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Effect of avalglucosidase alfa on disease-specific and general patient-reported outcomes in treatment-naïve adults with late-onset Pompe disease compared with alglucosidase alfa: Meaningful change analyses from the Phase 3 COMET trial

Antonio Toscano [a], Laurence Pollissard [b,*], Jérôme Msihid [b], Nadine van der Beek [c], Priya S. Kishnani [d], Mazen M. Dimachkie [e], Kenneth I. Berger [f], Pronabesh DasMahapatra [g], Nathan Thibault [g], Alaa Hamed [g], Tianyue Zhou [g], Kristina An Haack [b], Benedikt Schoser [h]

[a] *ERN-NMD Center of Messina for Neuromuscular Disorders, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy*
[b] *Sanofi, Chilly-Mazarin, France*
[c] *Center for Lysosomal and Metabolic Diseases, and Department of Neurology, Erasmus University Medical Center, Rotterdam, the Netherlands*
[d] *Department of Pediatrics, Division of Medical Genetics, Duke University Medical Center, Durham, NC, USA*
[e] *Department of Neurology, University of Kansas Medical Center, Kansas, KS, USA*
[f] *Division of Pulmonary, Critical Care and Sleep Medicine, NYU Grossman School of Medicine, and the André Cournand Pulmonary Physiology Laboratory, Bellevue Hospital, New York, NY, USA*
[g] *Sanofi, Cambridge, MA, USA*
[h] *Department of Neurology, Friedrich-Baur-Institute, LMU Klinikum München, München, Germany*

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ABSTRACT

Background: The Phase 3 COMET trial (NCT02782741) comparing avalglucosidase alfa and alglucosidase alfa included health-related quality of life (HRQoL) assessments in treatment-naïve patients with late-onset Pompe disease (LOPD). Here, we further characterize results from disease-specific and general patient-reported outcome (PRO) measures.

Methods: Adults who participated in the COMET trial receiving avalglucosidase alfa or alglucosidase alfa (both 20 mg/kg biweekly) during the 49-week double-blind treatment period were included in the analysis. Proportions of patients exceeding meaningful change thresholds at Week 49 were compared *post hoc* between treatment groups. PROs and their meaningful change thresholds included: Pompe Disease Severity Scale (PDSS; decrease 1.0–1.5 points), Pompe Disease Impact Scale (PDIS; decrease 1.0–1.5 points), Rasch-built Pompe-specific Activity Scale (R-PAct; change from unable to able to complete activity), 12-item Short Form Health Survey (SF-12; physical component summary [PCS] score: increase ≥6 points, mental component summary [MCS] score: increase ≥7 points), EuroQol 5 Dimension 5 Level (EQ-5D-5L; improvement of ≥1 category), and Patient Global Impression of Change (PGIC; any improvement).

Results: The analysis included 99 adult patients (avalglucosidase alfa $n = 50$; alglucosidase alfa $n = 49$). Patients who received avalglucosidase alfa had significantly greater odds of achieving a meaningful change versus alglucosidase alfa for the PDSS Shortness of Breath (OR [95% CI] 11.79 [2.24; 62.18]), Fatigue/Pain (6.24 [1.20; 32.54]), Morning Headache (13.98 [1.71; 114.18]), and Overall Fatigue (5.88 [1.37; 25.11]) domains, and were significantly more likely to meet meaningful change thresholds across multiple PDSS domains (all nominal $p <$ 0.05). A numerically greater proportion of patients in the avalglucosidase alfa group were able to complete

Abbreviations: BMI, body mass index; CI, confidence interval; eCDF, empirical cumulative distribution function; EQ-5D-5L, EuroQol 5 Dimension 5 Level questionnaire; EQ-VAS, EuroQol visual analog scale; EPOC, European consortium of Pompe disease; ERT, enzyme replacement therapy; FDA, Food and Drug Administration; FVC%, forced vital capacity percent; GAA, acid α-glucosidase; HRQoL, health-related quality of life; LOPD, late-onset Pompe disease; MCS, mental component summary; mITT, modified intent-to-treat; OR, odds ratio; PCS, physical component summary; PDIS, Pompe Disease Impact Scale; PDSS, Pompe Disease Severity Scale; PGIC, Patient Global Impression of Change; R-PAct, Rasch-built Pompe-specific Activity Scale; PRO, patient-reported outcome; SD, standard deviation; SF-12, 12-item Short Form Health Survey.

* Corresponding author at: Sanofi, 1 Avenue Pierre Brossolette, Chilly-Mazarin 91380, France.
E-mail address: laurence.pollissard@sanofi.com (L. Pollissard).

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selected activities of the R-PAct compared with the alglucosidase alfa group. Significantly greater proportions of patients who received avalglucosidase alfa achieved meaningful improvements for EQ-5D-5L usual activities dimension, EQ visual analog scale, and all four PGIC domains. The proportion of patients with improvements in SF-12 PCS and MCS was greater in the avalglucosidase alfa group versus alglucosidase alfa group, but was not significant ($p > 0.05$).

Conclusions: These analyses show that avalglucosidase alfa improves multiple symptoms and aspects of daily functioning, including breathing and mobility. This supports the clinical relevance of the effects of avalglucosidase alfa on HRQoL for patients with LOPD.

1. Introduction

Pompe disease is a genetic lysosomal storage disorder that arises from the deficiency of acid α-glucosidase (GAA), an enzyme that breaks down glycogen [1]. Late-onset Pompe disease (LOPD) has a variable time of onset and rate of progression [1,2]. Patients with LOPD can present with symptoms as early as the first year of life and in early childhood, adolescence, or adulthood [3–5]. If untreated, patients experience progressive degeneration of respiratory function (related to the diaphragm and intercostal muscle dysfunction) and motor function, leading to substantial disability and early mortality [3,6]. The broad spectrum of symptoms that can develop in people living with LOPD also includes vascular, gastrointestinal, urogenital, and cardiac symptoms, and highly disabling pain and fatigue [3,6,7].

Enzyme replacement therapy (ERT) has been the mainstay of treatment for Pompe disease since 2006, following the approval of recombinant human acid α-glucosidase (alglucosidase alfa; Lumizyme® in the US; Myozyme® in other regions) [3,8]. Despite disease-modifying treatment, people living with LOPD experience poorer health-related quality of life (HRQoL) than unaffected individuals [9]. A systematic literature review of studies of both treated and untreated patients with LOPD demonstrated that, despite improvements in HRQoL with ERT, outcomes for affected patients remained substantially worse compared with people without Pompe disease [9]. Furthermore, improvements in physical HRQoL (i.e., general health, vitality) did not persist long-term with the current standard-of-care treatment [9]. This highlights a need for an improved effective treatment that also ameliorates functional, social, and emotional impairment for affected patients, maintaining the benefits over time.

Avalglucosidase alfa (Nexviadyme® in Europe/Nexviazyme® in other regions) is a next-generation ERT designed for enhanced targeting of the mannose-6-phosphate receptor to improve uptake by skeletal muscle and trafficking to lysosomes [10]. It gained approval in the United States in 2021 and Europe in 2022 [11,12], as well as several other countries worldwide, based on the efficacy and safety results of the pivotal Phase 3 COMET trial (NCT02782741) [13]. This study compared avalglucosidase alfa with alglucosidase alfa in people with LOPD [13]. At Week 49 of the trial, patients treated with avalglucosidase alfa showed a 2.43% (95% confidence interval [CI]: [−0.13; 4.99]; $p = 0.0074$, non-inferiority margin 1.1%) greater increase from baseline in forced vital capacity percent (FVC%) predicted compared with those treated with alglucosidase alfa, although superiority was not reached ($p = 0.0626$) [13]. In addition to respiratory function, the overall results demonstrated clinically meaningful improvements with avalglucosidase alfa therapy compared with alglucosidase alfa in ambulation and functional endurance, with no new safety signals [13]. Generic and disease-specific patient-reported outcome (PRO) questionnaires were also used in COMET to provide unique information on the physical, functional, and psychological impact of both ERTs from the patient's perspective while blinded to treatment. Improvements favoring avalglucosidase alfa were observed at the treatment group-level compared with alglucosidase alfa at Week 49 across these PROs [13].

Evaluating PRO data at the group-level demonstrates the overall impact of treatment and can provide information about population health outcomes [14]. Comparatively, patient-level data provide insight into individual patient changes over time and thus enables healthcare professionals to manage care in routine clinical practice [14]. Therefore, to aid the interpretation of those primary PRO results [15], *post hoc* analyses were conducted to evaluate the benefit at the patient level of avalglucosidase alfa compared with alglucosidase alfa on Pompe disease (symptoms, impacts, and specific activities) and general HRQoL during the COMET 49-week double-blind treatment period. Here, we evaluate the proportion of patients in each treatment group who experienced a meaningful improvement in symptoms, function, or broader aspects of HRQoL.

2. Methods

2.1. Trial design and participants

Details of the Phase 3 COMET trial have been published previously [13], In brief, the COMET trial was a randomized double-blind trial conducted to investigate the safety and efficacy of avalglucosidase alfa compared with alglucosidase alfa in treatment-naïve people with LOPD. The trial included a 49-week double-blind treatment period (primary analysis period) and an open-label extended treatment period. Here, we present results from the double-blind treatment period.

Eligible patients were aged ≥3 years with a diagnosis of Pompe disease confirmed by GAA enzyme deficiency from any tissue source and/or two confirmed pathogenic *GAA* variants and were naïve to Pompe-specific treatment. Patients 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. Current or previous use of immune-tolerance induction therapy was not permitted.

Eligible patients were randomized 1:1 to receive 20 mg/kg intravenous avalglucosidase alfa or alglucosidase alfa every 2 weeks, stratified by baseline upright FVC% predicted (<55% or ≥55%), sex, age (<18 years or ≥18 years), and region among participants aged ≥18 years (Japan or outside Japan [regional regulatory requirements]).

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

2.2. Study endpoints

The primary efficacy endpoint was change from baseline to Week 49 in upright FVC% predicted during the primary analysis period; these results have been previously reported [13].

PROs covering ten domains (breathing, mobility, fatigue, upper extremity weakness, pain, morning headache, daily activities, disease-related symptoms, physical functioning, and mental health) were collected in adult participants (aged 18 years or older) and evaluated as secondary, tertiary, or exploratory endpoints at baseline and Weeks 13, 25, 37 and 49 during the primary analysis period. An overview of each PRO measure is shown in Table 1. Disease-specific PROs included the Pompe Disease Severity Scale (PDSS; each domain ranges 0–10) [16,17],

Table 1
PRO measures assessed in adults in the COMET trial.

Measure	Domain	Description	Scoring	Criterion for meaningful change
Pompe disease-specific PRO measures				
Pompe Disease Severity Scale (PDSS) [16,17]	Disease-specific: severity of disease-related symptoms in Pompe disease	Measures severity based on 12 items, evaluating six domains: Shortness of Breath, Fatigue/Pain, Morning Headache, Overall Fatigue, Upper Extremity Weakness, and Pain. Recall period: 24-h e-diary administered for 14 days (7-day recall, one-time entry, prior to first infusion).	Each item score ranges from 0 to 10 (0, 'none' to 10, 'as bad as I can imagine'). Domain scores range from 0 to 10. Higher scores indicate greater severity of symptoms.	Score reduction from baseline of 1.5 points for Pain, Shortness of Breath, Overall Fatigue, Fatigue/Pain, and Upper Extremity Weakness domains, and 1.0 for Morning Headache domain [17]. Anchor- and distribution-based analyses were conducted on data from the COMET trial to estimate thresholds for meaningful change [17].
Pompe Disease Impact Scale (PDIS) [16,17]	Disease-specific: impact of Pompe disease on mood and mobility-related activities	Measures impact based on 15 items, evaluating two domains: Mood and Difficulty Performing Activities. Recall period: 24-h e-diary administered for 14 days (7-day recall, one-time entry, prior to first infusion).	The Mood domain score ranges from 0 to 10 (0, 'no impact' to 10, 'as bad as I can remember'). The Difficultly Performing Activities domain score ranges from 0 to 4 for participants who answer 'Yes' for ability to perform: 0, 'not at all difficult'; 1, 'a little difficult'; 2, 'somewhat difficult'; 3, 'very difficult', and 4, 'extremely difficult'. Higher scores indicate greater impact of symptoms.	Score of 1.5 points for Mood and 1.0 for Difficulty Performing Activities [17]. Anchor- and distribution-based analyses were conducted on data from the COMET trial to estimate thresholds for meaningful change [17].
Rasch-built Pompe-specific activity (R-PAct) scale [18]	Disease-specific: impact of Pompe disease on activities of daily living and social participation	18 self-administered items relating to daily activities, with three possible responses: 0: 'unable to perform' 1: 'able to perform, but with difficulty' 2: 'able to perform without difficulty' Only assessed patients ≥18 years speaking Dutch or English. Recall period: At trial visit.	A raw score ranging from 0 to 36 points is generated and then translated to a 0–100 score. Higher scores indicate lower impact on activities of daily living and social participation.	Response for individual items was defined empirically as moving from being unable to complete an activity at baseline to being able to complete the activity (with or without difficulty).
Generic PRO measures				
12-Item Short Form Survey (SF-12) [19,20]	Generic physical and mental HRQoL	Measures HRQoL using 12 questions on eight domains (general health, physical functioning, role – physical, body pain, vitality, social functioning, role – emotional, and mental health). Scores are summarized in a PCS score and MCS score. Recall period: past 4 weeks.	Response options for items include yes/no responses and five to six-point Likert scales. Raw scores were normalized to the general population, and the total scores were reported from 0 to 100 (0, 'worst level of functioning' to 100, 'best level of functioning'), with higher scores indicating better HRQoL.	Increase of ≥6 points from baseline for SF-12 PCS and ≥ 7 points from baseline for SF-12 MCS [25]. Within-patient thresholds were estimated in the general population or other chronic conditions [25].
EuroQol 5 Dimension 5 Level (EQ-5D-5L) questionnaire [21,22]	Generic HRQoL	EQ-5D-5L consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Overall general health status is measured using the EQ-VAS. Recall period: day of assessment.	Dimensions are assessed using a 5-point Likert scale, ranging between: 1, 'no problems'; 2, 'slight problems'; 3, 'moderate problems'; 4, 'severe problems'; and 5, 'extreme problems or unable.'[a] The EQ-VAS uses a continuous scoring system ranging from 0 to 100 (0, 'the worst health you can imagine' to 100, 'the best health you can imagine'); with higher scores indicating a better health status.	Response was empirically defined as an increase of ≥1 category (improvement) from baseline for the five categories of the EQ-5D-5L. Defined empirically as ≥10 points increase from baseline for the EQ-VAS [26].
Patient Global Impression of Change (PGIC) scale [23,24]	Generic change in disease-related symptoms	PGIC assesses the participant's subjective satisfaction of the treatment. It includes four questions including change in overall disease-related symptoms, change in ability to perform daily activities, overall change in mobility, and change in ability to breathe. Recall period: beginning of the COMET trial.	Uses a seven-point categorical scale: 1: 'A great deal worse' 2: 'Moderately worse' 3: 'Somewhat worse' 4: 'No change' 5: 'Somewhat better' 6: 'Moderately better' 7: 'A great deal better'	Response was empirically defined as any improvement in score between baseline and Week 49 (5 = 'somewhat better', 6 = 'moderately better' or 7 = 'a great deal better').

EQ-VAS, visual analog scale; HRQoL, health-related quality of life; MCS, mental component summary; N/A, not available; PCS, physical component summary; PRO, patient-reported outcome.

the Pompe Disease Impact Scale (PDIS; Mood domain range 0–10, Difficulty Performing Activities range 0–4) [16,17], and the Rasch-built Pompe-specific Activity Scale (R-PAct; 0–100 range, administered to a subset of English- or Dutch-speaking participants) [18]. Generic HRQoL PROs included the 12-item Short Form Health Survey (SF-12; 0–100 range) [19,20], and the EuroQol 5 Dimension 5 Level questionnaire (EQ-5D-5L; five-point scale for each domain, 0–100 range for visual analog scale [EQ-VAS]) [21,22]. Patient-perceived change was assessed using the Patient Global Impression of Change (PGIC) seven-point scale [23,24]. HRQoL assessed using the SF-12 was a secondary endpoint and using EQ-5D-5L was a tertiary endpoint; all other PROs were assessed as exploratory endpoints. Between-group differences (avalglucosidase alfa versus alglucosidase alfa) for change in score from baseline to Week 49 in the overall trial population have been previously published for all PRO measures [13].

2.3. Definition of meaningful change

To aid the interpretation of between-group differences and in line with guidance from the United States Food and Drug Administration (FDA) [15], the proportion of patients who, at an individual level, achieved an improvement or clinically meaningful change in score at Week 49 was evaluated in both treatment groups for each PRO measure.

Clinically meaningful within-patient improvement thresholds for each PRO are shown in Table 1 and discussed below; these thresholds have either been validated in Pompe disease or are accepted empirical definitions of meaningful change. The meaningful change thresholds for the PDSS and PDIS were estimated through anchor- and distribution-based analyses of data from the COMET trial, as previously reported [17]. For the anchor-based analyses, meaningful change was evaluated using scores from PGIC items as anchors [17]. For the PDSS, a meaningful change was defined as a score reduction from baseline of 1.5 points for Pain, Shortness of Breath, Overall Fatigue, Fatigue/Pain, and Upper Extremity Weakness domains, and 1.0 for the Morning Headache domain [17]. For the PDIS, a score of 1.5 points for the Mood domain and 1.0 for the Difficulty Performing Activities domain was defined as a meaningful change [17]. No within-patient threshold for improvement has been established for the R-PAct score. Meaningful change for the individual R-PAct items was defined empirically as moving from being unable to complete an activity at baseline to being able to complete the activity (with or without difficulty) at Week 49. Therefore, only the subset of individuals unable to complete each activity at baseline was used in the R-PAct analysis. Patients who were able to complete a task with some level of difficulty at baseline were not considered in the analysis due to the potential bias in assessing difficulty levels. The meaningful change threshold for the SF-12 physical component summary (PCS) score was an increase of $\geq$6 points from baseline and for mental component summary (MCS) score was an increase of $\geq$7 points from baseline (both were estimated in the general population or other chronic conditions) [25]. For the EQ-5D-5L, a meaningful change was empirically defined as an improvement from baseline of $\geq$1 category for the five dimensions. Patients who reported improvement and patients with ‘no problem’ at baseline and Week 49 (as no improvement was possible) were considered as having a meaningful change, while patients who worsened and patients with problems at baseline who did not change were not considered as having a meaningful change. For the EQ-VAS, an empirical threshold of $\geq$10 points increase from baseline (i.e., 10%) was used [26]. For PGIC, a patient with any improvement in score between baseline and Week 49 (‘somewhat better’, ‘moderately better’, or ‘a great deal better’) was empirically defined as having a meaningful change.

2.4. Statistical analysis

Analysis of the primary analysis period was performed following the completion of the blinded treatment phase for all patients in the modified intent-to-treat (mITT) population, which included all patients who received at least one infusion (partial or full) of the assigned treatment at Week 49. Patients were summarized according to the randomized treatment allocation.

The proportion of patients meeting or exceeding the meaningful change threshold for each PRO (except the R-PAct) was compared between avalglucosidase alfa and alglucosidase alfa treatment groups using a logistic regression model, adjusted for age at baseline and sex. Odds ratios with 95% CI and *p*-values were derived from the model. Analyses for PDSS and PDIS were pre-specified, analyses for all other PROs were *post hoc*. No statistical comparison between treatment groups was performed for the R-PAct because of the small sample size of patients unable to complete an activity at baseline (subpopulation of analysis). Patients with LOPD may experience symptoms across multiple domains measured in the PDSS and PDIS, therefore, the proportion of patients who experienced a meaningful improvement on multiple domain scores across both PROs was also evaluated. As recommended by the FDA [15], empirical cumulative distribution functions (eCDFs) were generated to depict the percentage of patients experiencing an improvement from baseline greater than or equal to the value of different improvement thresholds described above for PDSS and PDIS scores.

The last values gathered before the first infusion (i.e., Day 1) were considered baseline values; where baseline or Week 49 values were missing, patients were considered as having no improvement. No adjustment on multiplicity was performed, and nominal *p*-values were provided.

3. Results

3.1. Trial participants

Overall, 100 patients were randomized to receive avalglucosidase alfa (n = 51) or alglucosidase alfa (n = 49) in the primary analysis period. Of these patients, 99 were adults ($\geq$18 years old) (n = 50, avalglucosidase alfa; n = 49 alglucosidase alfa) and were included in this *post hoc* analysis.

Baseline demographics and scores for PRO measures are presented in Table 2**.** Demographics were generally similar between treatment groups. The mean (SD) age was 48 years (13.9); however, the mean age in the avalglucosidase alfa group (46.1 [14.0] years) was slightly lower than that in the alglucosidase alfa group (49.8 [13.7] years). The proportion of patients of Hispanic or Latino ethnicity was numerically higher in the alglucosidase alfa group (24.5%) than in the avalglucosidase alfa group (6.0%). The most frequent variant in the *GAA* gene in adult patients in this study, c.-32–13 T > G, was found in at least one allele in 43 (86%) patients in the avalglucosidase alfa group and 44 (89.8%) in the alglucosidase alfa group.

Baseline scores for PRO measures were also generally similar between patient treatment groups. The highest (most impaired) mean (SD) scores observed for the PDSS were for the Overall Fatigue (4.2 [1.9]), Pain (3.7 [2.3]), and Fatigue/Pain (3.6 [1.8]) domains, and mean (SD) scores for the PDIS Mood and Difficulty Performing Activities domains were 2.0 (1.8) and 2.2 (0.9), respectively (Table 2). Overall, 46 (46.5%) participants completed the R-PAct at baseline (only administered to English- or Dutch-speaking participants), with a mean (SD) baseline score of 57.3 (16.6) (Table 2). Seven R-PAct items were selected for which at least two patients in each treatment group were unable to complete the task at baseline, and that reflected everyday activities

[a] For pain/discomfort and anxiety/depression domains, scores described outcomes as the following: 1: none, 2: slight, 3: moderate, 4: severe, 5: extreme.

Table 2
Baseline characteristics and PRO scores (adult mITT population).

Parameter	Avalglucosidase alfa ($n = 50$)	Alglucosidase alfa ($n = 49$)	Total($N = 99$)
Age, years			
Mean (SD)	46.1 (14.0)	49.8 (13.7)	48.0 (13.9)
Min; max	19; 78	19; 77	19; 78
Age at first symptom of Pompe disease (years)			
Mean (SD)	33.3 (16.5)	37.7 (15.7)	35.5 (16.2)
Min; max	4; 66	6; 73	4; 73
Sex, n (%)			
Male	26 (52.0)	25 (51.0)	51 (51.5)
Female	24 (48.0)	24 (49.0)	48 (48.5)
Race, n (%)			
White	47 (94.0)	47 (95.9)	94 (94.9)
Black or African American	1 (2.0)	2 (4.1)	3 (3.0)
Asian	2 (4.0)	0	2 (2.0)
Ethnicity, n (%)			
Hispanic or Latino	3 (6.0)	12 (24.5)	15 (15.2)
Not Hispanic or Latino	43 (86.0)	32 (65.3)	75 (75.8)
Not reported	4 (8.0)	5 (10.2)	9 (9.1)
BMI (kg/m^2)			
Mean (SD)	26.48 (6.84)	26.69 (5.42)	26.58 (6.14)
Min; max	14.0; 42.7	16.9; 44.6	14.0; 44.6
Pompe disease-specific PRO measures			
PDSS, mean (SD)	$n = 38$	$n = 38$	$N = 76$
Shortness of Breath score	2.79 (2.03)	2.27 (2.20)	2.53 (2.12)
Fatigue/Pain score	3.60 (1.58)	3.68 (1.99)	3.64 (1.79)
Morning Headache score	1.25 (1.53)	0.90 (1.38)	1.07 (1.46)
Overall Fatigue score	4.22 (1.79)	4.20 (2.06)	4.21 (1.91)
Upper Extremity Weakness score	1.97 (1.66)	2.33 (2.23)	2.15 (1.96)
Pain score	3.69 (2.14)	3.72 (2.50)	3.70 (2.31)
PDIS, mean (SD)	$n = 38$	$n = 38$	$N = 76$
Mood score	2.08 (1.75)	1.98 (1.76)	2.03 (1.75)
Difficulty Performing Activities score[a]	2.35 (0.81)	1.96 (1.03)	2.15 (0.94)
R-PAct score, mean (SD)[b]	$n = 21$	$n = 25$	$N = 46$
	57.05 (16.03)	57.48 (17.44)	57.28 (16.63)
Generic PRO measures			
SF-12, mean (SD)	$n = 50$	$n = 48$	$N = 98$
PCS	35.95 (7.82)	36.76 (9.40)	36.35 (8.60)
MCS	48.31 (10.11)	50.58 (8.69)	49.42 (9.46)
EQ-5D-5L	$n = 50$	$n = 48$	$N = 98$
Mobility, *n* (%)			
No problems	6 (12.0)	8 (16.7)	14 (14.3)
Slight problems	12 (24.0)	13 (27.1)	25 (25.5)
Moderate problems	25 (50.0)	19 (39.6)	44 (44.9)
Severe problems	7 (14.0)	8 (16.7)	15 (15.3)
Unable to walk	0	0	0
Self-care, *n* (%)			
No problems	22 (44.0)	18 (37.5)	40 (40.8)
Slight problems	16 (32.0)	16 (33.3)	32 (32.7)
Moderate problems	11 (22.0)	11 (22.9)	22 (22.4)
Severe problems	0	3 (6.3)	3 (3.1)
Unable to wash or dress independently	1 (2.0)	0	1 (1.0)
Usual activities, *n* (%)			
No problems	7 (14.0)	7 (14.6)	14 (14.3)
Slight problems	11 (22.0)	18 (37.5)	29 (29.6)
Moderate problems	22 (44.0)	17 (35.4)	39 (39.8)
Severe problems	10 (20.0)	6 (12.5)	16 (16.3)
Unable to perform usual activities	0	0	0
Pain/discomfort, *n* (%)			
No pain or discomfort	7 (14.0)	8 (16.7)	15 (15.3)
Slight pain or discomfort	16 (32.0)	19 (39.6)	35 (35.7)
Moderate pain or discomfort	22 (44.0)	15 (31.3)	37 (37.8)
Severe pain or discomfort	4 (8.0)	4 (8.3)	8 (8.2)
Extreme pain or discomfort	1 (2.0)	2 (4.2)	3 (3.1)
Anxiety/depression, *n* (%)			
Not anxious or depressed	17 (34.0)	19 (39.6)	36 (36.7)
Slightly anxious or depressed	21 (42.0)	14 (29.2)	35 (35.7)
Moderately anxious or depressed	9 (18.0)	15 (31.3)	24 (24.5)
Severely anxious or depressed	3 (6.0)	0	3 (3.1)
Extremely anxious or depressed	0	0	0
EQ-VAS score, mean (SD)	61.18 (15.90)	66.69 (18.28)	63.88 (17.24)

Baseline values are last non-missing values prior to the first treatment. Treatment groups are randomized arms in the modified intent-to-treat population. Baseline values for PGIC were not available.
BMI, body mass index; EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-VAS, EQ visual analog scale; max, maximum; MCS, mental component summary; min, minimum; mITT, modified intent-to-treat; n/N, number of patients; PCS, physical component summary; PDIS, Pompe Disease Impact Scale; PDSS, Pompe Disease Severity Scale; PGIC, Patient Global Impression of Change; PRO, patient-reported outcome; R-PAct, Rasch-built Pompe-specific Activity Scale; SD, standard deviation; SF-12, 12-item Short Form Survey.
[a] Available data at baseline for PDIS Difficulty Performing Activities score: $n = 37$ for avalglucosidase alfa, $n = 37$ for alglucosidase alfa ($n = 74$ total).
[b] Only participants who were not able to complete an R-PAct activity at baseline were included.

across patients and regions: stand from a seated position ($n = 6$ total participants unable to complete the task at baseline), walk >1 km ($n = 12$), walk up and down a set of stairs ($n = 13$), bend over to pick something up ($n = 10$), walk at a rapid rate ($n = 24$), bend at the knee and then stand up ($n = 25$), and run ($n = 34$). The EQ-5D-5L questionnaire responses indicated that, overall, the majority of patients experienced problems with mobility (85.7%), self-care (59.2%), usual activities (85.7%), pain (84.7%), and/or anxiety/depression (63.3%) at baseline (Table 2).

Relative to scores in the general population, baseline scores for generic PROs in COMET were poorer than that of the general population for the SF-12 PCS score, dimensions of the EQ-5D-5L questionnaire, and EQ-VAS score (Fig. 1A–C). However, the baseline SF-12 MCS scores were within 1 SD of the general population norm (Fig. 1A) [25].

3.2. Analyses of Pompe disease-specific PROs

The proportion of patients achieving a meaningful change was numerically higher in the avalglucosidase alfa group compared with the alglucosidase alfa group for all six domains of the PDSS, with statistically significant higher odds of a meaningful change at nominal *p*-value for Shortness of Breath ($p < 0.01$), Fatigue/Pain, Morning Headache, and Overall Fatigue domain scores ($p < 0.05$ for other scores) (Fig. 2A).

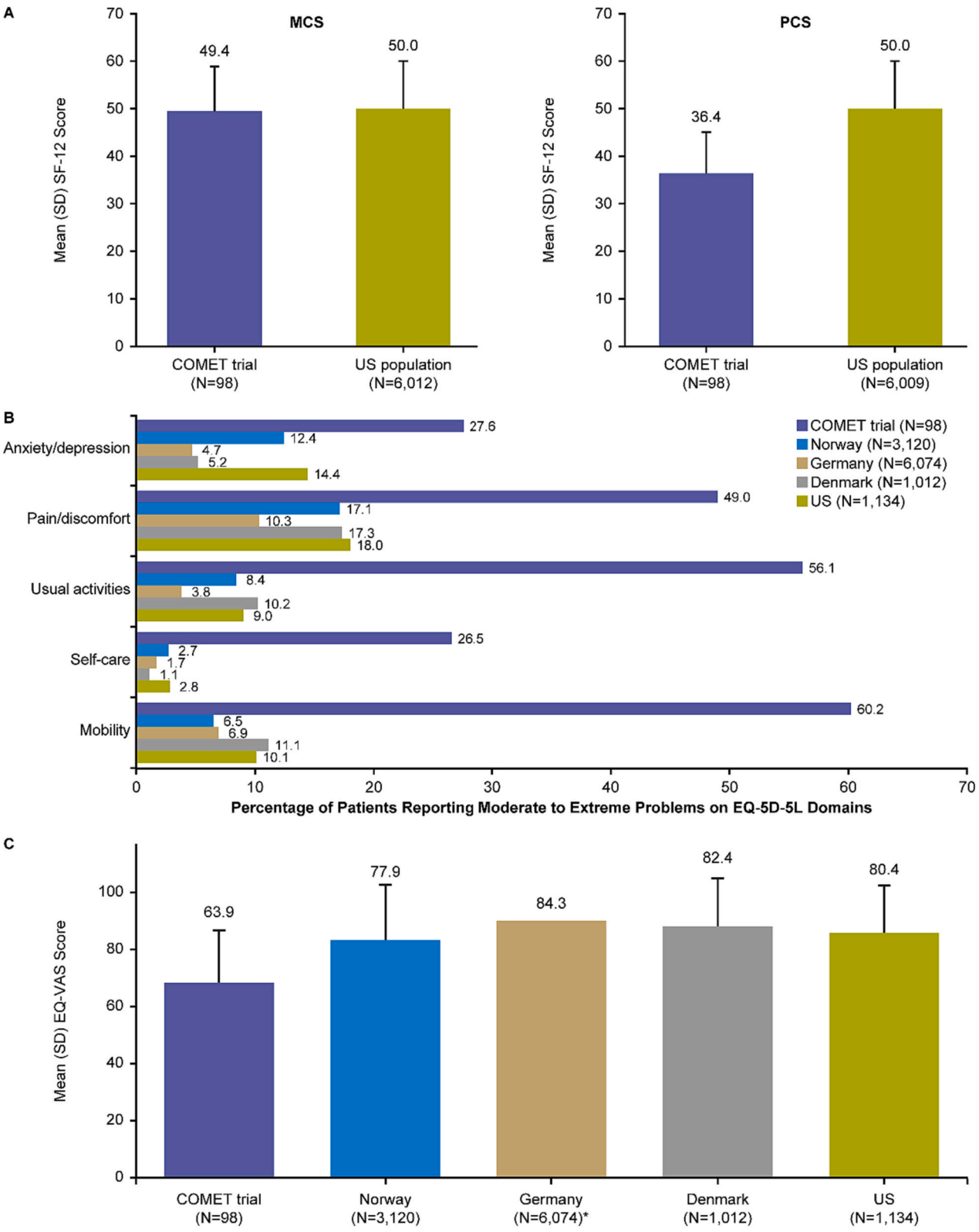

Fig. 1. Baseline scores for SF-12 (A), EQ-5D-5L dimensions (B), and EQ-VAS (C) in the COMET trial relative to scores in the general population.
SF-12 MCS and PCS scores from the COMET trial and the US population [25] are presented in Fig. 1A; the proportion of patients with moderate to extreme problems (Levels 3–5) in EQ-5D-5L dimensions and baseline EQ-VAS scores in the COMET trial and the general population in different countries (Norway [27]; Germany [28]; Denmark [29]; US [30]) are presented in Fig. 1B–C. General population samples were derived from a variety of aggregated surveys and time ranges.
Baseline data for the COMET PRO study include total number of patients from avalglucosidase alfa (n = 50) and alglucosidase alfa (n = 48) groups. *Standard deviation for the German population was not reported.
EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-VAS, EQ visual analog scale; MCS, mental component summary; PCS, physical component summary; SF-12, 12-item Short Form Survey.

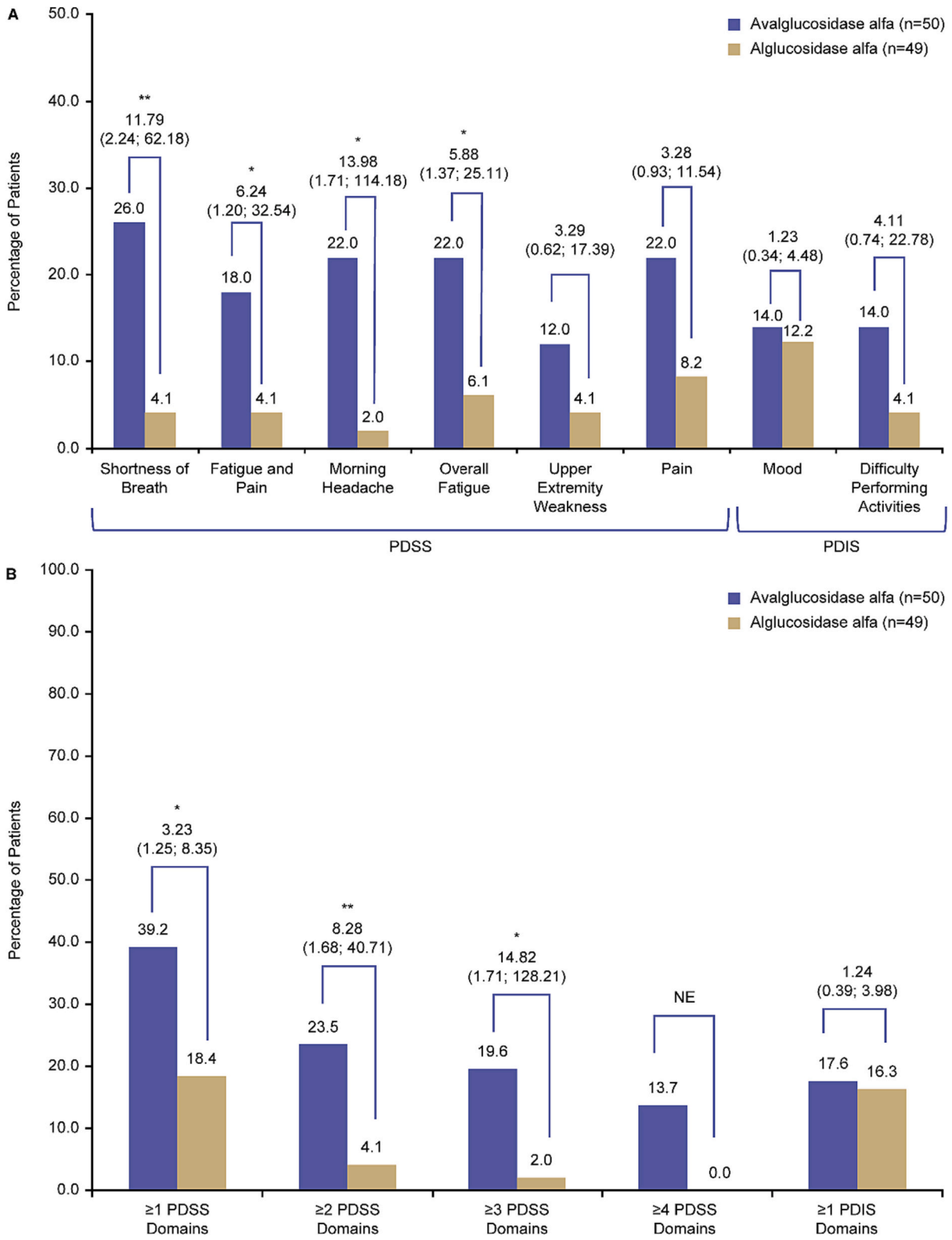

Fig. 2. Proportion of patients achieving a meaningful change in individual domains (A) and multiple domains (B) at Week 49 for the PDSS and PDIS (adult mITT population).

Numbers above bars are OR (95% CI). *Nominal $p < 0.05$; **nominal $p < 0.01$. OR, 95% CI, and p-value derived from logistic regression model, adjusted for age at baseline and gender, for avalglucosidase alfa versus alglucosidase alfa.

CI, confidence interval; mITT, modified intent-to-treat; NE, not estimable; OR, odds ratio; PDIS, Pompe Disease Impact Score; PDSS, Pompe Disease Severity Score.

Additionally, the proportion of patients with improvements in the PDIS was numerically higher in the avalglucosidase alfa group compared with the alglucosidase alfa group at Week 49 for both impacts (Difficulty Performing Activities: 14.0% versus 4.1%, OR 4.11 [0.74, 22.78], $p = 0.106$; Mood: 14.0% versus 12.2%, OR 1.23 [0.34, 4.48], $p = 0.751$); however, these did not reach nominal significance (Fig. 2A). For both the PDSS and PDIS, the proportion of patients with improvements in multiple domains was numerically higher with avalglucosidase alfa compared with alglucosidase alfa, and nominally significantly higher for the comparisons of ≥1 ($p = 0.016$), ≥2 ($p = 0.009$), and ≥ 3 ($p = 0.014$) domains improvement in the PDSS (Fig. 2B).

The eCDFs for the change from baseline to Week 49 in PDSS domains show a clear separation between treatment groups, favoring the avalglucosidase alfa group over the alglucosidase alfa group, for the Shortness of Breath and Overall Fatigue domains (Fig. 3). The eCDFs for the Upper Extremity Weakness, Pain, and Morning Headache domains of the PDSS were similar between the two treatment groups (Fig. 3); however, for Morning Headache, there was separation between the two treatment

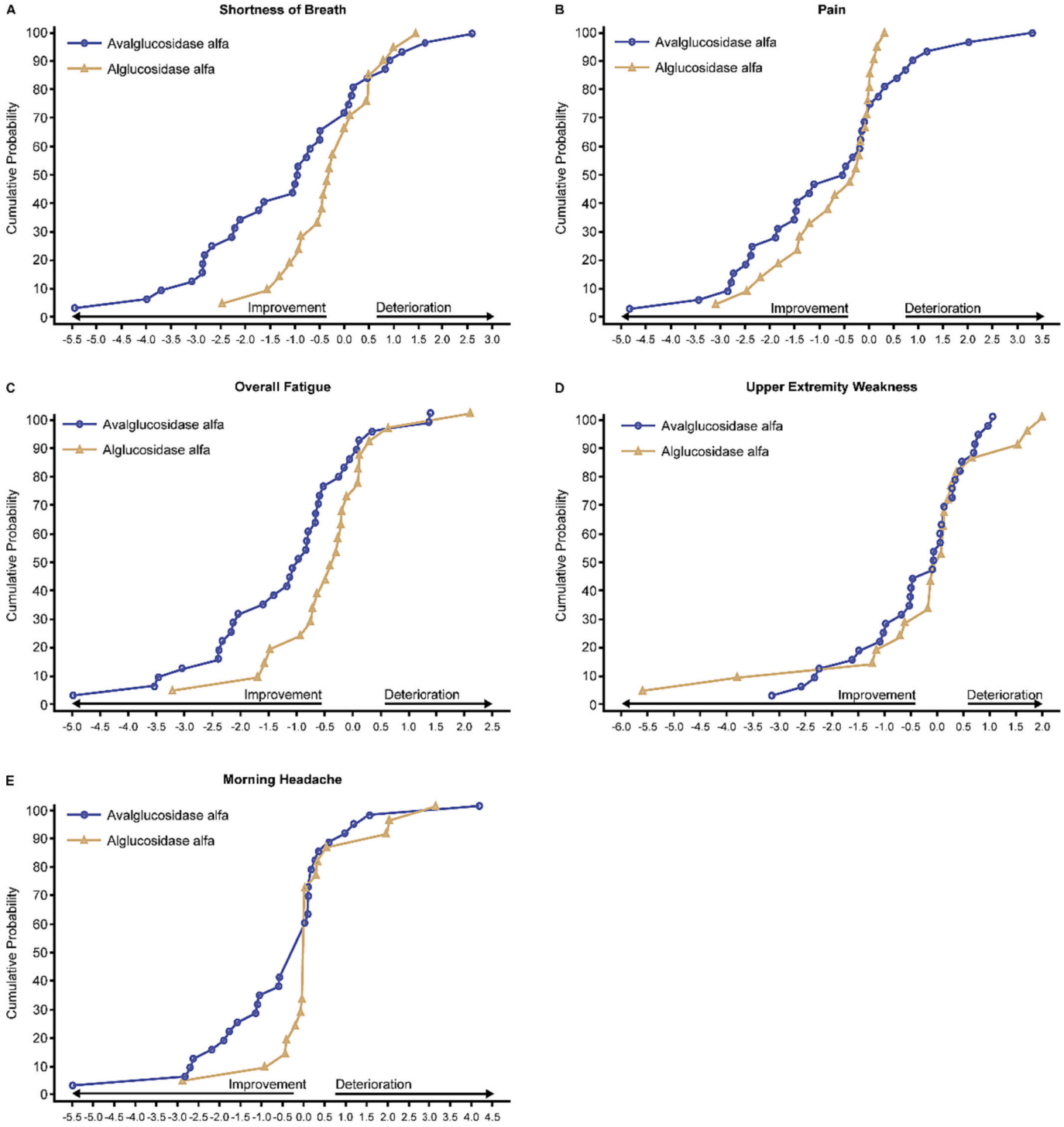

Fig. 3. Empirical cumulative distribution functions for change from baseline to Week 49 in the PDSS domains: A) Shortness of Breath, B) Pain, C) Overall Fatigue, D) Upper Extremity Weakness, and E) Morning Headache (adult mITT population).
mITT, modified intent-to-treat; PDSS, Pompe Disease Severity Scale.

groups for improvement, consistent with the meaningful change analysis.

Regarding PDIS domains at Week 49, the eCDF depicted a clear separation between treatment groups for Difficulty Performing Activities, favoring avalglucosidase alfa (Fig. 4). Conversely, eCDFs were overlapping for the Mood domain of the PDIS (Fig. 4).

Across all selected activities of the R-PAct, a numerically greater percentage of patients in the avalglucosidase alfa group were able to complete an activity at Week 49 that they could not do at baseline, compared with the alglucosidase alfa group (Fig. 5). The activities for which there were the highest percentages of patients who changed from being unable to perform the activity at baseline to being able to perform the activity at Week 49 were 'bend over to pick something up' (83% for avalglucosidase alfa versus 25% for alglucosidase alfa), 'stand up from a seated position' (75% versus 50%), and 'walk at a rapid rate' (55% versus 27%).

3.3. Analysis of generic HRQoL PROs and patient-perceived change

The proportion of patients achieving a meaningful change and corresponding odds ratios for achieving a meaningful change in the avalglucosidase alfa group versus the alglucosidase alfa group for the SF-12 and EQ-5D-5L instruments are shown in Table 3.

The proportion of patients who achieved a ≥ 6-point improvement in the SF-12 PCS score by Week 49 was numerically slightly higher in the avalglucosidase alfa group versus alglucosidase alfa (26.0% versus 22.4%; $p = 0.962$; Table 3). Similarly, the proportion of patients who achieved a ≥7-point improvement in the SF-12 MCS score by Week 49 was numerically higher in the avalglucosidase alfa group versus alglucosidase alfa (28.0% versus 14.3%; $p = 0.101$; Table 3). The proportion

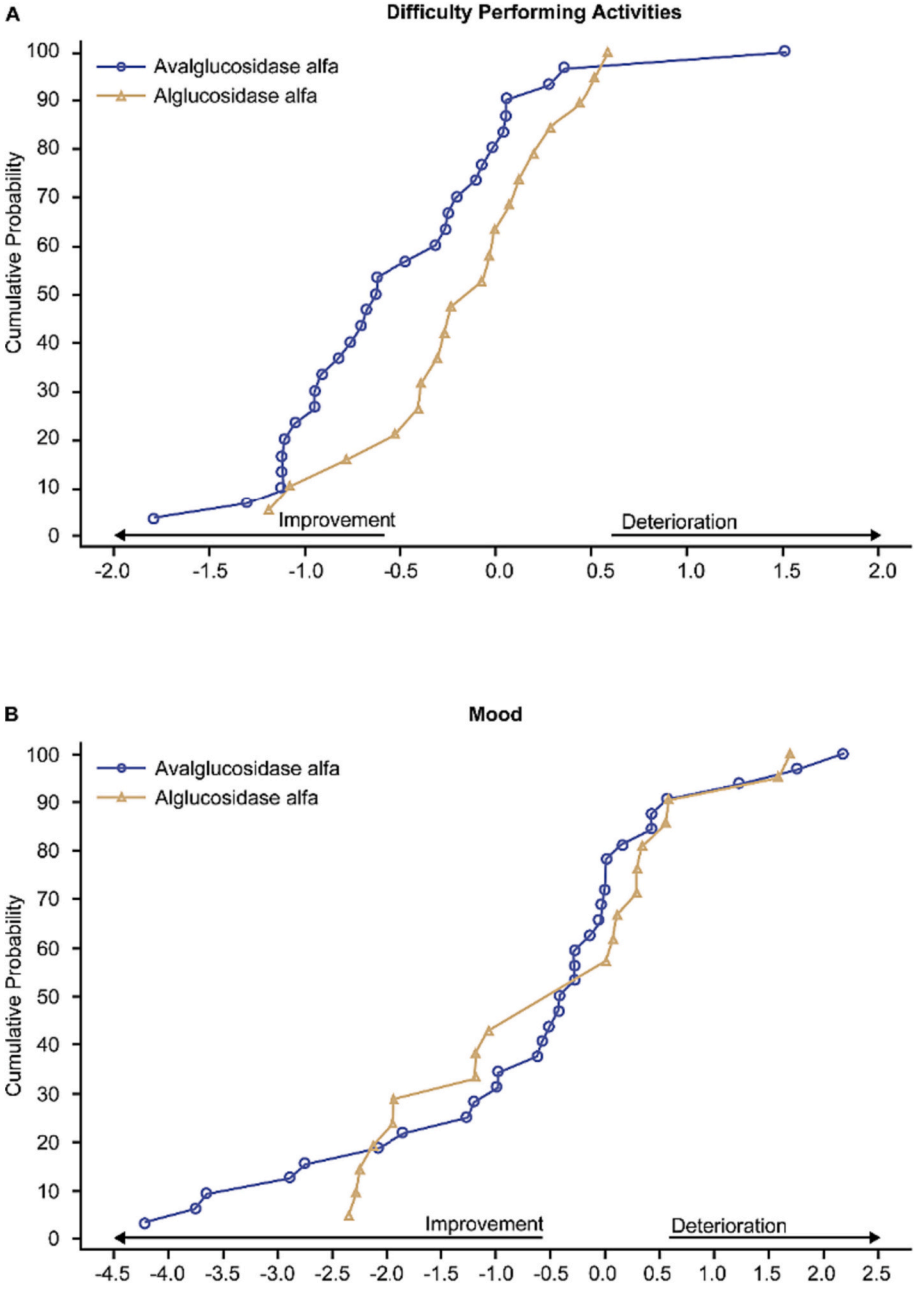

Fig. 4. Cumulative distribution functions for change from baseline to Week 49 for the PDIS domains: A) Difficulty Performing Activities and B) Mood (adult mITT population).
mITT, modified intent-to-treat; PDIS, Pompe Disease Impact Score.

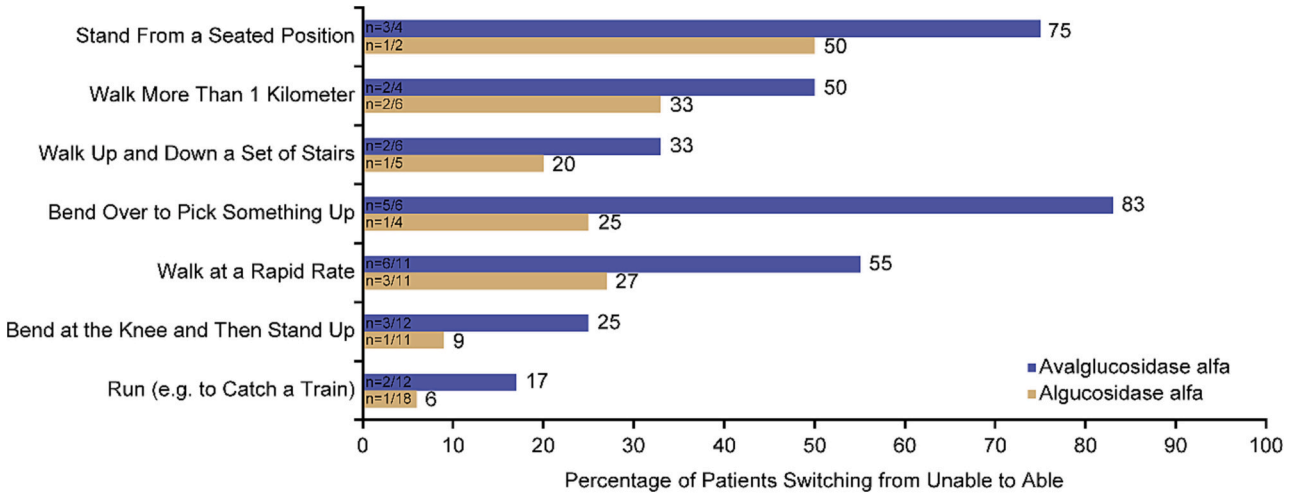

Fig. 5. Proportion of patients who switched from "unable" at baseline to "able" to do an activity at Week 49 for seven selected activities of the R-PAct (adult mITT population).
Administered to a subset of English- or Dutch-speaking participants. Numbers in the bars are the number of patients who switched from "unable" at baseline to "able" at Week 49. Confidence intervals and *p*-values were not determined for this analysis.
The items included were selected because (a) at least two patients in each treatment group reported that they were unable to complete the activity at baseline and (b) they reflect common activities that apply across patients and regions (e.g., gardening was not included). No statistical test was performed due to the small sample size of patients unable to perform activity at baseline.
mITT, modified intent-to-treat; R-PAct, Rasch-built Pompe-specific Activity Scale.

of patients achieving a meaningful change at Week 49 for each of the EQ-5D-5L dimensions was numerically greater with avalglucosidase alfa compared with alglucosidase alfa (mobility: 54.0% versus 36.7%; self-care: 54.0% versus 36.7%; usual activities: 54.0% versus 30.6%; anxiety/depression: 70.0% versus 59.2%; pain/discomfort: 46.0% versus 44.9%) (Table 3). However, the pain/discomfort dimension was the only dimension with an OR <1. Significantly more patients in the avalglucosidase alfa group achieved a meaningful change for the usual activities dimension (OR [95% CI] 2.47 [1.06; 5.76]; $p = 0.0365$) and the EQ-VAS (50.0% versus 18.4%; 4.45 [1.77; 11.18]; $p = 0.002$; Table 3).

Higher proportions of patients in the avalglucosidase alfa group achieved improvement for PGIC domains at Week 49 versus patients who received alglucosidase alfa (Fig. 6). Additionally, the ORs were significantly above 1 for all four domains: improvement in their ability to perform daily activities, disease-related symptoms, ability to breathe, and mobility (all nominal *p*-values <0.05).

4. Discussion

This analysis assessed the impact of avalglucosidase alfa compared with alglucosidase alfa using multiple disease-specific and general HRQoL PROs in treatment-naïve adult patients with LOPD in the Phase 3 COMET trial. The analysis highlighted the high disease burden at baseline among adult patients with LOPD and found that avalglucosidase alfa demonstrated a greater therapeutic benefit on clinically meaningful change in HRQoL compared with alglucosidase alfa. The improvements in disease-specific and general HRQoL show the additional value of avalglucosidase alfa treatment to the patient beyond the clinically relevant improvements in respiratory function, ambulation, and functional endurance, previously reported in the COMET trial [13].

Baseline data illustrate the high physical and sociopsychological disease burden associated with LOPD, with poorer scores than would be expected for the general population. These results are in line with those reported in a similarly-designed randomized, placebo-controlled trial of alglucosidase alfa in LOPD, in which the 36-Item Short-Form Health Survey (SF-36) was used to demonstrate that baseline physical health status was reduced in patients with LOPD (PCS score >1.5 SD below US general population norms), although this study did not go into as much detail on PROs as COMET [8]. Similar findings have been reported in other studies, including a large international study of 210 patients with LOPD that reported lower SF-36 scores than in the general population, with the 'physical functioning' domain being most affected [31], and a 10-year observation study of 174 adults with Pompe disease which reported that the PCS and physical functioning domain scores remained below the population norm after 4 years of ERT [32]. These results demonstrate the clinical impact of LOPD as well as its effect on physical functioning, highlighting the need for a safe and effective treatment that improves both the physical manifestations of LOPD and the associated reduction in HRQoL [6].

The COMET trial incorporated a broad range of PROs to comprehensively evaluate patient wellbeing, using both Pompe disease-specific measures and more general instruments. The data for group mean changes from baseline in each measure were previously reported for both the alglucosidase alfa and avalglucosidase alfa treatment groups [13]. Although the published point estimates favored avalglucosidase alfa therapy, statistical significance was not evident [13]. The present study extends these observations by using individual patient reports of treatment responses to perform meaningful change analyses and generate cumulative distribution curves. For the Pompe disease-specific measures (PDSS, PDIS and R-PAct), the data demonstrated that treatment with avalglucosidase alfa was more likely to result in clinically meaningful improvements in numerous disease domains compared with alglucosidase alfa therapy, with statistical significance evident in Shortness of Breath, Overall Fatigue, Fatigue/Pain, and Morning Headache domains. The clear separation of curves observed in the eCDF analysis also indicates a greater effect of avalglucosidase alfa across meaningful change thresholds for PDSS Shortness of Breath, and Overall Fatigue domains, as well as the PDIS Difficulty Performing Activities domain. Additionally, of particular importance was the observation that selected patients treated with avalglucosidase alfa regained the ability to perform physical tasks that are critical for daily living (e.g., 'ability to stand from a seated position', 'bend over to pick something up', 'walk quickly', and 'walk up and down stairs'); findings that occurred less frequently during alglucosidase alfa therapy. Analyses using generic HRQoL instruments provided additional support in favor of avalglucosidase alfa therapy. For example, statistically significant and clinically meaningful benefits were evident in questions that reflected underlying disease pathogenesis, such as PGIC ability to breathe and mobility, as

Table 3
Proportion of patients achieving a meaningful change at Week 49 for SF-12 and EQ-5D-5L (adult mITT population).

	Proportion of patients achieving a meaningful change, *n* (%)		OR (95% CI)[a]	*p*-value
Measure	Avalglucosidase alfa ($n = 50$)	Alglucosidase alfa ($n = 49$)		
SF-12[b]				
PCS	13 (26.0)	11 (22.4)	1.02 (0.39; 2.69)	0.962
MCS	14 (28.0)	7 (14.3)	2.38 (0.84; 6.71)	0.101
EQ-5D-5L dimension[c]				
Mobility	27 (54.0)	18 (36.7)	1.80 (0.77; 4.23)	0.1763
Self-care	27 (54.0)	18 (36.7)	1.88 (0.83; 4.26)	0.1297
Usual activities	27 (54.0)	15 (30.6)	2.47 (1.06; 5.76)	0.0365
Pain/ discomfort	23 (46.0)	22 (44.9)	0.96 (0.43; 2.15)	0.9135
Anxiety/ depression	35 (70.0)	29 (59.2)	1.57 (0.68; 3.65)	0.2928
EQ-VAS[d]	25 (50.0)	9 (18.4)	4.45 (1.77; 11.18)	0.002

CI, confidence interval; EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-VAS, EQ visual analog scale; MCS, mental component summary; mITT, modified intent-to-treat; OR, odds ratio; PCS, physical component summary; PRO, patient-reported outcome; SD, standard deviation; SF-12, 12-item Short Form Survey.

[a] OR, 95% CI, and *p*-value derived from logistic regression model, adjusted for age at baseline and gender, for avalglucosidase alfa versus alglucosidase alfa.

[b] A meaningful change was defined as an increase of ≥6 points for PCS and ≥7 points for MCS between baseline and Week 49.

[c] An increase of ≥1 category improvement for the five categories between baseline and Week 49 was defined as a meaningful change, patients with 'no problem' at baseline and Week 49 were included as achieving a meaningful change. Patients were considered not achieving a meaningful change if they had no change (if they had problems at baseline) or a worsening of outcome.

[d] An increase of ≥10 points between baseline and Week 49 was considered a meaningful change.

well as PGIC and EQ-5D-5L questions regarding general health status, usual daily activities, and disease-related symptoms. These disease-specific and generic PROs captured symptoms and functional limitations that are important to patients with LOPD and are critical manifestations of the underlying pathophysiology of the condition [16,18]. Across these PRO measures, our findings provide evidence of a greater therapeutic benefit of avalglucosidase alfa over alglucosidase alfa in the most patient-relevant LOPD domains of breathing, mobility, and daily activities. This supports a clinically relevant impact of avalglucosidase alfa on patient's HRQoL.

The use of PROs has become an integral component of clinical trials for measuring change in health outcomes and treatment satisfaction, as well as providing an important measurement of treatment efficacy [33]. Understanding the patient experience through PRO measures is essential for evaluating the impact of treatment on pain, function, symptoms, and HRQoL, particularly in rare diseases. The importance of the patient voice in clinical trials and shared decision making is increasingly recognized by healthcare professionals and stakeholders [34]. The COMET trial included one of the largest LOPD patient populations to have been evaluated with one of the most comprehensive set of PROs in a clinical trial of a rare disease. Therefore, these results provide valuable information on the patient perspective on the impact of LOPD and treatment on self-reported HRQoL, activities of daily life, disease-related symptoms, and psychological health. In addition, the use of empirical and established meaningful change thresholds at the patient level in this analysis allowed us to determine if the impact of avalglucosidase alfa on HRQoL improvement is clinically relevant for the individual patient. These data were collected in a treatment-naïve patient population, who were blinded to treatment, thus minimizing bias and strengthening the results. PRO measures also have clinical utility in real-world practice where they can be used to assess disease burden and treatment efficacy, particularly in scenarios in which other assessments, such as 6MWT, may not be practical. Pompe disease-specific PROs can be used to monitor progression once the signs of disease become apparent, and therefore, are relevant for healthcare professionals, patients, and payers. In the future, PROs will become important modern digital tools for the pharmacovigilance survey of new long-term therapies in rare diseases [35].

Limitations of the analysis include the *post hoc* nature; between-group comparisons were considered exploratory. Another limitation was that the generic PROs used in the study were not able to capture all aspects of Pompe disease. As PRO measures are subjective, outcomes may be impacted by internal factors, such as mood and expectations, and external factors such as interactions with the healthcare providers, which may lead to variations in outcomes [36]. In the real-world setting, the use of these PROs may also be limited if patients are not ambulatory. Clinician-reported outcome measures could be used to provide additional clinical context to the quality of life and physical well-being of patients and complement results from PROs. The analysis was also limited by a relatively low sample size in some analyses. For example, R-PAct was only administered to a subset of patients from the COMET trial, as it has currently only been validated in adult patients using English and Dutch language versions. However, a European consortium of Pompe disease (EPOC) validation study is underway to bridge this gap and validate the R-PAct in different European countries [37]. Furthermore, the number of patients in the R-PAct analysis switching from "unable" to "able" to do an activity was limited to the small number who answered "unable" at baseline. Similarly, the lack of significantly higher proportions of patients achieving a meaningful change for some of the EQ-5D-5L dimensions may be due to the small patient numbers with perceived problems reported as "extreme problems or unable" at baseline, partly reflecting the instruments' intrinsic insensitivity for Pompe disease-specific symptoms. In addition, the meaningful change definition used in the EQ-5D-5L analysis included those with no problems at baseline and Week 49, thus introducing a ceiling effect. Finally, the thresholds used to assess the change in the SF-12 PCS and MCS were not established in patients with LOPD.

5. Conclusions

In conclusion, this analysis of patient-level responses among treatment-naïve adults with LOPD in the COMET trial suggest that avalglucosidase alfa provides meaningful improvements in multiple domains of physical health measured using disease-related and generic PROs. Compared with alglucosidase alfa, significantly greater therapeutic benefit was demonstrated for patient-relevant aspects of LOPD, including mobility, usual activities, breathing, pain, fatigue, and general HRQoL, supporting the overall results from COMET. These data support avalglucosidase alfa as a new potential standard-of-care therapy for LOPD. Furthermore, this analysis suggests that the PROs used in the COMET trial are appropriate for use in the clinic to monitor the long-term benefits of emerging treatments in LOPD.

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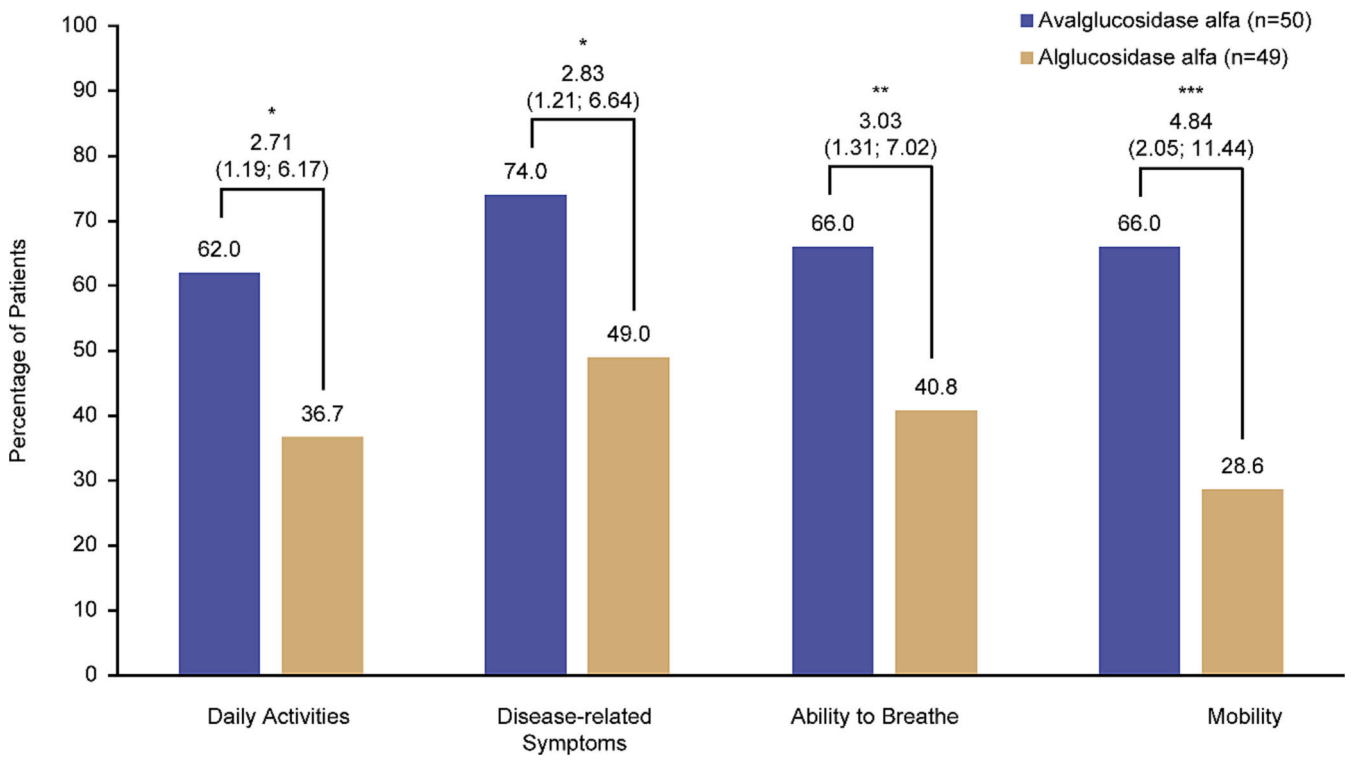

Fig. 6. Proportion of patients achieving a meaningful change at Week 49 for PGIC domains (adult mITT population). Any improvement in score between baseline and Week 49 (5 = 'somewhat better', 6 = 'moderately better' or 7 = 'a great deal better') was defined as a meaningful change.
Numbers above bars are OR (95% CI). *Nominal $p < 0.05$; **nominal $p < 0.01$; ***nominal $p < 0.001$.
OR, 95% CI, and *p*-value derived from logistic regression model, adjusted for age at baseline and gender, for avalglucosidase alfa versus alglucosidase alfa.
CI, confidence interval; mITT, modified intent-to-treat; OR, odds ratio; PGIC, Patient Global Impression of Change.

Author contributions

- **AH, BS, JM, KIB, KAH, LP, NvdB**, and **PD** made substantial contributions to study conception and design.
- **AH, AT, BS, MMD, NvdB**, and **PD** made substantial contributions to the acquisition of data.
- **AH, AT, BS, JM, KIB, KAH, LP, MMD, NvdB, NT, PSK, PD,** and **TZ** made substantial contributions to data analysis or interpretation of data.

All authors were involved in drafting the work or revising it critically for important intellectual content, and in final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Previous presentations

These data were presented in part at World Muscle Society 2021, September 20–24, 2021; at 18th Annual WORLDSymposium, February 7–11, 2022; at ISPOR Europe 2022, November 6–9, 2022; and at the 8th congress of the European Academy of Neurology, June 25–28, 2022.

CRediT authorship contribution statement

Antonio Toscano: Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Laurence Pollissard:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Jérôme Msihid:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Nadine van der Beek:** Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Priya S. Kishnani:** Formal analysis, Writing – original draft, Writing – review & editing. **Mazen M. Dimachkie:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Kenneth I. Berger:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Pronabesh DasMahapatra:** Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Nathan Thibault:** Formal analysis, Writing – original draft, Writing – review & editing. **Alaa Hamed:** Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Tianyue Zhou:** Formal analysis, Writing – original draft, Writing – review & editing. **Kristina An Haack:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Benedikt Schoser:** Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

KAH: is an employee and may hold stock and/or stock options in Sanofi.

KIB: has served as a consultant to Sanofi, Amicus Therapeutics, Takeda, Valerion, and has participated in advisory boards for Sanofi, AskBio, Spark Therapeutics and Takeda; he is currently an employee of Sanofi.

PD: is an employee and may hold stock and/or stock options in Sanofi.

MMD: serves or recently served as a consultant for Abcuro, Amazentis/Vandria, ArgenX, Astellas, Catalyst, Cello, CNSA, Covance/Labcorp, CSL-Behring, Dianthus, EcoR1, EMD Serono/Merck, Janssen, Kezar, MDA, Medlink, Momenta, NuFactor, Octapharma, Priovant, RaPharma/UCB, Roivant Sciences Inc., Sanofi Genzyme, Shire Takeda, Scholar Rock, Spark Therapeutics, TACT, Abata/Third Rock, UCB Biopharma, and UpToDate. MMD received research grants, contracts or

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AH: is an employee and may hold stock and/or stock options in Sanofi.

PSK: has received research/grant support from Sanofi Genzyme and Amicus Therapeutics; has received consulting fees and honoraria from Sanofi Genzyme, Amicus Therapeutics, Maze Therapeutics, Bayer and Asklepios Biopharmaceutical, Inc. (AskBio); is a member of the Pompe and Gaucher Disease Registry Advisory Board for Sanofi Genzyme, Pompe Disease Advisory Board for Amicus Therapeutics, and Advisory Board for Baebies; and has equity with Maze Therapeutics and has held equity in Asklepios Biopharmaceuticals, and may receive milestone payments related to that equity in the future.

JM: is an employee and may hold stock and/or stock options in Sanofi.

LP: is an employee and may hold stock and/or stock options in Sanofi.

BS: Unrestricted research grants from Amicus, Astellas, Marigold Foundation, AMDA Foundation. Speaker honoraria from Kedrion, Alexion. Scientific advisor for Amicus, Argenx, Astellas, Maze, Pepgen, Sanofi, Spark, and Taysha. No stocks or shares.

NT: is an employee and may hold stock and/or stock options in Sanofi.

AT: has received honorarium as a scientific board component (Sanofi, Amicus, and Aro) and as a speaker for Sanofi, Spark, and Amicus.

NvdB: received speaker honoraria from Sanofi and Amicus Therapeutics, and has served as scientific advisor for Sanofi under agreements with Erasmus MC University Medical Center and the relevant industry.

TZ: is an employee and may hold stock and/or stock options in Sanofi.

Data availability

Qualified researchers may request access to patient-level data and related trial documents including the trial protocol with any amendments, statistical analysis plan, and dataset specifications. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org.

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