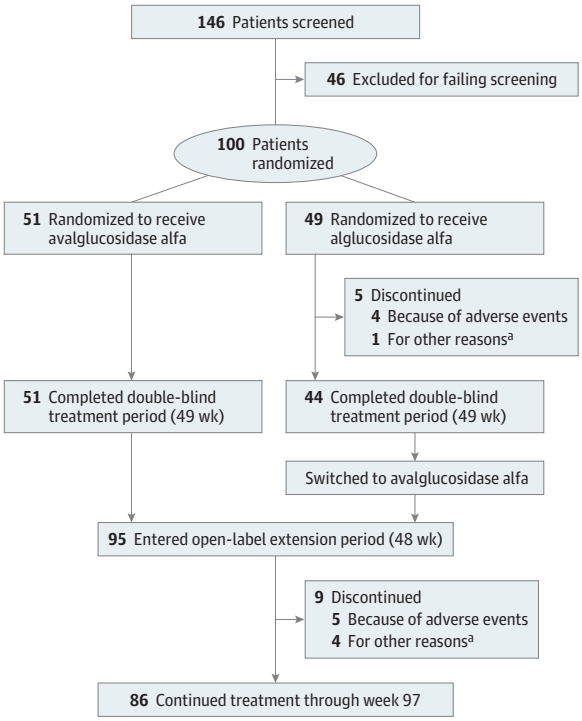
Methods

Study Design and Participants

The phase 3 COMET trial is a double-blind randomized clinical trial comparing avalglucosidase alfa treatment with alglucosidase alfa treatment in 100 participants with LOPD enrolled at 55 study sites in 20 countries.[17] During the 49-week, double-blind treatment period (reported previously), participants were randomly assigned 1:1 to receive intravenous infusions of 20 mg/kg every other week of either avalglucosidase alfa or alglucosidase alfa.[17] After the double-blind treatment period, participants continued in an open-label extension period, and all participants received intravenous infusions of 20 mg/kg of avalglucosidase alfa every other week for up to a total of 289 weeks in the study. At the data cutoff (February 10, 2021), participants had received 97 weeks or more of treatment. Efficacy outcomes are reported through week 97; participants initially randomized to avalglucosidase alfa had been receiving treatment for 97 weeks and patients initially randomized to alglucosidase alfa had been receiving avalglucosidase alfa treatment for 48 weeks (**Figure 1**). Safety data are reported until last follow-up, which extends beyond 97 weeks for patients enrolled earlier. The trial protocol can be found in Supplement 1, and the statistical analysis plan can be found in Supplement 2. This COMET extension study followed the Transparent Reporting of Evaluations With Nonrandomized Designs (TREND) reporting guideline.

At enrollment, participants were 3 years or older with a diagnosis of Pompe disease (confirmed by GAA enzyme deficiency and/or 2 confirmed pathogenic *GAA* gene variants) and naive to Pompe disease–specific treatment. Complete eligibility criteria have been published previously.[17] Race and ethnicity were self-reported. Race categories included American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and not reported; ethnicity categories included Hispanic or Latino, not Hispanic or Latino, not reported, and unknown. Written informed consent was obtained prior to study-related procedures. The study protocol was reviewed and approved by appropriate ethics committees and/or institutional

Figure 1. Participant Disposition



[a] Other reasons for discontinuation included patient decision (no reason given; n = 1), difficulty of the visits (n = 1), fear of COVID-19 exposure by coming to clinical site (n = 1), and inability to travel due to COVID-19 (n = 1).

review boards and conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Guidelines for Good Clinical Practice.

Study Assessments

Long-term efficacy assessments were performed at weeks 49, 61, 73, and 97. Respiratory function was measured by upright FVC percent predicted (a coprimary end point in other LOPD studies[22,24]). Inspiratory and expiratory muscle strength were measured by upright maximum inspiratory pressure (MIP) percent predicted and maximum expiratory pressure (MEP) percent predicted, respectively. Pulmonary function testing was performed locally and evaluated by a central laboratory according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[25] Functional endurance was measured by the 6MWT per ATS guidelines,[26] and 6MWT percent predicted was calculated based on normal reference equations for the age range of trial participants.[27,28] Lower extremity muscle strength was measured by hand-held dynamometry (HHD). Motor function was measured by the Quick Motor Function Test (QMFT) based on the Gross Motor Function Measure-88 (GMFM-88)[29] and by the Gait, Stair, Gower Maneuver, and Chair (GSGC) composite score.[30] Key clinical laboratory parameters and biomarkers for Pompe disease included urinary hexose tetrasaccharide, serum creatine kinase, and the serum transaminase enzymes, alanine aminotransferase and aspartate aminotransferase. Health-related quality of life was measured by the 12-Item Short-Form (SF-12) health survey physical component summary (PCS) and mental component summary (MCS) scales, the EuroQol 5-Dimension 5-Level (EQ-5D-5L) score and EQ-5D visual analog scale score.[31] Patient-reported Pompe disease symptoms were assessed with the Rasch-built Pompe-Specific Activity Scale (R-PAct),[32] Patient Global Impression of Change (PGIC) scale,[33] Pompe Disease Symptom Scale (PDSS), and Pompe Disease Impact Scale (PDIS).[34]

Adverse event (AEs) reports were collected at every treatment visit. Safety evaluations were based on the number of participants with AEs that developed, worsened, or became serious from the first administration of avalglucosidase alfa through last follow-up. Treatment-emergent AEs, including infusion-associated reactions (IARs), were reported by frequency, seriousness, severity, and relatedness. Immunogenicity was assessed using a tiered bioanalytical strategy and validated assays. Antidrug antibodies (ADA) were detected using a direct enzyme-linked immunosorbent assay, confirmed by binding inhibition and titer by enzyme-linked immunosorbent assay. ADA-positive participants were further evaluated for neutralizing antibodies using both inhibition of enzymatic activity assay and cell-based inhibition of enzyme uptake assay.[17] Testing was done at Sanofi US, Biomarkers and Clinical Bioanalyses, Cambridge, Massachusetts.[17]

Statistical Analysis

Efficacy end points were analyzed using a mixed model for repeated measures. Least squares (LS) means and SEs from the mixed model for repeated measures follow the intention-to-treat approach to include data from all participants to address the issue of missing data (assuming data are missing at random). Different covariate matrix structures were used for analysis of the double-blind treatment period[17] vs this analysis of the double-blind and extension periods combined for FVC, MIP, MEP, and 6MWT. An unstructured covariate matrix was used for analyses of the double-blind treatment period. Heterogeneous Toeplitz (heterogeneous variance and a separate correlation for each level of separation between the time points) was used for analysis of FVC, MIP, MEP, and 6MWT in the combined double-blind and extension periods because the model did not converge with the unstructured covariate matrix, as prespecified in the statistical analysis plan (Supplement 2). Unstructured covariate matrix was used for analysis of HHD (lower and upper extremities), QMFT, and SF-12 in the combined double-blind and extension periods. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

Results

Of 100 participants from the double-blind treatment period, 95 completed the double-blind treatment period (ie, week 49) and entered the extension period. Of these, 51 (54%) were men, and the mean (range) age was 48.3 (10-79) years. A total of 86 participants (91%) continued treatment through week 97 (Figure 1). Of these participants, 46 continued avalglucosidase alfa and 40 switched from alglucosidase alfa to avalglucosidase alfa after week 49.

As of the data cutoff on February 10, 2021, the mean (SD; range) duration of exposure to avalglucosidase alfa during the extension period was 21.96 (9.40; 1.8-38.7) months for participants continuing avalglucosidase alfa and 21.78 (10.26; 1.8-40.0) months for those who switched to avalglucosidase alfa. Of 9 participants who discontinued treatment during the extension period, 5 were continuing avalglucosidase alfa (2 discontinued due to AEs and 3 for other reasons) and 4 were switching to avalglucosidase alfa (3 discontinued due to AEs and 1 for other reasons).

As reported previously, baseline demographic characteristics were similar between treatment arms and representative of the general LOPD population.[17] Characteristics at the start of the extension phase are presented in **Table 1**. Treatment adherence (ie, patients who did not miss 2 or more consecutive infusions) during the extension period was 74% through the last follow-up. Among the 25 participants who missed 2 or more consecutive infusions, 19 were related to the COVID-19 pandemic.

Respiratory Function

From baseline to week 97, LS mean (SE) FVC percent predicted increased by 2.65 (1.05) points for participants who continued avalglucosidase alfa and by 0.36 (1.12) points for those who switched. From week 49 to week 97, participants who continued avalglucosidase alfa sustained the improvement in FVC percent predicted observed during the double-blind period, with continued improvements in MIP percent predicted and MEP percent predicted (**Figure 2**). For participants who switched to avalglucosidase alfa, stabilization of LS mean (SE) FVC percent predicted (change from week 49 to week 97, 0.09 [0.88]) and continued improvements in MIP percent predicted and MEP percent predicted were seen during their first 48 weeks of avalglucosidase alfa treatment (Figure 2). At 97 weeks, FVC percent predicted improved by more than 10% in 16 patients and worsened by more than 10% in 14 patients (eFigure 1 in Supplement 3).

Functional Endurance and Motor Function

From baseline to week 97, LS mean (SE) 6MWT distance increased by 18.60 (12.01) m for those continuing avalglucosidase alfa and by 4.56 (12.44) m for those switching to avalglucosidase alfa. Participants who continued avalglucosidase alfa sustained improvement from baseline during the double-blind period in 6MWT distance, 6MWT percent predicted, HHD lower and upper extremity scores, and QMFT score during the additional 48 weeks of avalglucosidase treatment (**Figure 3**). While declines in these measures among patients initially randomized to avalglucosidase alfa during their first 49 weeks of treatment were observed at later time points, improvements relative to baseline were maintained. Participants who switched had continued improvements, including an LS mean (SE) increase of 5.33 (10.81) m on the 6MWT from week 49 to week 97, during their first 48 weeks of avalglucosidase treatment (Figure 3). Individual participant results for 6MWT are shown in eFigure 2 in Supplement 3. Improvements in GSGC total score and GMFM-88 standing and walking total score were maintained during the additional 48 weeks of avalglucosidase alfa treatment for those who continued avalglucosidase alfa treatment and during the first 48 weeks of avalglucosidase alfa treatment for those who switched (eFigure 3 in Supplement 3).

Biomarkers

Urinary hexose tetrasaccharide and creatine kinase improved from baseline to week 97 in both treatment groups, decreasing to or near the normal range by week 97 (eFigure 4 in Supplement 3).

Quality of Life

Participants continuing avalglucosidase alfa treatment maintained improvements in SF-12 PCS and MCS during the extension period (eFigure 5 in Supplement 3). Participants initially randomized to alglucosidase alfa had continued improvements in SF-12 PCS and MCS during their first 48 weeks of avalglucosidase alfa treatment (eFigure 5 in Supplement 3). Similar trends were observed in EQ-5D-5L score and EQ-5D visual analog scale score (eFigure 5 in Supplement 3).

Patient-Reported Outcomes Assessing Pompe Disease Symptoms

Improvements in PGIC score, PDSS total symptom score, and PDIS difficulty performing activities score were maintained during the extension period for participants continuing avalglucosidase alfa treatment and for those who switched (eFigures 6 and 7 in Supplement 3). For the R-PAct summary score, participants continuing avalglucosidase alfa maintained improvements during the additional 48 weeks of treatment, and participants who switched showed little change during their first 48 weeks of avalglucosidase alfa treatment (eFigure 8 in Supplement 3).

Safety

AEs reported during treatment with avalglucosidase alfa are summarized in **Table 2**. These include events reported in the double-blind and extension periods for participants continuing avalglucosidase alfa treatment and events reported only in the extension period for those who switched. Protocol-defined IARs occurred less frequently in those who continued avalglucosidase alfa (20 of 51 [39.2%]) than in those who switched (21 of 44 [47.7%]). Potentially treatment-related AEs were reported with similar frequency in those who continued avalglucosidase alfa treatment (29 [56.9%]) and those who switched (25 [56.8%]). Severe AEs were reported with similar frequency in those continuing avalglucosidase alfa (11 [21.6%]) and those switching (9 [20.5%]) overall (primary analysis and extension periods combined) and during the extension period (9 [17.6%] and 9 [20.5%], respectively). The rate of serious AEs at last follow-up was 33.3% (17 of 51) among participants continuing avalglucosidase alfa (97 weeks or more) and 22.7% (10 of 44) among participants who switched (48 weeks or more); 4 (7.8%) and 2 (4.5%), respectively, were considered potentially treatment related.

Treatment-emergent AEs occurring in 10% or more of participants during avalglucosidase alfa treatment are summarized by number and percentage of participants experiencing

Table 1. Demographic and Clinical Characteristics at the Start of the Extension Period

Characteristic	No. (%)			
	Continued avalglucosidase alfa treatment (n = 51)	Switched to avalglucosidase alfa treatment (n = 44)	Entered extension period directly (n = 1)[a]	Total (N = 96)
Sex				
Female	24 (47.1)	20 (45.5)	1 (100)	45 (46.9)
Male	27 (52.9)	24 (54.5)	0	51 (53.1)
Race[b]				
Asian	3 (5.9)	0	1 (100)	4 (4.2)
Black or African American	1 (2.0)	1 (2.3)	0	2 (2.1)
White	47 (92.2)	43 (97.7)	0	90 (93.8)
Ethnicity[b]				
Hispanic or Latino	3 (5.9)	9 (20.5)	0	12 (12.5)
Not Hispanic or Latino	44 (86.3)	30 (68.2)	1 (100)	75 (78.1)
Not reported	4 (7.8)	5 (11.4)	0	9 (9.4)
Region				
Europe	31 (60.8)	20 (45.5)	0	51 (53.1)
North America	14 (27.5)	18 (40.9)	1 (100)	33 (34.4)
Latin America	2 (3.9)	5 (11.4)	0	7 (7.3)
Asia-Pacific	4 (7.8)	1 (2.3)	0	5 (5.2)
Age, mean (SD; range), y	47.0 (14.5; 17-79)	50.7 (13.9; 21-79)	9.8	48.3 (14.7; 10-79)
<18	1 (2.0)	0	1 (100)	2 (2.1)
18 to <45	21 (41.2)	15 (34.1)	0	36 (37.5)
≥45	29 (56.9)	29 (65.9)	0	58 (60.4)
Upright FVC percent predicted, mean (SD; range)	65.3 (17.1; 22-89)	61.5 (13.5; 39-84)	NA	63.6 (15.6; 22-89)
6MWT distance walked, mean (SD; range), m	433.4 (111.8; 131-636)	384.7 (139.6; 86-690)	NA	410.8 (127.2; 86-690)
6MWT percent predicted, mean (SD; range)	62.6 (15.4; 21-90)	55.8 (19.1; 15-98)	NA	59.4 (17.5; 15-98)
Upright MIP percent predicted, mean (SD; range)	60.9 (29.8; 18-133)	56.9 (22.4; 14-111)	NA	59.0 (26.6; 14-133)
Upright MEP percent predicted, mean (SD; range)	70.91 (29.14; 18.6-163.7)	77.41 (28.04; 31.5-144.0)	NA	73.92 (28.67; 18.6-163.7)
HHD composite score				
Lower extremity				
Total, No.	50	44	0	94
Mean (SD; range)	1587.19 (655.92; 371.6-3316.0)	1608.55 (669.99; 350.0-3260.0)	NA	1597.19 (659.05; 350.0-3316.0)
Upper extremity				
Total, No.	49	44	0	93
Mean (SD; range)	1696.03 (606.73; 497.6-3350.0)	1713.00 (696.12; 420.0-3243.0)	NA	1704.06 (647.01; 420.0-3350.0)
QMFT, mean (SD; range)	45.35 (9.96; 19.0-63.0)	43.45 (12.08; 13.0-62.0)	NA	44.47 (10.97; 13.0-63.0)
SF-12 PCS				
Total, No.	50	44	0	94
Mean (SD; range)	38.55 (8.17; 25.1-57.1)	38.28 (10.76; 11.0-62.5)	NA	38.42 (9.42; 11.0-62.5)
SF-12 MCS				
Total, No.	50	44	0	94
Mean (SD; range)	51.67 (8.19; 33.9-66.5)	50.85 (11.89; 18.7-77.9)	NA	51.28 (10.05; 18.7-77.9)

Abbreviations: 6MWT, 6-Minute Walk Test; FVC, forced vital capacity; HHD, hand-held dynamometry; MCS, mental health component score; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; NA, not applicable; PCS, physical component score; QMFT, Quick Motor Function Test; SF-12, 12-Item Short-Form.

[a] One pediatric participant enrolled and was assigned to receive avalglucosidase alfa and directly enter into the extension period without participating in the double-blind period, consistent with the protocol mandate that if fewer than 4 patients aged 3 to less than 18 years were enrolled, up to 2 additional pediatric patients were to be enrolled directly into the open-label extension period and receive avalglucosidase alfa. This patient was excluded from the analysis.

[b] Race and ethnicity were self-reported. Race categories included American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and not reported; ethnicity categories included Hispanic or Latino, not Hispanic or Latino, not reported, and unknown.

events in eTable 1 in Supplement 3. The most common events were headache (31 of 96 [32%]), nasopharyngitis (30 [31%]), arthralgia (28 [29%]), back pain (27 [28%]), diarrhea (23 [24%]), and nausea (22 [23%]).

During the extension period, 5 patients discontinued treatment due to AEs, including 2 participants continuing avalglucosidase alfa (mild to moderate treatment-related nonserious AE for 1 participant and a moderate non-treatment-related serious AE for 1 participant) and 3 participants who switched (severe treatment-related serious AEs for 2 participants and a severe non-treatment-related serious AE for 1 participant). The AEs leading to discontinuation were ocular hyperemia (mild), erythema (mild), urticaria (severe), and respiratory distress (severe), all considered related to treatment, and acute myocardial infarction (moderate), considered unrelated to treatment. During the extension period, 1 participant who switched died of pancreatic adenocarcinoma that was considered unrelated to treatment.

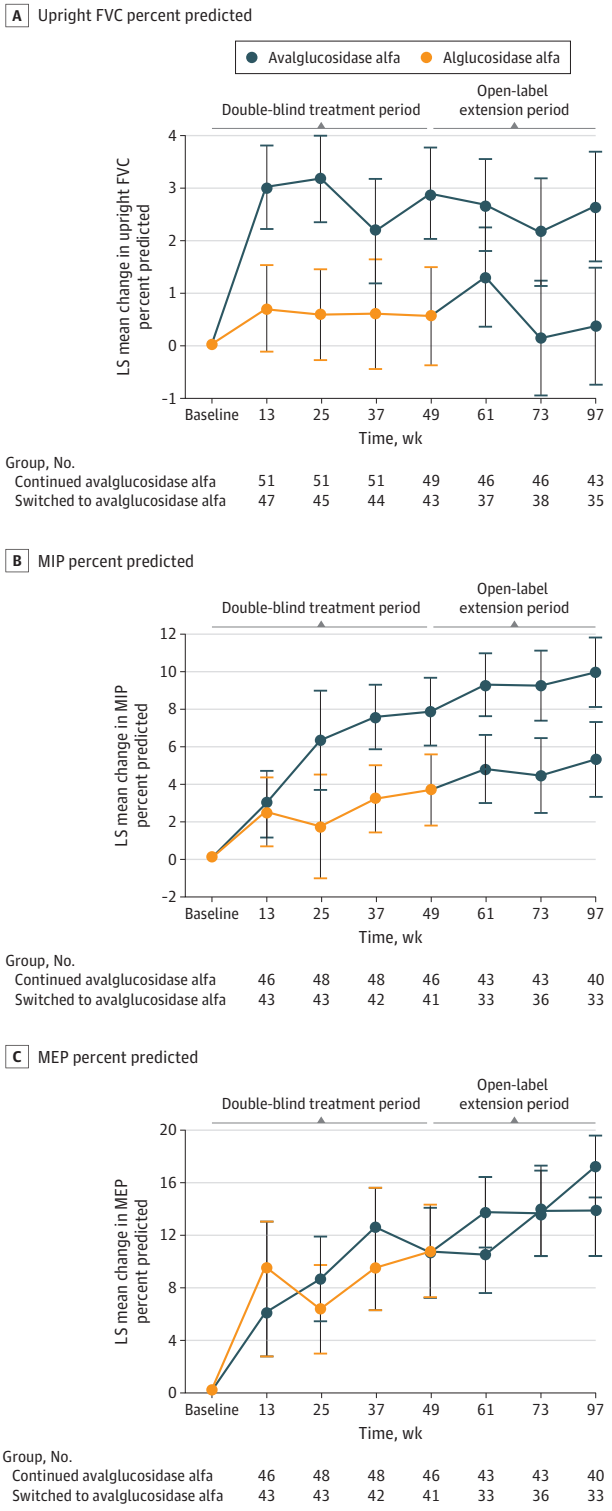
Most participants developed ADA during the primary analysis period, and given the cross-reactivity of ADA, most participants previously treated with alglucosidase alfa were positive for avalglucosidase alfa ADA at the time of switching (eTable 2 in Supplement 3). Patients originally randomized to avalglucosidase alfa continued to decrease in ADA titers and additional participants tolerized during the extension period. Of the participants who switched who were negative at baseline, 1 developed low ADA titers and the others tolerized during the extension period. Fewer participants who switched were positive for neutralizing antibodies that inhibited enzyme activity or cellular uptake.

Discussion

In the double-blind, primary analysis period of the phase 3 COMET trial, the totality of the data consistently showed a more favorable effect on respiratory function, ambulation, functional endurance, health-related quality of life, and safety for treatment-naive participants with LOPD treated with avalglucosidase alfa compared with alglucosidase alfa.[17] The COMET extension period has demonstrated stabilization and maintenance of these early improvements for participants treated with avalglucosidase alfa over 97 weeks of treatment as well as stabilization of these clinical parameters during the first 48 weeks of avalglucosidase alfa treatment among participants initially treated with alglucosidase alfa. Furthermore, participants who switched functionally stabilized and did not have an increase in AEs or immunogenicity, demonstrating the ability for patients to make this switch safely in a clinical setting.

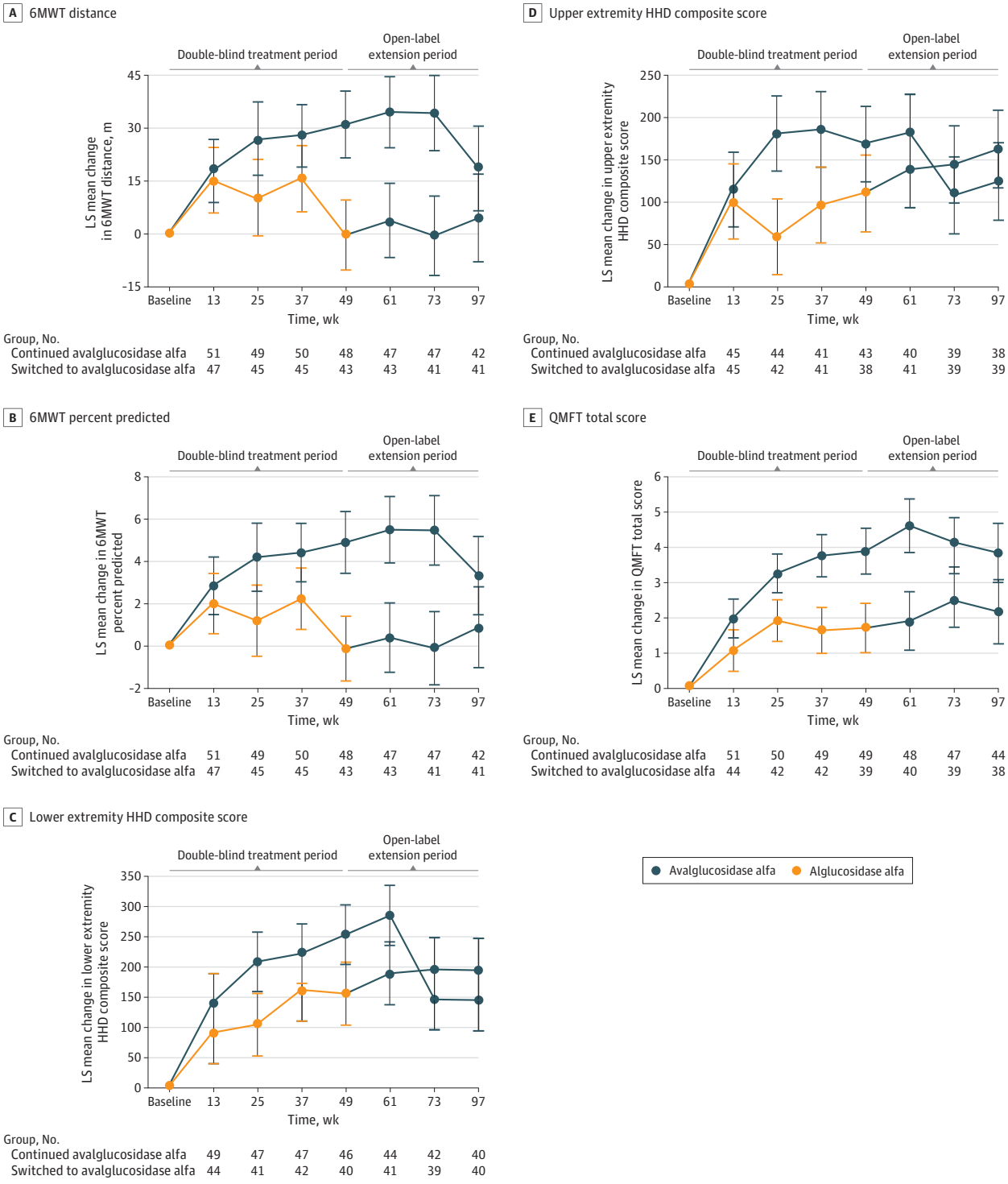
The initial results from the COMET trial extension add to a growing body of evidence supporting avalglucosidase alfa's ability to improve or stabilize disease parameters, including in treatment-naive and treatment-experienced patients with LOPD in the phase 1 NEO1 trial of avalglucosidase alfa[18] and up to 6 years in the phase 2 NEO-EXT extension study.[19] Patients in the NEO-EXT study received avalglucosidase alfa (5, 10, or 20 mg/kg every other week) for 6 months before entering the NEO-EXT study, and eventually all received 20 mg/kg every other week,

Figure 2. Least Squares (LS) Mean Change in Respiratory Function Parameters From Baseline to Week 97



Error bars indicate SEs. FVC indicates forced vital capacity; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure.

Figure 3. Least Squares (LS) Mean Change in Functional Endurance and Motor Function Parameters From Baseline to Week 97



Error bars indicate SEs. 6MWT indicates 6-minute walk test; HHD, hand-held dynamometry; QMFT, Quick Motor Function Test.

which is what patients in the COMET trial received. In the phase 2 Mini-COMET trial of children with IOPD and incomplete response to alglucosidase alfa, avalglucosidase alfa, 40 mg/kg every 2 weeks, demonstrated stabilization or improvement in exploratory efficacy outcomes, including GMFM-88, QMFT, Pompe-Paediatric Evaluation of Disability Inventory, and left ventricular mass *z* score, even in a subset of patients who had previously received 40 mg/kg per week.[35]

Stabilization of respiratory function, ambulation, and functional endurance are important benefits for patients with LOPD

in the context of the progressive decline of untreated Pompe disease[4,20-23] and the decline observed during long-term treatment with alglucosidase alfa.[9,10] Participants of the COMET trial who switched from alglucosidase alfa to avalglucosidase alfa after week 49 did not show the same improvements observed among treatment-naive participants who started avalglucosidase alfa treatment in the double-blind treatment period. This lack of improvement may be related to ongoing progression of disease pathology, incomplete degradation of glycogen during alglucosidase alfa treatment, and potential irreversible muscle damage during time taking alglucosidase alfa, which is known to yield lower cellular enzyme uptake compared with avalglucosidase alfa.[11-14] Although the relative improvements in FVC and 6MWT with avalglucosidase alfa are small, they show that avalglucosidase alfa can offset the natural course of this progressive disease more potently than alglucosidase alfa, which is meaningful for patients and their families. The positive effect on patient quality of life is evident in the consistent patient-reported improvements across Pompe-specific measures (PGIC score, PDSS total symptom score, and PDIS difficulty performing activities score). Taken together, these findings suggest a benefit to treating patients with avalglucosidase alfa earlier in their disease.

We observed small declines in functional endurance measures (6MWT, HHD, and QMFT) during weeks 73-97. In the NEO-EXT study, declines in 6MWT distance during long-term follow-up were seen among patients 45 years and older, but those younger than 45 years had gains in 6MWT distance.[19] The authors attributed this to interaction of age-related physiologic muscle wasting (sarcopenia) with LOPD and possibly other comorbidities affecting mobility or exercise tolerance in older patients. In addition, the first year of the COVID-19 pandemic overlapped with the COMET extension period, and treatment compliance was affected; 19 of 25 patients who missed 2 or more consecutive infusions were attributable to the pandemic. While it is difficult to assess the impact of stay-at-home orders and self-imposed restrictions on physical activity, declines in functional measures may also reflect a more sedentary lifestyle during the COVID-19 pandemic. In addition, the pandemic requirement to wear face masks may have affected assessment of functional measures at later time points.

Data from the COMET double-blind treatment period suggested a more favorable safety profile with avalglucosidase alfa compared with alglucosidase alfa, with similar proportions of participants experiencing AEs (44 of 51 [86%] vs 45 of 49 [92%], respectively) and lower rates of serious AEs (8 [16%] vs 12 [25%]) and protocol-defined IARs (13 [26%] vs 16 [33%]).[17] The longer-term results show a similar safety profile for avalglucosidase alfa among participants who were treatment naive at the start of avalglucosidase alfa treatment and those who switched from alglucosidase alfa. Serious AE rates during the extension period were similar for those continuing avalglucosidase (12 of 51 [23.5%]) and those who switched (10 of 44 [22.7%]).

Table 2. Summary of Treatment-Emergent Adverse Events (TEAEs) During Avalglucosidase Alfa Treatment

Adverse event	No. (%)	
	Continued avalglucosidase alfa treatment (n = 51)	Switched to avalglucosidase alfa treatment (n = 44)
Any TEAE	50 (98.0)	49 (96.1)
TEAEs potentially related to treatment	29 (56.9)	25 (56.8)
Serious TEAEs	17 (33.3)	10 (22.7)
Serious TEAEs potentially related to treatment	4 (7.8)	2 (4.5)
Severe TEAEs	11 (21.6)	9 (20.5)
TEAEs leading to permanent treatment discontinuation	2 (3.9)	3 (6.8)
TEAEs leading to death	0	1 (2.3)
Infusion-associated reactions (protocol-defined)[a]	20 (39.2)	21 (47.7)

[a] Defined as an adverse event that occurred during either the infusion or observation period following the infusion, related or possibly related to the investigational treatment.

Limitations

This study has limitations. During the extension phase of COMET, there was no comparator group because all patients were receiving avalglucosidase alfa, and thus no direct comparison can be made over this period to long-term alglucosidase alfa treatment. Data from the ongoing real-world experience with avalglucosidase alfa will provide additional evidence of its effectiveness and safety.

Conclusions

In the COMET trial extension period, participants treated with avalglucosidase alfa for up to 97 weeks maintained improvements in respiratory function, motor function, muscle strength, and health-related quality of life that began in the first 49 weeks of treatment. Furthermore, participants who switched to avalglucosidase alfa after 49 weeks of treatment with alglucosidase alfa maintained disease stability as assessed by these parameters. In both treatment groups, no new safety or immunogenicity-related concerns were observed. Data from the COMET trial support long-term maintenance of positive clinical outcomes for patients receiving avalglucosidase alfa treatment.

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