


Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systematic review and meta-analysis

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Abstract A number of studies have assessed the efficacy of alglucosidase alfa as an enzyme replacement therapy (ERT) on motor and respiratory endpoints in patients with late-onset Pompe disease (LOPD). A previous review evaluated the clinical efficacy and safety of alglucosidase alfa; however, it is difficult to draw inferences from individual studies due to small patient populations, particularly in evaluating the benefit on survival. To evaluate the current evidence on the long-term efficacy of alglucosidase alfa with regard to survival, motor, and respiratory function in patients with LOPD in relation to the natural progression of the disease, a new systematic literature review was performed identifying studies that assessed either mortality, percent predicted forced vital capacity (% FVC), or the 6-min walk test (6MWT) among treated and untreated LOPD patients. Patient overlap was avoided by removing smaller studies or ensuring the use of only one conflicting study per outcome. Mortality was modeled using Poisson models for each treatment group. Outcomes were modeled using first- and second-order fractional polynomial meta-analysis with fixed- and random-effects. Meta-regression was used to explore sources of heterogeneity.

Twenty-two publications pertaining to 19 studies/trials were selected, including 438 patients when accounting for overlaps, with the average study duration being 45.7 months. Patients treated with alglucosidase alfa in these studies had a nearly five-fold lower mortality rate than untreated patients (rate ratio: 0.21; 95 % credible interval: 0.11, 0.41). On average, % FVC declined consistently among untreated patients, including a 2.3 % decline after 12 months follow-up and 6.2 % decline after 48 months. This is in contrast to alglucosidase alfa-treated patients, who, on average, improved rapidly, with an increase of 1.4 % FVC after 2 months, followed by a slow regression back to baseline over a three-year period. Nonetheless, the relative difference between those treated and not grew over time, from 4.5 % FVC after 12 months to 6 % FVC after 48 months. In the 6MWT, alglucosidase alfa-treated patients on average had the largest improvement over the first 20 months of treatment of approximately 50 meters increase over baseline, with its substantial stabilization in the following years. By comparison, untreated patients do not show 6MWT improvement over time. Alglucosidase alfa has a beneficial effect in LOPD patients as demonstrated by improvements in survival and ambulation maintained over time, as well as prevention of deterioration in respiratory function.

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Introduction

Pompe disease, also called glycogen storage disease type II, is a rare, autosomal recessive, and metabolic disorder caused by a deficiency of the lysosomal enzyme acid alpha-

glucosidase (GAA). Affected individuals suffer from an accumulation of glycogen in various tissues, most notably in the skeletal muscles and respiratory system, causing irreversible muscle damage [1, 2]. Pompe disease typically affects 1 in 40,000 to 1 in 200,000 people globally [3, 4], with regional variances in prevalence, and is classified as either infantile-onset (IOPD) or late-onset Pompe disease (LOPD), based on the age of symptom-onset and progression. The most severe form, IOPD, is characterized by the presence of cardiomegaly and generalized muscle weakness in the first year of life. LOPD typically shows greater heterogeneity in symptoms with a variable progression and is usually characterized by general, proximal, and axial muscle weakness leading to respiratory insufficiency and ambulatory problems, without cardiac involvement in the majority of cases [2, 5]. Longer disease duration tends to lead to a more severe and more rapidly progressive disease, increasing the likelihood for ventilation support and wheelchair dependency [5].

Alglucosidase alfa is a recombinant, lysosomal, and glycogen-cleaving enzyme indicated for use in patients with Pompe disease and is the first and currently only disease-specific treatment for LOPD. It received approval in the EU in 2006, and first received FDA approval in 2006 based on IOPD data (as Myozyme[®], Genzyme) and later again in 2010 based on LOPD data (as Lumizyme[®], Genzyme) [6]. Because Pompe disease has a very low prevalence, the evidence base for the utility of alglucosidase alfa in LOPD consists primarily of small and uncontrolled studies. The only clinical trial conducted in LOPD was the landmark Late-Onset Treatment Study (LOTS), a randomized, placebo-controlled trial involving 90 patients [7]. This trial demonstrated that over the course of 78 weeks, those treated with alglucosidase alpha showed significant improvements in walking distance and stabilization of respiratory function. This trial also included an extension study following the initial 78 weeks, as well as an observational study prior to the study called Late-Onset Pompe Observational Study (LOPOS: ClinicalTrials.gov Identifier: NCT00077662) [8, 9].

A recent systematic literature review evaluating the use of alglucosidase alfa in patients with LOPD reported on outcomes for 368 patients [10]. Although no formal statistical pooling was conducted owing to a high degree of reported heterogeneity, the authors found that treatment with alglucosidase alfa was associated with improved ambulation and respiratory function in most patients (as demonstrated by the 6-min walk test (6MWT) and forced vital capacity (FVC), respectively). They also found that the need for both invasive and non-invasive ventilation, as well as ambulatory support, either improved or remained stable in a majority of LOPD patients on treatment. Since its publication, however, several additional studies have been published that can be added to the current evidence

base, including a large UK cohort of 62 patients [11]. This study aims to update and build on the previous literature review and conduct a meta-analytic comparison of evidence on the natural history of LOPD with respect to the progression of the disease, while patients are receiving alglucosidase alfa, including using quantitative methods to assess and better describe these comparative progressions.

Methods

Search strategy

We conducted a systematic search of the following electronic databases: Medline, EMBASE, and Cochrane Central Register of Controlled Trials. The search strategies involved a series of terms for LOPD defining the population, terms describing alglucosidase alfa, natural history, and, finally, Boolean statement requiring the population and either of the other two categories. The specific search strategies are presented in Tables A1 and A2 of the Web Appendix. These searches used terms related to each intervention of interest, study population, and study designs of interest. Manual searches of the website www.clinicaltrials.gov were also conducted. Two reviewers performed abstract and full-text screening independently and in duplicate. All disagreements were resolved by discussion between the two reviewers, and all persisting disagreements were resolved by a third arbitrator.

Inclusion criteria

Table 1 presents the PICOS (Population, Interventions, Comparisons, Outcomes, and Study Design) statement

Table 1 Scope of the literature review in PICOS form

Criteria	Definition
Population	Patients with LOPD
Interventions	Alglucosidase alfa (myozyme and lumizyme)
Comparison	None; natural course of disease
Outcomes	6-min walk test (6MWT) distance Forced vital capacity (FVC) Survival Ambulation status Ventilator use
Study design	RCTs Open-label extension phases of included RCTs Single-arm trials Prospective/retrospective observational studies

PICOS population, interventions, comparisons, outcomes, and study design, *LOPD* late-onset Pompe disease, *RCT* randomized controlled trial

used to assist in the identification and selection of studies relevant to this systematic literature review. Randomized controlled trials and observational studies pertaining to alglucosidase alfa were eligible, as were studies evaluating the natural course of LOPD. Case reports and case series of only two patients were considered ineligible; as were studies of recombinant human GAA (rhGAA) that is not yet approved by the FDA for LOPD. As LOPD is a rare disorder, there was a significant potential for patient overlap between studies, and particular attention was paid to this. Patient overlap was determined using information on country, hospital and university centres, span of study, and text discussing overlap directly in the paper. A priori, we decided to allow for up to 10 % overlap between studies to avoid removing large data based on a smaller overlap, particularly considering that this is a rare disease. When multiple studies evaluated the same patient, one of two actions were taken: if all outcomes were present in a larger study, then the smaller studies within it were excluded; however, if a smaller study had better data on an outcome, i.e., more patients, longer follow-up, then the smaller study was retained and the larger study was excluded from the analysis of that particular variable. Follow-up studies were eligible only if they provided additional outcome data.

Data extraction and variable definitions

Data were extracted in three categories: study characteristics, patient characteristics, and outcomes. Study characteristics extracted included design, eligibility criteria, treatment duration, follow-up duration, sample size, location, time period, and number of study sites. Patient baseline characteristics included sex, age at study onset, age at treatment onset, age at diagnosis, functional skill score, proportion in wheelchairs, proportion requiring ventilators, 6MWT distance (meters), FVC (upright/sitting and supine), other respiratory function tests (MIP, MEP, FEV1, etc.), and health-related quality of life (various measures). Patient characteristics were extracted at the treatment arm level, not the study-level. Extracted outcomes included mortality, 6MWT (including longitudinal measures), FVC (including longitudinal measures), ventilator use, and ambulation status. For data presented in only graphs, such as FVC curves over time, information was extracted using the DigitizeIt software (version 15; Braunschweig, Germany).

Statistical analysis

We analyzed survival data by first converting data into events over person-time and modeling these using Poisson models. Given the paucity of data, we conducted single-

sample meta-analyses for treated and untreated arms and compared the resulting effect estimates. Continuous outcomes (6MWT and FVC) were modeled using fractional polynomial meta-analysis, which estimates the development of outcomes over time [12]. Both first-order and second-order fractional polynomial models were evaluated regarding their goodness of fit to the data. Dichotomous outcomes (ambulation and ventilator status) were reported as proportions at baseline and follow-up (which is not the cumulative incidence). The models for these outcomes considered differential follow-up durations and used study-specific intercepts and slopes in a random-effects meta-analysis model. For further details on these methods, please refer to the Web Appendix.

When modeling evidence bases that contained both comparative and non-comparative data, a two-step approach was used to combine these into a single analysis. In the first step, the outcome measure within the single-arm evidence was modeled using non-comparative meta-analysis (either the traditional non-comparative meta-analysis or non-comparative fractional polynomial meta-analysis). In the second step, the comparative data were analyzed using comparative modeling; however, rather than using non-informative priors, informative priors informed by the first step were used instead. Thus, data from the comparative and non-comparative studies were combined into a single analysis.

Meta-regression analysis was used to model the development of outcomes over time as a function of patient characteristics to explain between-study heterogeneity [13]. Four variables were assessed using meta-regression, including sex, disease duration, age, and disease severity, measured as the maximum value between the proportion of patients using wheelchairs and proportion of patients using ventilators. Since the meta-analysis was performed with study-level data, covariates that relate to continuously distributed patient characteristics were reduced to dichotomous variables to avoid any issues with the ecological fallacy [13]. All variables were measured at the study-level (i.e., not arm-specific). Therefore, percentage of males was the percentage of study participants that were male. The threshold values used to dichotomize the variables were as follows: ≥ 50 % males, >46 years of age, >12 years disease duration, and >35 disease severity score. The values were chosen to be whole numbers (with the exception of age) that were close to the median value. To identify the most appropriate model, the deviance information criterion (DIC) was used to compare competing models and curves were visually inspected. The DIC provides a measure of model fit that penalizes model in a manner similar to the Akaike Information Criterion (AIC) used in frequentist scenarios [14, 15].

All analyses were conducted in the OpenBUGS software package and R version 3.1.2 (Vienna, Austria).

Results

The systematic search identified 808 abstracts, and of these, 124 were selected for full-text review, as shown in the flow diagram of Fig. 1. A total of 22 publications pertaining to 19 studies were included. Two of these studies were comparative [7, 16], three studies were on the natural course of disease [9, 17, 18], and 14 were studies on alglucosidase alfa [11, 19–31]. The LOTS trial was the only randomized, controlled trial within the evidence base, and had a secondary paper pertaining to an extension study [7, 8]. Study and patient characteristics are presented in Table 2, and the list of included papers is presented in Table A2 of the Web Appendix, along with some study characteristics. The included studies were published between 2004 and end of 2015 with an average study duration of 45.7 months. The mean age was 46.0 years (SD 12.9 years), and there were 48.5 % males among trials reporting gender.

Exclusions for repeat-patients

The studies reported on 826 patients; however, once overlapping studies were considered, this was reduced to 438 unique patients. Geography played a major role in determining patient overlap. Studies including patients from countries unique to their study (Denmark, France, Greece, Japan, and Poland) were not considered at risk of

repeated patients. Five trials were deemed to have met the inclusion criteria and removed following evaluation of repeat-patients. Two German studies [32, 33] were included in the larger study by Strothotte and Regenry [29, 34]. The identification of overlap in Italian studies ultimately led to the removal of three further studies [35–37]. One study by Bembi et al. [21] was deemed to have overlap with the other Italian studies, but it had the best data on ambulation (largest reported sample size), and, thus, was removed from all but that outcome analysis. For studies conducted in The Netherlands, one study by Van Der Beek et al. [17] had seven patients overlapping with the LOTS trial [7]. Given that two-thirds of LOTS patients were randomized to treatment, the overlap within the no-treatment group is likely to be minimal and meets the 10 % criterion (7/88) that had been previously set. There was also overlap between the two studies by Van Der Beek et al. [17, 18]; however, the study authors explain that while 12 patients participated in both studies, the analysis in the later study was based only on new prospectively obtained data. Thus, both studies were included. Finally, 42 of the patients in the LOPOS study were also in the LOTS study. Again, the overlap between-study periods was negligible, so both populations were included [7, 9].

Mortality

Mortality was reported in most studies and included a total of 47 deaths. After removing studies with potential overlap with the study by Güngör et al., six studies remained [11, 16, 22, 24, 26, 38]. Analysis was performed using Poisson meta-analysis, where the number of deaths per person-year (PY) of follow-up was modeled. The fixed-effects model had the best fit, where alglucosidase alfa patients had nearly a five-fold lower mortality rate than untreated patients (rate ratio: 0.21; 95 % CrI: 0.11, 0.41). As most arms had no deaths, adjusting for potential effect-modifiers was inconclusive. The results of this meta-analysis are compared to results from the Güngör et al. [16] study in Fig. 2.

Forced vital capacity

FVC was reported in 11 studies (12 arms) with 298 patients providing data on treatment and 153 providing information on the natural course of the disease (Fig. 3) [7, 9, 11, 17, 23, 24, 27–30, 34, 38]. A single study compared alglucosidase alfa with untreated patients [7], two were single-arm studies in untreated patients [9, 24], and nine were single-arm studies of alglucosidase alfa [11, 23, 24, 27–30, 34, 38]. Follow-up time varied from 3 to 48 months. The best fitting models were the fixed and random-effects second-order polynomial with square-root

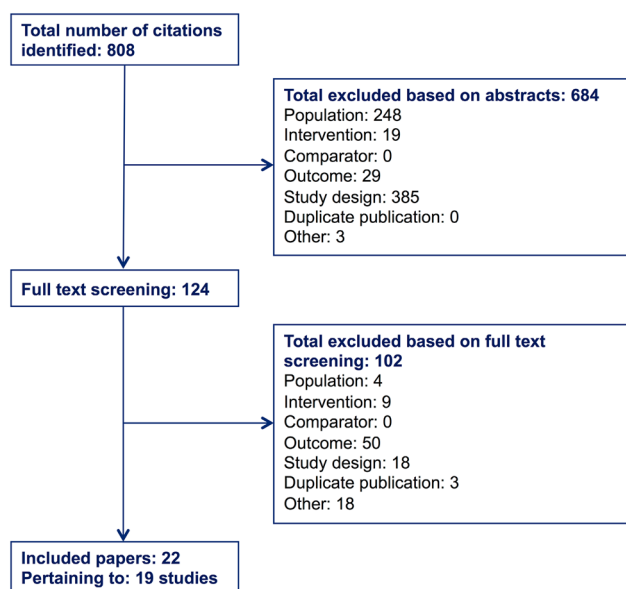


Fig. 1 Study flowchart

Table 2 Study patient characteristics

Primary author (year)	Treatment	N	Male (%)	Age at study onset (years)	Disease duration (years)	Proportion in wheelchairs (%)	Proportion requiring ventilators (%)	6MWT (M)	% FVC (upright/sitting position)
Adreassen et al. (2014) [19]	Alglucosidase alfa	4	3 (75)	48 (10.03)	2–11*	0 (0)	1 (25)	–	–
Angelimi et al. (2012) [38]	Alglucosidase alfa	74	33 (44.5)	43 (15.4)	14.7 (8.7)	7 (9.4)	27 (36.4)	320 (161)	65.2 (26.5)
Bembi et al. (2010) [21]	Alglucosidase alfa	24	14 (58.3)	–	–	9 (37.5)	13 (54.1)	264.8 (236.5)	–
De Vries et al. (2012) [23]	Alglucosidase alfa	71	36 (52)	–	9.3 (0.2, 31.2)†	27 (39.1)	25 (36.2)	–	68.3 (11.3, 106.9)†
Furusawa et al. (2012) [24]	Alglucosidase alfa	5	2 (40)	–	26 (4.5)	5 (100)	5 (100)	–	16.86 (16.79)
Gungor et al. (2013) [16]	Combined	283	134 (47.3)	48 (19, 81)†	9 (0, 32)†	37 (13)	42 (14.8)	–	–
Gungor et al. (2013) [16]	Alglucosidase alfa	204	100 (49)	47 (19, 73)†	11 (0.2, 33)†	26 (12.7)	31 (15.2)	–	–
Gungor et al. (2013) [16]	No treatment	79	34 (43)	51 (20, 81)†	12 (0, 32)†	11 (13.9)	11 (13.9)	–	–
Hagemans et al. (2006) [39] ^a	No treatment	52	21 (40)	48 (16)	13 (9)	24 (46.1)	19 (36.5)	–	–
Merk et al. (2009) [25]	Alglucosidase alfa	4	0 (0)	–	–	1 (25)	2 (50)	660**	–
NCS-LSD cohort study [11]	Alglucosidase alfa	62	37 (60)	46.5 (13.8)	16.8 (14.7)	10 (16)	25 (43.9)	246 (88 – 560)*	59.6 (10–130)*
Orlikowski et al. (2011) [22]	Alglucosidase alfa	5	2 (40)	47.8 (14.39)	23.4 (6.58)	3 (60)	5 (100)	–	–
Papadimas et al. (2011) [26]	Alglucosidase alfa	5	1 (20)	48.6 (13.93)	–	1 (20)	1 (20)	–	–
Patel et al. (2012) [27]	Alglucosidase alfa	3	1 (33.3)	–	–	0 (0)	0 (0)	–	87.3 (22.2)
Restel et al. (2014) [28]	Alglucosidase alfa	4	–	–	–	–	–	–	62.6**
Strothotte/regnery [29]	Alglucosidase alfa	44	24 (54.5)	48.9 (12.9)	–	8 (19.5)	16 (43.2)	341 (149,49)	69.6 (28.1)
Van Capelle et al. (2010) [30]	Alglucosidase alfa	5	3 (60)	–	–	0 (0)	1 (20)	456 (86,197)	81.54 (18,33)
Van Capelle et al. (2010b) [32]	Alglucosidase alfa	62	2 (66.6)	19.7 (10.9)	10 (12.1)	2 (66.6)	2 (66.6)	–	–
Van Der Beek et al. (2009) [18]	No treatment	16	6 (37.5)	–	–	0 (0)	4 (25)	–	–
Van Der Beek et al. (2012) [23]	Alglucosidase alfa	66	29 (44.6)	51.1 (38.3, 60.6) ^{††}	–	18 (27.6)	16 (24.6)	–	80.4**
Van Der Ploeg et al. (2010) [7]	Alglucosidase alfa	60	34 (57)	–	9 (6.3)	0 (0)	20 (33.3)	332.2 (126.7)	55.4 (14.4)
Van Der Ploeg et al. (2010) [7]	No treatment (placebo)	30	11 (37)	–	10.1 (8.4)	0 (0)	11 (36.6)	317.9 (132.3)	53 (15.7)
Van Der Ploeg et al. (2012) [8]	Alglucosidase alfa	60	34 (56.7)	–	9 (6.3)	0 (0)	20 (33.3)	362.7 (145.3)	56 (16)
Van Der Ploeg et al. (2012) [8]	No treatment (placebo)	30	11 (36.6)	–	10.1 (8.4)	0 (0)	11 (36.6)	312.7 (147.2)	51 (15)
Wokke et al. (2008) [9]	No treatment	61	22 (37.9)	43.8 (9.11)	14.7 (9.12)	–	12 (20.6)	–	66.9**

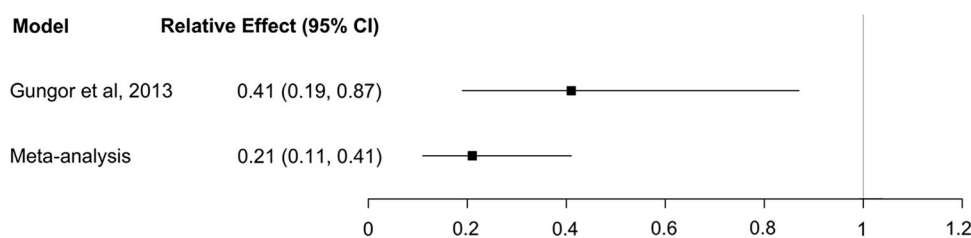
All data are mean (sd) unless specified

–: not reported

^a Sub study of Gungor et al. (2013)

* Data are range; † Data are median (range); ** Data are mean; †† Data are median (IQR)

Fig. 2 Comparison of estimated effects according to the meta-analysis and Güngör et al. [16] study



time ($P1 = 0.5$ and $P2 = 0.5$). Given the similar fit between both models, the simpler fixed-effects model was selected (Fig. 4). This model shows that on average, untreated patients declined by 2.3 % FVC after 12 months follow-up and by 6.2 % FVC after 4 years. Patients on alglucosidase alfa improved rapidly, showing an average increase of 1.4 % FVC after 2 months of treatment, and then gradually returned to baseline at approximately 36 months, followed by a slight decline thereafter. This subsequent decline is largely attributed to the trends seen in the NCS-LSD and Strothotte/Regnery cohorts, that both suggest a return to baseline over an extended period of time [29, 34]. The relative difference between the treated and untreated arms for % FVC grew over the study period, from 4.5 % FVC after 12 months to 6 % FVC after 4 years. Results from meta-regression did not improve in fit, nor did treatment effects appear to be influenced by them (suggesting little bias from the selected covariates).

Six-minute walk test

Eight studies, including 201 patients (171 on alglucosidase alfa), reported 6MWT results [7, 11, 19, 20, 25, 28, 29, 31, 34]. The raw data are presented in Fig. 3. Follow-up time varied from 3 to 75 months. One trial included both treated and untreated patients [7], while the others were single-arm studies evaluating alglucosidase alfa [11, 19, 20, 25, 28, 29, 31, 34]. Several flexible first- and second-order fractional polynomial meta-analyses were compared. Given that there was only a single comparative trial, a fixed-effects model combining comparative and non-comparative data was possible; however, random-effects models were found to have a much better fit, suggesting some heterogeneity between the various studies. Therefore, the selected model was a random-effects second-order polynomial, shown in Fig. 4. This model demonstrated that after 12 months, patients on alglucosidase alfa showed improvements in 6MWT that were, on average, approximately 43 m greater, even reaching 59 m during the observed period, compared to patients who are not on treatment. As Fig. 4 demonstrates, this analysis suggests that patients receiving alglucosidase alfa, on average, have the largest improvements over the first

20 months of treatment with a maintained benefit over the observed period.

Ambulation and ventilator status

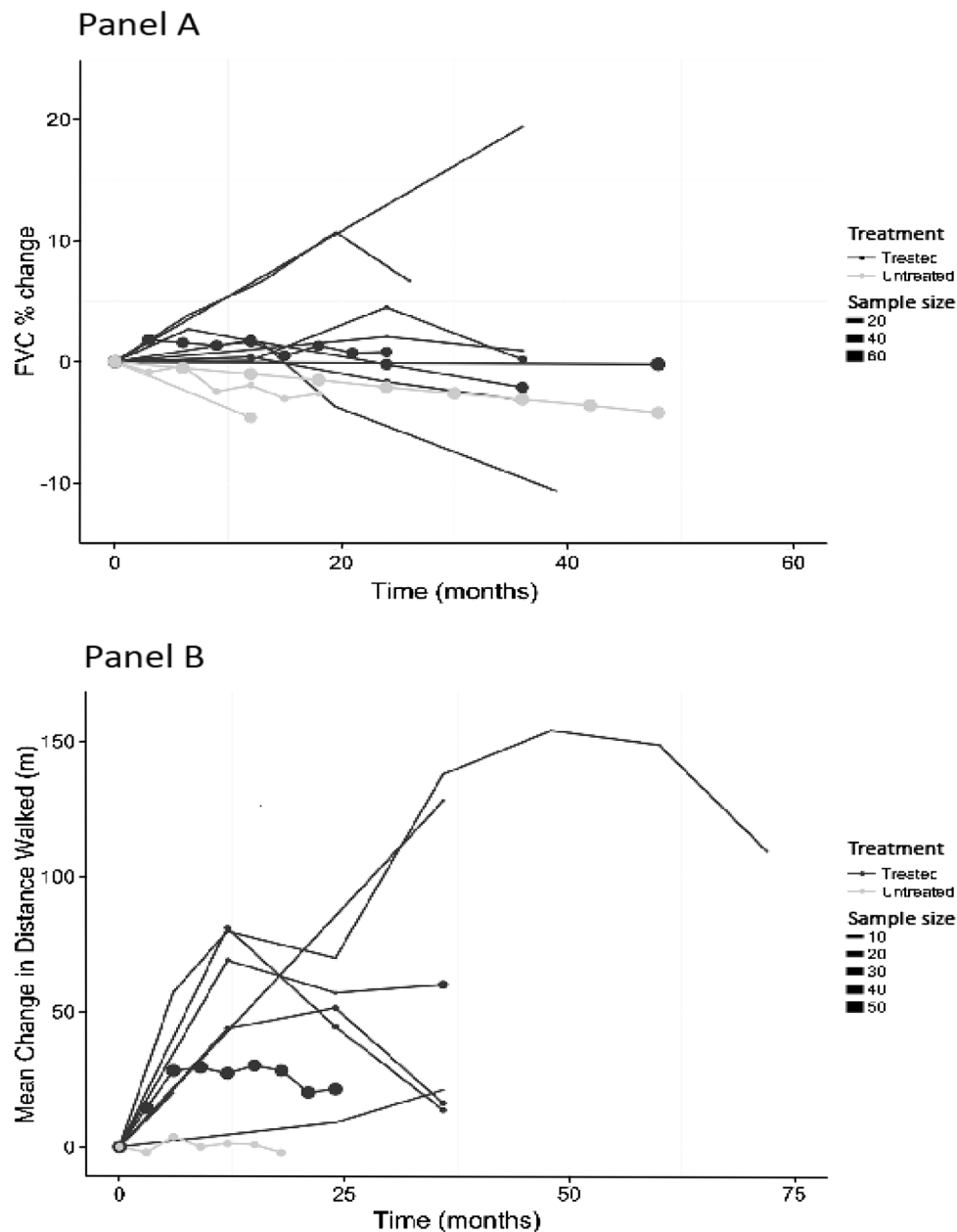
Ambulation status was reported in 12 studies [17, 18, 21–25, 27, 29–31, 39] and ventilator status was reported in 13 studies (Figure A1) [9, 11, 17, 18, 22, 24, 29–31, 38, 39]. As shown in Figures A2 and A3, the models for ambulation status and ventilator status were of limited utility given how wide the credible intervals about the slopes were due to the heterogeneity between the trials. Ambulation status improved over time for patients on alglucosidase alfa and was relatively constant for untreated patients. Similarly, the random-effects model showed that the proportion of patients on a ventilator increased over time for those not on treatment and was relatively constant for those on alglucosidase alfa.

Discussion

This systematic literature review (SLR) synthesizing the literature on the effects of alglucosidase alfa on LOPD patients builds upon our previous systematic review [10] in three ways. First, this study adds numerous new publications, including the large UK cohort (NCS-LSD), while also accounting for patient overlap between studies. Second, it uses fractional polynomial meta-analysis to provide further insights into the nature of the benefits of treatment. To this end, adjusting for repeat measures and different follow-up time reduced the heterogeneity in a way that allowed for the combination of these data. This allowed us to characterize the progression of key clinical outcomes over time while on or off treatment. Finally, it allows for trends to be compared between alglucosidase alfa-treated and untreated patients over time, allowing for more precise conclusions regarding the benefits of treatment.

With respect to heterogeneity, we also investigated its sources. For many models, the random-effects were favored suggesting heterogeneity between the studies. This was entirely expected given the propensity of observational studies, including case series. Among the potential effect-

Fig. 3 Observed change in % FVC and 6MWT over time for treated and untreated arms. Each *colored line* represents a single study. The size of the *circles* represents the approximate sample sizes at each time point. **a** The absolute change in percent predicted FVC over time among studies, including patients on (*black lines*) and not on (*grey lines*) treatment. **b** The mean change (in meters) over time in distance walked among studies, including patients on (*black lines*) and not on (*grey lines*) treatment



modifiers identified at the outset of the study, none were found to explain a large proportion of the heterogeneity. Age, sex, and disease severity all explained some of the heterogeneity, with better estimates towards better results for less severe disease status and younger patients. This hints that earlier diagnosis and treatment initiation is beneficial, but the evidence for this is of low quality.

Given the complexity of the analytical methods for this study, only efficacy measures were used (i.e., no safety measures were considered for this analysis). An important new finding of our study is that alglucosidase alfa revealed strong effects for survival when compared to untreated patients, which was also reflected in improvement and/or

stabilization in the 6MWT and FVC. Integrating survival results across all selected studies led to an estimated hazard ratio that was lower than that reported in the Güngör et al. [16] study, 0.21 versus 0.41, respectively [16]. However, the difference between the risks of mortality estimates between the studies only borders on significance.

Only a single trial, the LOTS study and extension compared changes in the 6MWT over time between treated and untreated patients [7, 8]. Results from our comparative analysis showed trends and differences in trends over time similar to those in the LOTS trial. However, by combining results across the evidence base for the 6MWT among treated patients, the model suggests that improvements are

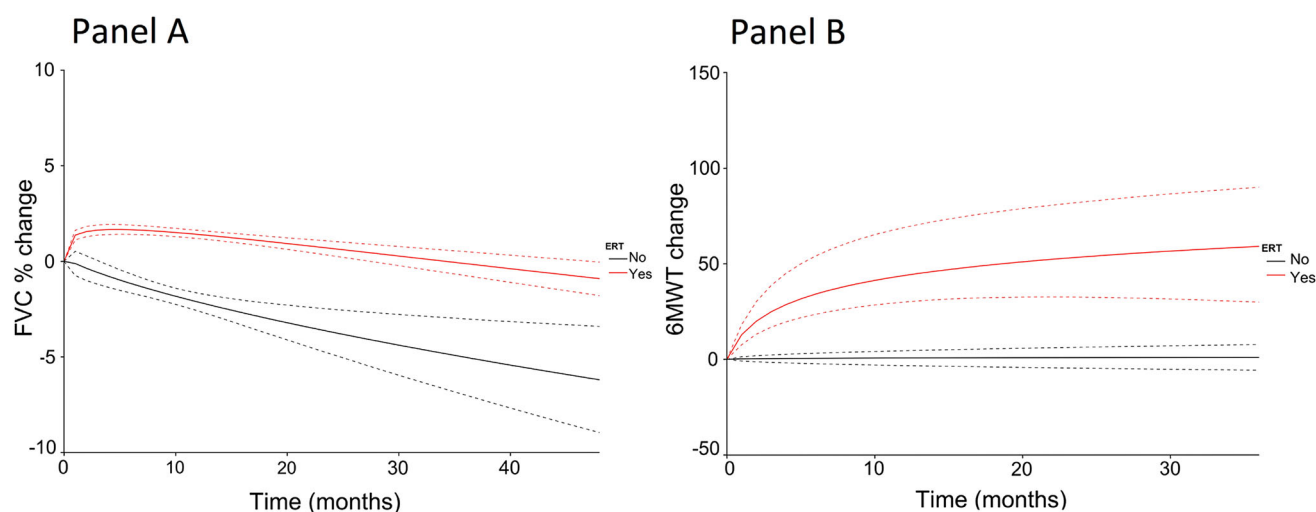


Fig. 4 Modeled changes in % FVC and 6MWT over time for treated and untreated arms. **a** The modeled % FVC changes from baseline, combined fixed-effects second-order polynomial meta-analysis. **b** The modeled 6MWT changes from baseline, non-comparative random-

effects second-order polynomial meta-analysis. The *full lines* represent the modeled outcomes over time. The *dashed lines* of corresponding color represent the 95 % credible intervals for the modeled outcomes

by some means larger than those reported in the LOTS trial. Moreover, while there was heterogeneity in the shape of the progression in 6MWT results between studies, our aggregate estimate proposes a rapid enhancement followed by stabilization over time, suggesting that an earlier initiation of treatment could ensure the maximization of muscle endurance. However, through the meta-regression analysis, there was a little evidence of differences in the effect according to the baseline ambulatory capacity.

Finally, % FVC was compared between treated and untreated patients over time in the LOTS trial only. Results from our analyses differed slightly from those of the LOTS trial in that the initial improvement in % FVC seen in the treated arm was not sustained over time as demonstrated by the LOTS extension study over 104 weeks. Nonetheless, the differences in % FVC between treated and untreated patients grew over time over the entire course of the analysis period. Given that the average % FVC at study entry was 61 %, reflecting moderate restrictive lung disease, a further decrease of 6.2 % over a 4-year period in untreated patients can be considered as having a clinically relevant impact, especially given the disease-stabilizing effect seen with alglucosidase alfa treatment over that time period [40, 41].

This study has several strengths, including its comprehensive evidence base as well as methods that allow describing trends in outcomes over time. Another important strength is that potential effect-modifiers were investigated using meta-regression, and efforts were put forth to ensure that there were no negligible repeat-patients across studies. This study is also subject to several limitations. First, the evidence base utilized in this analysis was sparse, only

reporting on 438 patients. This was expected given how rare LOPD is. Second, there was a lack of comparative studies within the evidence base. The consequences of this were that: (1) it was not possible to model survival over time using the flexible fractional polynomial methods; (2) it did not allow for the use of random-effects modeling for certain models; and (3) it required that curves be fit individually for each treatment rather than within a single comparative analysis. The fitting of individual curves rather than the comparative model is an important limitation, because it means that results from these analyses (those not including comparative evidence) should principally be used to infer on trends over time for the individual treatment arms and less for inferences on the differences over time. Third, and finally, given the meta-analytic design of the study and that studies came from a variety of settings and designs, results are susceptible to selection bias. Although we did use meta-regression on observed potential confounders, there are many unobserved variables that may be confounders to the relationships modeled in this study.

In conclusion, our study used a variety of analytic methods to evaluate the evidence of treating LOPD using enzyme replacement therapy with alglucosidase alfa. These analyses show that treatment with alglucosidase alfa reduces the risk of mortality to close to a fifth of that experienced in the natural course of LOPD. Furthermore, we found that on average, patients on treatment demonstrated improved % FVC within the first few months, followed by a gradual return to baseline. This is in contrast to the consistent decline and earlier death seen in untreated patients over time and the difference in % FVC between treated and untreated patients grows with time. Our

analysis also demonstrated improvements in the 6MWT and found that the greatest improvements tend to occur quickly and are sustained over time. Thus, early initiation of treatment could also potentially optimize patient health over time by maintaining patients at a higher clinical status.

Compliance with ethical standards

Conflict of interest BS has received research support, honoraria, and travel funding from Sanofi Genzyme during the past 5 years. Dr. Schoser is member of the Genzyme Pompe Disease Global Advisory Board. Dr. Schoser received honoraria and travel funding as member of the Global Advisory Boards from Biomarin Pharmaceutical, Amicus Therapeutics, and Audentes Therapeutics. AS is an employee of Sanofi Genzyme and stockholder of Sanofi. SK is an employee of Redwood Outcomes, a research consulting firm owned by Precision for Medicine and, holds no Sanofi stock. AH is an employee of Sanofi Genzyme and stockholder of Sanofi. JJ is an employee of Redwood Outcomes, a research consulting firm owned by Precision for Medicine and, holds no Sanofi stock. KC is an employee of Redwood Outcomes, a research consulting firm owned by Precision for Medicine, and holds no Sanofi stock. MK was an employee of Redwood Outcomes, a research consulting firm owned by Precision for Medicine, and holds no Sanofi stock. In the last 5 years, AT has received, from Sanofi Genzyme, travel grants and honoraria for teaching courses, lectures and, being also a member of the Genzyme Pompe Disease Global Advisory Board for his participation to the related meetings. Prof. Toscano has also received travel grants and honoraria from Biomarin Pharmaceuticals for his participation to the Biomarin Pompe Advisory Board meetings.

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