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Research Article

Enzyme replacement therapy compared with best supportive care for the treatment of Pompe Disease: a systematic review and network meta-analysis

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Abstract

Background: Late-onset Pompe disease is a rare inherited genetic condition that causes progressive muscle dysfunction and damage. As the disease advances, the progressive weakening of respiratory muscles significantly increases the risk of respiratory failure, which is a major contributor to premature mortality. Enzyme replacement therapy is the primary treatment for Pompe disease.

Objective: To investigate the clinical impact of enzyme replacement therapies for the treatment and management of late-onset Pompe disease and establish the relative effectiveness of enzyme replacement therapy compared to best supportive care (in the absence of enzyme replacement therapy).

Methods: A systematic review and network meta-analysis of published evidence on the clinical effectiveness of enzyme replacement therapy and best supportive care was undertaken. Comprehensive bibliographic database searches were conducted up to May 2024 to identify randomised controlled trials or any other prospective enzyme replacement therapy studies in patients with Pompe disease. Network meta-analyses of randomised controlled trials were undertaken to estimate indirect treatment effects for forced vital capacity % predicted and the 6-minute walk test. Other studies were summarised using narrative synthesis.

Results: The review included 60 studies: 38 on enzyme replacement therapy and 22 on best supportive care. Enzyme replacement therapy studies comprised 3 randomised controlled trials, 3 randomised controlled trial extensions, 7 registry studies and 25 single-group prospective studies. Two randomised controlled trials had a high risk of bias. Best supportive care studies included 14 longitudinal and 8 cross-sectional studies.

In the network meta-analyses, after approximately 1 year, enzyme replacement therapy-naive patients showed significant 6-minute walk test improvements versus placebo: ~25 m with alglucosidase alfa and ~54 m with avalglucosidase alfa. No significant differences were found for forced vital capacity % predicted or comparisons with cipaglucosidase alfa, although very few enzyme replacement therapy-naive patients taking cipaglucosidase alfa were available for inclusion in the analyses. Intra-enzyme replacement therapy comparisons showed a significant 6-minute walk test advantage for avalglucosidase alfa. However, a sensitivity analysis adjusting for skewed data revealed no significant differences.

Long-term enzyme replacement therapy effectiveness was assessed in single-group studies, showing initial gains maintained for 1–3 years, followed by gradual 10- to 15-year declines in 6-minute walk test and forced vital capacity % predicted. However, small sample sizes and missing data introduce uncertainty.

Long-term evidence on best supportive care is limited, with most of the evidence focused on characterising basic demographic information and support needs. A small number of studies reported declines in forced vital capacity %

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predicted. Formal comparisons with long-term enzyme replacement therapy studies were not possible, but declines appear to be similarly gradual.
Conclusions: The network meta-analyses shows enzyme replacement therapy modestly improves 6-minute walk test and forced vital capacity % predicted after 1 year versus placebo in enzyme replacement therapy-naive patients. However, there is limited evidence to suggest meaningful differences in outcomes between alglucosidase alfa, avalglucosidase alfa and cipaglucosidase alfa with miglustat. Observational data suggest declines beyond 2–3 years, lasting up to 15 years. Long-term comparative effectiveness remains uncertain, as does enzyme replacement therapy's impact on disease progression and supportive care needs.
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Background

Pompe disease, also known as glycogen disease type II, is a rare autosomal recessive disorder classified as both a glycogen and lysosomal storage disorder. It is caused by pathogenic variants in the GAA gene, resulting in a partial or complete deficiency of the enzyme acid α-glucosidase (GAA).[1] The GAA enzyme is responsible for breaking down glycogen, a complex sugar molecule, into simpler forms in the body's cells, and this results in an accumulation of glycogen in all tissues, especially skeletal, and smooth muscles.[2,3] This buildup triggers a series of disruptions in cell behaviour, ultimately causing muscle dysfunction and damage, along with broader systemic effects.[2,3]

While Pompe disease presents as a spectrum of phenotypes, it is typically categorised into two forms: infantile-onset Pompe disease (IOPD)[4] and late- (juvenile/adult) onset Pompe disease (LOPD).[5,6] IOPD is the most severe and common form of Pompe disease, typically presenting within the first few months of life and untreated is typically fatal within the first year due to cardiopulmonary failure.[4] LOPD typically manifests later in life and is often diagnosed well into adulthood. It is characterised by slower disease progression (compared to IOPD) and predominant muscular–skeletal involvement, with limited or no cardiac involvement.[5,6] Most individuals with LOPD experience a gradual, progressive decline in muscle function, typically beginning in proximal muscles and eventually affecting ventilatory function.[2,3] As the disease advances, many patients require mobility aids and ventilatory support. The progressive weakening of respiratory muscles significantly increases the risk of respiratory failure, which is a major contributor to premature mortality.[7]

Individuals with LOPD face significant challenges that severely impact their daily lives. Progressive muscle and respiratory damage profoundly affect multiple aspects of health-related quality of life (HRQoL), including physical function, general health, vitality and social well-being.[7–10] As the disease advances, these limitations increase, contributing to a heightened risk of depression and anxiety.[7–10]

The primary treatment for LOPD is enzyme replacement therapy (ERT) which provides an exogenous source of the GAA enzyme to reduce and clear glycogen buildup in cells. This can lead to some initial functional improvement and then a slowing of the rate of progression of disease.[11,12] Eligibility for ERT treatment is typically based on specific criteria, including a confirmed diagnosis, symptomatic presentation of the disease preserved skeletal and respiratory muscle function, and the absence of other advanced, life-threatening conditions. In addition to ERT, patients will receive comprehensive supportive treatment which may include respiratory support, mobility aids, physiotherapy and/or dietary interventions.[1] Managing LOPD effectively often requires a multidisciplinary approach, involving specialists such as pulmonologists, and physical therapists to manage the different symptoms associated with the disease.

However, ERT is associated with exceptionally high drug acquisition costs which exceed £250,000 per patient annually. Thus, while ERTs have been long established in practice, uncertainties remain regarding their value for money compared to best supportive care (BSC) in the absence of ERT treatment. This issue is particularly relevant in the UK, where alglucosidase alfa was introduced in 2006 by the National Specialised Commissioning Advisory Group as part of the Lysosomal Storage Disorders Service.[13–15] This occurred before the National Institute for Health and Care Excellence (NICE) established formal processes for evaluating highly specialised technologies, meaning alglucosidase alfa has never undergone a formal NICE assessment.[16] As a result, recent NICE evaluations of avalglucosidase alfa and cipaglucosidase alfa with miglustat have not considered BSC as a comparator. Consequently, the clinical effectiveness and cost-effectiveness of ERT relative to BSC remain uncertain.

This paper presents a systematic review and network meta-analysis (NMA) of all published evidence on the

clinical effectiveness of ERT and BSC. It forms part of a research project funded by the National Institute for Health and Care Research (NIHR; Programme number NIHR153779, Project number NIHR161219) aimed at evaluating the clinical and cost-effectiveness of ERT for treating LOPD. Other aspects of the project include an economic analysis assessing the cost-effectiveness of ERT and policy-focused papers examining the UK's approach to evaluating new healthcare technologies. These are published elsewhere. The review is registered on PROSPERO (CRD42024527306), with the full protocol available online through the NIHR.

Methods

This review was conducted in line with the Centre for Reviews and Dissemination's guidance on undertaking systematic reviews. Results are reported in accordance with updated 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17]

Review methods

Literature searches

Literature searches were undertaken to identify studies evaluating the effectiveness of ERT and BSC for the treatment and management of LOPD. An Information Specialist (HF), in collaboration with the review team, designed an initial search strategy in Ovid MEDLINE. This strategy incorporated subject headings and free-text terms related to Pompe disease. It was then adapted as needed for other databases and sources. No restrictions were placed on study design for any searches. The searches were limited to studies published in English from the year 2000 onward. A second Information Specialist conducted a peer review of the MEDLINE strategy, making adjustments and corrections as required.

The initial bibliographic searches were conducted on 12 December 2023, and later updated on 29 May 2024. The databases searched included MEDLINE (Ovid), EMBASE (Ovid), KSR Evidence (Ovid), EconLit (Ovid), NHS Economic Evaluations Database (NHS EED) (CRD), Cochrane Database of Systematic Reviews (Wiley), Cochrane Central Register of Controlled Trials (Wiley) and the International HTA database (https://database.inahta.org/).

In addition, sources for unpublished, ongoing, or completed studies were searched, including ClinicalTrials.gov, the European Union Clinical Trials Register and the World Health Organization International Clinical Trials Registry Platform. All searches were initially conducted on 12 December 2023, with an update on 29 May 2024. References were deduplicated using EndNote 21 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA]. Detailed search strategies for all sources are provided in *Appendix 1*.

Inclusion and exclusion criteria

Population: The population of interest consisted of juveniles or adults with LOPD. Subgroups were defined based on whether prior treatment with ERT had been received.

Interventions: Studies evaluating the clinical effectiveness of ERT, administered at their UK-licensed doses, for the treatment and management of LOPD were included in the review. The ERT options considered were:

- alglucosidase alfa
- avalglucosidase alfa
- cipaglucosidase alfa with miglustat.

Comparators: Eligible comparator or BSC therapies including studies evaluating one or more of the following:

- respiratory support (supplemental oxygen)
- ambulatory support
- physiotherapy
- dietary treatment.

These therapies had to be evaluated in the absence of concomitant ERT. Studies involving non-ERT patients that did not assess a specific comparator therapy (or combination of therapies) were also considered eligible, provided that some patients received at least one of the listed outcomes.

Outcomes: Outcomes considered covered a range of end points relevant to LOPD, including motor and respiratory function, muscle strength and patient-reported outcomes.

To be included, studies had to report one or more of the following outcomes:

- change in motor function [assessed using the 6-minute walk test (6MWT)]
- change in respiratory function [assessed using forced vital capacity (FVC) % predicted, slow vital capacity, or maximal inspiratory pressure (MIP)]
- change in muscular function [assessed using manual muscle testing and the Gait, Stairs, Gowers' manoeuvre, and Chair assessments, Medical Research Council (MRC) grading scale, quantitative muscle testing (QMT), Quick Motor Function Test (QMTF)]
- HRQoL

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- adverse effects from treatments and treatment discontinuation due to adverse events
- ambulation and ventilator status/support, including time on ventilator
- mortality

Study design: For studies of ERTs: any randomised trial or extended follow-up study of a randomised controlled trial (RCT) cohort was considered eligible. Prospective single-group studies, including registry studies, were also eligible, provided they included 10 or more LOPD patients and reported results for individual ERTs (i.e. they must not report results for only a mixed ERT group).

Evidence for BSC therapies was also sought from clinical trials as well as from observational studies with 10 or more patients.

Study selection

Titles and abstracts of all identified records were screened independently by two researchers (MC and CUC). Full paper publications were then obtained for potentially relevant studies. Two researchers (MC and CUC) independently assessed full papers for relevance against the inclusion criteria. Any disagreements were resolved through discussion and, when necessary, consultation with a third reviewer.

Data extraction

Data were extracted by one reviewer and independently checked by a second reviewer. Discrepancies were resolved by discussion, with the involvement of a third reviewer where necessary. Data from the identified studies were recorded in a Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) spreadsheet and a Microsoft Word® (Microsoft Corporation, Redmond, WA, USA) document. For studies with multiple publications, the data were consolidated and presented as a single study. The most recent or most comprehensive publication was used when the possibility of overlapping populations could not be ruled out.

Individual participant data

Study investigators from eligible RCTs were invited to supply anonymised individual patient data (IPD) for inclusion in the IPD meta-analysis. Authors or sponsors of the eligible RCTs were contacted either directly or via the data-sharing platform Vivli, Inc, per the stated data-sharing agreement.

Critical appraisal

Risk of bias was assessed in identified RCTs using the Cochrane Risk of Bias 2.0 tool.[18] Judgements were made based on published papers and associated supplementary files, together with information from European Medicines Agency (EMA) regulatory documents.

Methods of synthesis and statistical analysis

The identified RCT evidence allowed an indirect comparison of all three ERT treatments and BSC using alglucosidase alfa as a common comparator; see *Figure 1* for a depiction of the network diagram. Non-comparative evidence was not included in the statistical synthesis due to the high

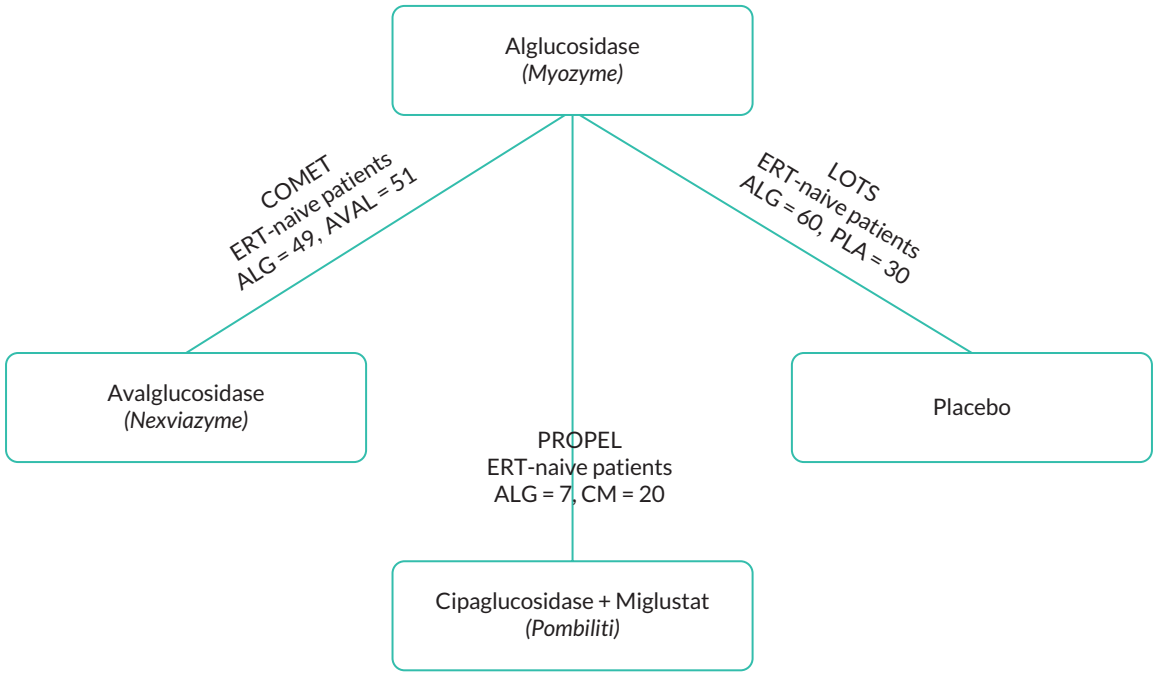

FIGURE 1 Network meta-analyses diagram. ALG, alglucosidase alfa; AVAL, avalglucosidase alfa; PLA, placebo.

levels of uncertainty associated with incorporating single-arm evidence into a NMA.

The NMAs were performed for the outcomes FVC % predicted and 6-minute walk distance (6MWD). For all other outcomes, there were insufficient data to perform a full NMA. The primary analysis focused on outcomes at 49/52 weeks (or the closest available time point) and was conducted in the ERT-naive population using a random effects estimator. Sensitivity analyses were also conducted using data cut-offs of 12/13 weeks, 24/26 weeks, 37/38 weeks, 49/52 weeks and the last follow-up (LFU) time for all the studies (week 78 in the LOTS trial, week 49 in the COMET trial and week 52 in the PROPEL trial). Synthesis of outcomes in an ERT-experienced population was not possible as only the PROPEL trial reported outcomes in this population.

Following data extraction, an outlier in 6MWD at week 49 of the COMET trial was identified, potentially distorting the mean difference between avalglucosidase alfa and alglucosidase alfa in favour of avalglucosidase alfa (see *Appendix 2*, *Table 3*). The variation in 6MWD changes within the alglucosidase alfa group (−394.0 to 193.0 m) suggests that at least one patient experienced a significant decline, which appears to have skewed the mean 6MWD for alglucosidase alfa at week 49. This distortion is further supported by the considerable gap between the mean and median values for alglucosidase alfa (−1.79 m vs. 16.0 m). To adjust for this, a sensitivity analysis was conducted which carried forward the COMET week 37 6MWD alglucosidase alfa result, to week 49. This approach was used because the week 37 mean 6MWD result (15.4 m) was very similar to the week 49 median (16 m).

The NMA was performed using a Bayesian Markov Chain Monte Carlo approach in R [version 4.2.3; The R Foundation for Statistical Computing, Vienna, Austria, R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2023. URL: www.R-project.org/ (accessed 14 February 2025)] with the rjags package.[19] The code was based on the NICE Decision Support Unit's Technical Support Document 2.[20] After a burn-in of 5000 iterations, 3 chains were run for 500,000 iterations with a thinning interval of 20. Convergence was assessed through visual inspection of trace plots and the Brooks–Gelman–Rubin diagnostic. Estimated relative treatment effects were reported as means and 95% credible intervals (CrI) from their posterior distributions. The R code is provided in *Appendix 3*.

Both fixed- and random-effects models were assessed, and between-trial heterogeneity was evaluated using the between-study standard deviation. Vague uninformative priors were used both relative treatment effects and between trial variances. No inconsistency analysis was possible, as no loops were present in the network.

Stakeholder involvement

An advisory group was established that included representation from the UK Pompe Support Network, people with lived experience of LOPD and UK-based clinical academics (see *Appendix 4* for a list of members). The Advisory Focus Group's role was to fill the gaps in our understanding of the topic and to help bridge the gap between the research team and the LOPD patient community. Consultation with the advisory group aimed to ensure that stakeholder perspectives were properly considered and that our work is both relevant to the LOPD community and an accurate reflection of the impact of LOPD.

The advisory focus group met three times during the project. The first two meetings provided the research team with a better understanding of life with LOPD and contextualised the available research within the experiences of the LOPD patient community. The third meeting, held towards the end of the project, focused on discussing and interpreting the findings of the research. Additionally, input from two content experts was incorporated during protocol and final manuscript development.

A Guidance for Reporting Involvement of Patients and the Public 2 (GRIPP2) reporting checklist is reported in *Appendix 5*.

Results

Search results

The results of the study selection process and reasons for exclusion are presented in the PRISMA flow chart (*Figure 2*). A total of 4286 titles and abstracts were identified following deduplication of the searches, and 237 full texts were retrieved for screening. Fifty-nine studies (encompassing 127 unique records) were identified as eligible for inclusion in the review. This included: 3 RCTs (LOTS,[12] PROPEL[21] and COMET[22]), 3 RCT extension studies,[23–25] 7 Pompe disease registry studies,[26–32] 25 single-group prospective studies[10,11,33–55] and 21 natural history studies.[30,56–76] A registry study had some evidence relating to natural history patients.[30] The process of identifying and selecting records is presented in the PRISMA flow chart (see *Figure 2*).

Study details and baseline characteristics

The study and baseline characteristics of participants included in the three RCTs are summarised in *Appendix 2*,

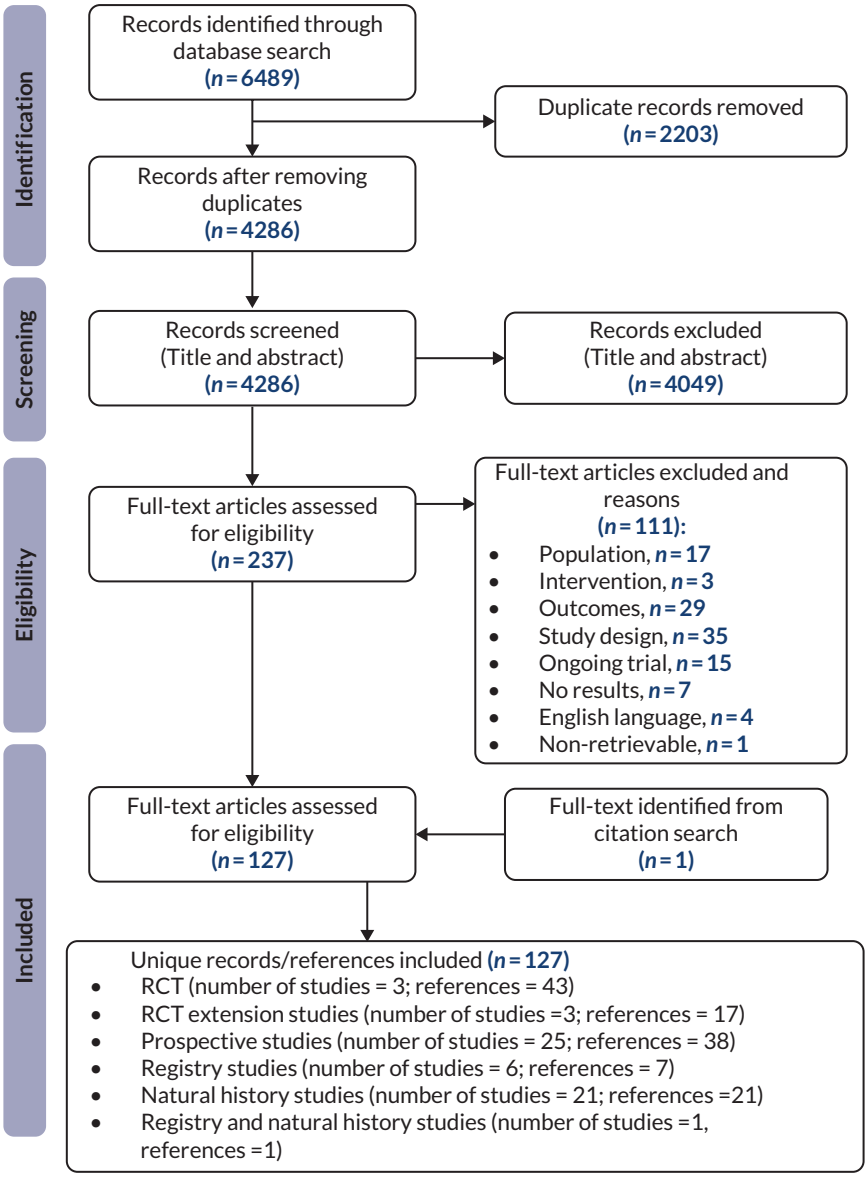

FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

Table 2. The LOTS[12] RCT evaluated the safety and efficacy of alglucosidase alfa compared to placebo plus BSC and was sponsored by Sanofi. The COMET[22] and PROPEL[77] RCTs assessed the safety and efficacy of avalglucosidase alfa and cipaglucosidase alfa with miglustat, respectively, using alglucosidase alfa as a comparator. The COMET trial was sponsored by Sanofi, while the PROPEL trial was sponsored by Amicus Therapeutics. Across the three trials, the mean participant age ranged from 44 to 48 years. At baseline, 43% of LOTS participants and 23% of PROPEL participants used a walking aid (baseline data were not reported for COMET). Previous use of ERT varied across studies: LOTS and COMET included only ERT-naive patients, whereas PROPEL primarily enrolled ERT-experienced patients. Baseline 6MWD ranged from a mean of 327.4 m to 388.9 m, while mean FVC % predicted ranged between 54.6% and 70.4%.

Of the seven registry studies, three analysed data from Sanofi's international Pompe Registry cohort (*N* = 396–1390),[26–28] three focused on the French Pompe disease registry (*N* = 29–177)[29–31] and one examined the Spanish Pompe registry (*N* = 113) (see *Appendix 6*, *Table 8*).[32] The largest study was reported only as a conference abstract.[28] Mean ages at ERT initiation ranged from 45 to 56 years, except in the Spanish registry study, which included a younger cohort (mean age 29 years). Follow-up durations varied from 1 to 10 years.

All other prospective studies included in the review were single-group studies evaluating the effectiveness of ERT. None directly compared an ERT with any specific comparator including any type of BSC, although some compared ERT-treated patients with those not receiving ERT. Sample sizes ranged from 11 to 209 patients (see *Appendix 6*, *Table 11*). Eleven studies included 30 or fewer patients, while 6 had 100 or more. However, the number of patients analysed was often smaller than the number recruited, as some were unable to complete assessments such as the 6MWD. Two studies were reported only as conference abstracts.[38,43] All studies investigated alglucosidase alfa, except for the NEO1/NEO-EXT study on avalglucosidase alfa[54] and the ATB200-02 study on cipaglucosidase alfa with miglustat.[55] Most studies were conducted in Italy, Germany, or the Netherlands. Five studies[36,37,41,51,78] reported results for paediatric cohorts or subgroups (mean age range: 6–12 years), while the remaining studies focused on adults (mean age range: 43–53 years). One small study included only ERT-experienced patients,[37] who had on average been receiving treatment for approximately 9 years at study entry.

There was substantial variation between studies in the proportion of patients requiring a wheelchair (range 0–90%) or respiratory support at baseline (range 0–90%). Follow-up durations ranged from 6 months to 15 years, with most studies following patients for between 2 and 5 years.

Individual patient data received from eligible studies

Individual patient data were sought from the three identified RCTs: PROPEL, LOTS and COMET. However, no IPD were provided for any of the studies. Amicus Therapeutics was contacted regarding sharing data from the PROPEL trial. In e-mail correspondence, Amicus Therapeutics representatives indicated they were working on a process and platform to make these data available but subsequently failed to respond to further e-mail contacts. Access to data from the LOTS and COMET trials was sought from the sponsor Sanofi via the data-sharing platform Vivli. Sanofi declined these requests, stating in their response that they did not consider the proposed research to be in the best interest of patients or the patient community. In the absence of IPD from the sponsors of the RCTs, we digitised the mean difference plots of the outcomes (FVC % predicted and 6MWD) using the PlotDigitzer website (https://plotdigitizer.com/) to obtain estimates of the mean differences at 12/13 weeks, 24/25 weeks, 36/38 weeks and 49/52 weeks (see *Appendix 7*).

Risk-of-bias assessment

The risk-of-bias assessment for each of the RCTs is presented in *Appendix 8*, *Table 17*. The COMET trial was judged to have a low overall risk of bias, whereas the LOTS and PROPEL trials were deemed to have a high risk of bias. Both LOTS and PROPEL received high-risk judgements for the 'bias in the selection of the reported result' domain, as neither trial reported results for all prespecified analyses, as noted in the respective EMA reports.[79,80]

Another key quality issue identified was the reporting of results using only mean values in published reports. Data from regulatory documents revealed that the 6MWD results were skewed by outliers, leading to substantial discrepancies between mean and median values. Reporting only means in the presence of outliers can misrepresent efficacy data. For example, in the COMET trial, the mean change in 6MWD from baseline to week 49 for the alglucosidase alfa arm was −1.7 m, while the median was 16.0 m.[81] Similarly, in the LOTS trial, the mean change in 6MWD from baseline to week 78 for the alglucosidase alfa arm was 26.1 m, whereas the median was 15.0 m.[82]

Randomised controlled trial evidence

Results from the primary analysis are summarised in *Table 1*, while findings from the sensitivity and additional analyses are provided in *Appendix 9*.

In the primary analysis of FVC % predicted at 49/52 weeks, all three ERTs demonstrated numerical superiority over placebo (BSC). However, none achieved statistical significance in estimated mean differences (see *Table 1* and *Figures 3* and *4*). In contrast, in the primary analysis of 6MWD, both alglucosidase alfa (~25 m) and avalglucosidase alfa (~54 m) showed statistically significant improvements over placebo. Cipaglucosidase alfa with miglustat also exhibited numerical superiority but did not reach statistical significance. The wide CrIs for this comparison reflect the limited number of ERT-naive patients in the PROPEL trial.

Analysis of additional time points revealed a consistent pattern (see *Appendix 9*, *Tables 20* and *21*), with no statistically significant differences in FVC % predicted between any ERT and placebo at any time point. For 6MWD, alglucosidase alfa showed statistically significant improvements over placebo from week 12/13 onward, while avalglucosidase alfa demonstrated significant differences starting at week 24/26, with sustained effects at later time points. Cipaglucosidase alfa with miglustat exhibited numerical superiority throughout but did not reach statistical significance at any time point.

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Intra-ERT comparisons revealed a numerical difference between avalglucosidase alfa and alglucosidase alfa at 49/52 weeks for both FVC % predicted and 6MWD, with the latter showing a significant numerical difference. Sensitivity analyses at other time points, including those at 49/52 weeks using imputed values from the COMET trial, similarly did not show statistically significant differences for either outcome. The sensitivity analysis results (see *Appendix 6*, *Table 12*) indicated a smaller numerical difference between avalglucosidase alfa and alglucosidase alfa (mean difference 12.43 m, 95% CrI −13.17 to 38.07 vs. 28.87 m, 95% CrI 1.74 to 55.66).

Cipaglucosidase alfa with miglustat showed numerical inferiority compared to avalglucosidase alfa for both outcomes across all time points and sensitivity analyses (see *Appendix 9*, *Tables 20* and *21*). However, these differences were not statistically significant, and CrIs were wide. When compared to alglucosidase alfa, cipaglucosidase alfa with miglustat also demonstrated numerical inferiority for both outcomes in the primary and sensitivity analyses, although the differences were small and the CrIs wide. This pattern of numerical inferiority was consistent across all time points, except for week 24/26 for 6MWD. Differences in FVC % predicted were inconsistent: weeks 12/13 and 24/26 favoured alglucosidase alfa, while the week 37/38 analysis favoured cipaglucosidase alfa with miglustat. At all time points and for both outcomes, the differences between alglucosidase alfa and cipaglucosidase alfa with miglustat were not statistically significant.

A class-based analysis using pooled evidence from ERTs combined showed a numerical superiority over placebo for both 6MWD and FVC % predicted for all the time points (see *Appendix 9*, *Table 22*). Differences were, however, not statistically significant in the primary random-effects model.

Evidence in the ERT-experienced population was limited to a subgroup from the PROPEL trial, which included participants who had received ERT for at least 2 years. Results from this subgroup favoured cipaglucosidase alfa with miglustat, showing statistically significant differences in both 6MWD and FVC % predicted, with a mean difference of 16.8 m (95% CrI 0.2 to 33.3) and 3.5 (95% CrI 1.0 to 6.0), respectively (see *Appendix 2*, *Table 4*).

Randomised controlled trial extension studies

Each of the three RCTs had open-label extension studies in which all patients received the study drug. PROPEL was extended by 52 weeks,[23] LOTS by 26 weeks (with 2 weeks follow-up for a subset of US patients),[24] and COMET by

TABLE 1 Relative treatment effects of FVC and 6MWD (random-effect NMA), primary analysis (49/52 weeks of follow-up for all RCTs)

Relative treatment effects measured as mean differences (95% CrI)				
	PBO	**ALG**	**AVAL**	**CM**
Outcome: FVC % predicted				
PBO		3.58 (−2.95 to 10.13)	6.01 (−3.40 to 15.33)	3.11 (−6.79 to 13.00)
ALG	−3.58 (−10.13 to 2.95)		2.43 (−4.22 to 9.07)	−0.48 (−7.97 to 6.98)
AVAL	−6.01 (−15.33 to 3.40)	−2.43 (−9.07 to 4.22)		−2.90 (−2.91 to 7.07)
CM	−3.11 (−13.00 to 6.79)	0.48 (−6.98 to 7.97)	2.90 (−7.07 to 12.91)	
DIC: 13.94				
Outcome: 6MWD in metres				
PBO		24.68 (3.97 to 45.65)	53.55 (19.66 to 87.31)	19.29 (−17.43 to 56.09)
ALG	−24.68 (−45.65 to −3.97)		28.87 (1.74 to 55.66)	−5.39 (−35.72 to 25.58)
AVAL	−53.55 (−87.31 to −19.66)	−28.87 (−55.66 to −1.74)		−34.26 (−74.80 to 6.96)
CM	−19.29 (−56.09 to 17.43)	5.39 (−25.58 to 35.72)	34.26 (−6.96 to 74.80)	
DIC: 26.76				

ALG, alglucosidase; AVAL, avalglucosidase; CM, cipaglucosidase + miglustat; PBO, placebo.

Note
A negative symbol indicates that the treatment in the top row is less effective than the treatment in the first column.

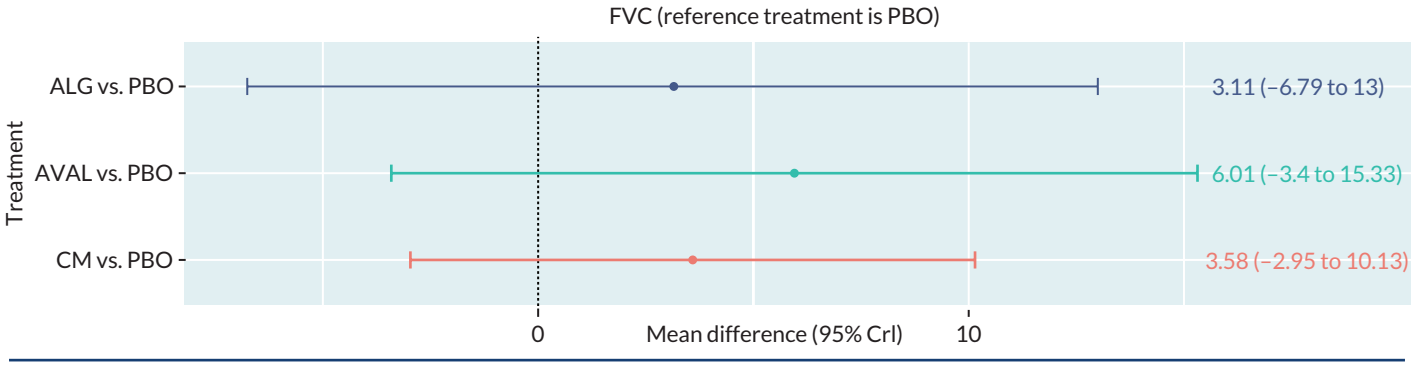

FIGURE 3 Forest plot of ERT alternatives vs. placebo FVC % predicted.

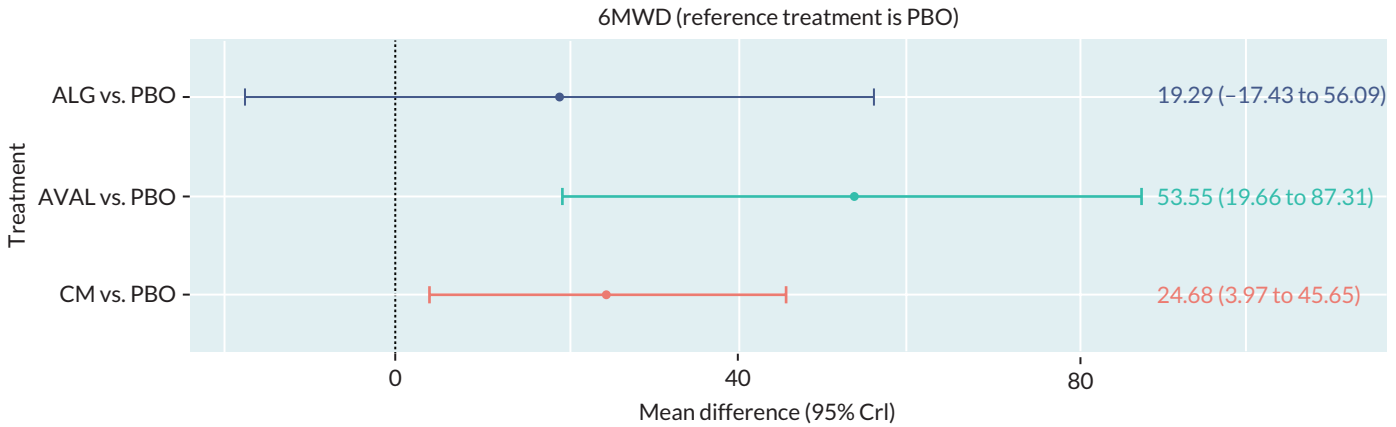

FIGURE 4 Forest plot of ERT alternatives vs. placebo 6MWD.

48 weeks (reported in a published paper[25]) and 96 weeks (reported in two conference abstracts[83,84]). The study characteristics and results from each extension study are detailed in *Appendix 2*, *Tables 6* and *7*.

All three extension studies concluded that efficacy improvements observed in the randomised phases were maintained. In PROPEL, the ERT-experienced group continuing cipaglucosidase alfa with miglustat showed small increases in 6MWD and FVC % predicted from week 52 to week 78, followed by slight declines by week 104. However, no details were reported on how missing data were handled in the analyses (11 patients discontinued treatment) which may have impacted study results. The LOTS cohort also showed a small decline in 6MWD and FVC % predicted from week 78 to week 104 in the group continuing alglucosidase alfa, with data missing for only 1 patient. In the COMET extension study, FVC % predicted remained relatively stable, but 6MWD and hand-held dynamometry (HHD) notably decreased by week 97. The authors attributed some of this to missed infusions during the COVID-19 pandemic. However, interpreting the COMET extension results is complicated by missing data at week 97 or 9 (6MWD), and 8 (FVC % predicted), of the 51 patients who continued taking avalglucosidase alfa and the analyses assumed that data were missing at random. This assumption does not appear reasonable for those patients who discontinued due to adverse events.

Registry studies

Semplicini *et al.*[29] followed 158 patients over a median of approximately 5 years, observing an annual 1.4% increase in % predicted 6MWD for up to 2.2 years, followed by a 2.3% decline (see *Appendix 6*, *Table 9*). Regarding muscle function outcomes, the Motor Function Measurement D2 subscore declined progressively by 1.0% per year, while the D3 subscore showed a slower decline of 0.2% per year.

Tard *et al.*[31] assessed the impact of switching from alglucosidase alfa to avalglucosidase alfa in 29 patients, reporting stabilisation of 6MWD after 1 year of avalglucosidase alfa, in contrast to pre-switch data, which showed declines. Lefeuvre *et al.*'s study also reported a decline in 6MWD, though data presentation was unclear. Martinez–Marin *et al.*'s (a Spanish registry study)

reported annual 6MWD declines of between 5 and 9 m across subgroups treated for < 5 years, 5–10 years and > 10 years.[32]

All studies reported FVC % predicted, primarily as a long-term outcome. Annual declines in FVC % predicted after up to 5 years of ERT ranged from 0.17% to 0.9%, while two studies observed similar declines (1.0–1.2%) after between 5 and 13 years of ERT.[26,32] Tard *et al.*[31] found no statistically significant difference in FVC % predicted in patients who switched ERT.

Mortality data were reported in three studies, with mean or median ages at death ranging from 60 to 66 years.[26,29,30]

Other prospective studies

6-minute walk test/distance results

The reporting of 6MWD results varied across the 18 studies (see *Appendix 6*, *Table 12*). Only three studies presented results as medians[36,44,49] while seven reported absolute changes from baseline.[33,37,43,44,47,52,55] Five studies expressed results as changes in % predicted 6MWD.[38,42,51,54,55] The remaining studies either reported results only graphically,[45] or provided baseline and follow-up data with differences indicated solely by *p*-values.[34–36,48,49]

Among studies reporting changes from baseline, two small studies observed improvements at 6 months of 37 m[52] and 47 m,[43] with statistical significance reported only for the former. Another study found a statistically significant improvement of ~44 m at up to 1 year, though based on a small cohort (n = 20).[35] For later time points, a non-statistically significant improvement of 16 m at > 3 years,[33] and a statistically significant increase of 41 m at 5 years[44] were reported. Ravaglia *et al.*[46] followed a small cohort (n = 15) up to 15 years; although most of the data were only reported graphically, the study's results showed significant improvement of around 55 m at 1 year, a return to baseline at around 3 years, and continued decline thereafter up to a maximum of 15 years follow-up.

Studies reporting 6MWD % predicted were generally limited by small sample sizes or were available only as abstracts. Harlaar *et al.*,[42] analysing 30 patients from the LOTS trial cohort, found initial improvements for ~2 years, followed by a gradual decline up to a maximum of 10 years follow-up. By the end of follow-up, 13 patients had some wheelchair dependency compared to 7 at baseline. The other studies reporting 6MWD studies observed statistically significant improvements up to 2 years. Among the two studies with 3-year data, one found a significant improvement,[36] while the other did not.[48]

Other outcomes

The 16 studies which reported FVC % predicted results. They indicated minimal change during the first 1–2 years of ERT, followed by a gradual decline thereafter up to a maximum of 10 years of follow-up (see *Appendix 6*, *Table 12*).

The most commonly reported muscle function or strength outcomes were the MRC scale (eight studies), HHD (four studies) and the QMFT (three studies). Studies assessing MRC scores yielded mixed results: two larger studies (both n > 50) reported small but statistically significant increases during the first 2–3 years of ERT[33,39] while others with up to 3 years of follow-up found no significant improvements.[48,49] No studies reported statistically significant MRC score improvements beyond 3 years.

Two larger studies (n = 69 and n = 102) assessing HHD found significant improvements after up to 2 years of ERT[39,44] with one also reporting a plateauing of effect at around 3 years.[44] Both studies also evaluated QMFT, which showed no significant improvements at up to 5 years of follow-up.

One study analysed the effect of ERT on mortality by comparing ERT patients with patients not taking ERT.[10] It found that the use of ERT was positively and statistically significantly associated with survival. Similarly, van der Meijden *et al.*[50] reported that ERT significantly reduced the risk of wheelchair dependence but had no significant effect on the need for respiratory support.

Among the six studies reporting ERT infusion-associated reactions, most found an occurrence rate of approximately 25% (see *Appendix 6*, *Table 13*).

Natural history studies

Twenty-two natural history studies were included in the review: 14 had a longitudinal design (with sample sizes ranging from 16 to 268 patients) and 8 had a cross-sectional study design (sample sizes ranged from 30 to 257 patients; see *Appendix 10*, *Table 23*)

Of the longitudinal studies, 11 were conducted prospectively and 3 were retrospective. Where reported, the mean or median age at diagnosis ranged from 27 to 44 years. Follow-up durations ranged from 1 year to more than 15 years, with patients in most studies being followed up for between 1 and 3 years. Where reported, the proportion of patients at baseline needing a wheelchair ranged from around 20% to 50%, and the proportions needing respiratory support ranged from 7% to 55%. The two studies by Gungor *et al.*[57,58] and the three studies by van der Beek *et al.*[65–67] had overlapping cohorts (i.e. some patients appeared in more than one study).

Results for 6MWT were reported in only one study,[68] whereas eight studies reported FVC % predicted.[30,56,63–68] (see *Appendix 10*, *Table 24*). Across van der Beek *et al.*'s two largest studies, the annual reduction in (upright) FVC % predicted was around 1% (over a median follow-up of 1.6 years).[66,67] Wokke *et al.* reported a much larger annual reduction in FVC % predicted of 4.6% after 1 year's follow-up.[68] Slonim *et al.* evaluated the effect of a high-protein, low-carbohydrate nutrition and exercise therapy,[64] finding the rate of FVC % predicted decline to be lower (0.21%) in the 26 compliant patients than in the 8 non-compliant patients (1.70%). However, this was a small, uncontrolled study and the difference was not statistically significant. The reporting of how FVC % predicted changed over time was limited in two studies.[30,56]

Two studies reported HRQoL outcomes.[61,68] Kanters *et al.* found lower utilities with longer disease durations, although the association was not significant, whereas Wokke *et al.* looked at Short Form questionnaire-36 items (SF-36), finding no significant changes from baseline in either the mental or physical component summaries after 1 year of follow-up.[68]

Although eight cross-sectional studies were included in the review, three of these were part of the same cohort.[70–72] Three studies did not report mean or median ages at onset or at diagnosis, although one was a study in children (mean age 7.6 years). In the other studies of adults, mean or median ages at diagnosis ranged from 33 to 43 years. van Capelle *et al.*[75] studied a child cohort (median age at diagnosis of 4 years) and Rigter *et al.* included a child subgroup.[74]

De Filippi *et al.* studied genetic polymorphisms, concluding that angiotensin-converting enzyme (ACE) and alpha-actinin-3 polymorphisms were genetic factors able to modulate clinical phenotypes, although these polymorphisms did not demonstrate significant associations with vital capacity (compared to controls), Walton score, or walking distance.[69] Studies by Hagemans *et al.*, which covered patients across all ages (range 3–81 years), reported that just under half of patients used a wheelchair and needed respiratory support, with the rates being quite similar across five different age groups.[70–72] Winkel *et al.*'s review of case reports reported lower rates of wheelchair use (8%) and ventilator use (28%), although the level of documentation varied across the included cases.[76] Much higher proportions were reported in Haley's child cohort, where over three-quarters of patients used a wheelchair and had respiratory support.[85] Rigter *et al.*'s study focused on describing health and functional status at the time of diagnosis, noting (among other outcomes) small numbers of patients needing a wheelchair and ventilation.[74]

Discussion

This review included 38 studies assessing the efficacy of ERT. Most of the evidence was derived from single-group studies, including RCT extension studies, prospective cohorts and registry studies, and primarily evaluated the clinical effectiveness of alglucosidase alfa. Comparative evidence was limited to three RCTs that together assessed the effectiveness of alglucosidase alfa, avalglucosidase alfa and cipaglucosidase alfa alongside miglustat and placebo (with BSC).

For ERT-naive patients, the NMA of RCT found evidence supporting the effectiveness of alglucosidase alfa and avalglucosidase alfa in comparison to placebo (BSC) after approximately 52 weeks, with statistical improvements observed in 6MWD and FVC % predicted. Evidence for the superiority of cipaglucosidase alfa combined with miglustat, however, remains limited due to the PROPEL trial's enrolment of a small number of ERT-naive patients. As a result, the NMA findings only reflect a subset of the trial participants. Nevertheless, the results from ERT-experienced individuals in the PROPEL study endorse the effectiveness of cipaglucosidase alfa with miglustat for those who had used alglucosidase alfa for several years. However, it is still uncertain whether these findings are applicable to ERT-naive populations.

Evidence from comparative studies indicates that avalglucosidase alfa may outperform alglucosidase alfa, showing statistically significant improvements in 6MWD at about 52 weeks, along with numerical but not statistically significant improvements in FVC % predicted. The observed differences noted in 6MWD, however, may have been affected by one or more outliers. Sensitivity analyses, which investigated earlier time points or utilised median differences, did not reveal statistically significant improvements.

To help contextualise the results of the NMA, it is useful to consider studies on minimum clinically important differences (MCIDs), which represent the smallest change that patients would notice and regard as important. Claeys *et al.*,[86] using data from the PROPEL trial (n = 123), found that within-group MCIDs for 6MWD (both % predicted and in metres) depend on the method used to calculate them and on various aspects of disease severity, including baseline 6MWD, body mass index

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and comorbidities. For their overall population, the MCIDs ranged from 24 m to 57 m (2.3–8.1% for % predicted). They concluded that applying a single MCID for all patients can be misleading, and a range should be considered. Lika *et al.*[87] used data from two prospective Dutch studies (*n* = 102) to estimate both between-group and within-group MCIDs. They also reported a range of MCIDs, depending on the methodology employed. For the most suitable anchor methods, the between-group MCIDs ranged from 2.5% to 4.8% for FVC % predicted and from 0.4% to 7.5% for 6MWD % predicted. The within-group MCID was slightly lower than the between-group MCID for FVC % predicted and higher for 6MWD.

Comparing cipaglucosidase alfa with miglustat to other ERTs is challenging due to the limited availability of direct comparative data in ERT-naive populations. A recent indirect comparison utilised IPD from the PROPEL study and aggregate data from LOTS and COMET, along with their respective RCT extension studies. This analysis employed multilevel network meta-regression (ML-NMR) to adjust for population differences, suggesting that cipaglucosidase alfa with miglustat may be more effective than both alglucosidase alfa and avalglucosidase alfa[88]

However, concerns remain regarding the ML-NMR methodology's ability to fully account for prior ERT exposure, as COMET included only ERT-naive patients. Additionally, the findings were heavily influenced by non-randomised data. Sensitivity analyses restricted to RCT data confirmed cipaglucosidase alfa with miglustat's superiority over alglucosidase alfa but suggested that avalglucosidase alfa may be more effective. Notably, this analysis did not incorporate relevant data from LOTS, omitting comparisons between cipaglucosidase alfa with miglustat and BSC. Furthermore, the study was funded by Amicus Therapeutics, the manufacturer of cipaglucosidase alfa, and four of its authors were Amicus Therapeutics employees, raising potential concerns about bias.

Long-term evidence on ERT effectiveness is limited to single-group studies. Findings from trial extensions, which provide data up to 2 years post randomisation, suggest that initial improvements observed at earlier time points are generally sustained for 12–18 months before a decline occurs. This pattern is broadly consistent with results from prospective studies identified in the review, although these studies indicate benefits may persist slightly longer (up to 2–3 years). Beyond this period, evidence suggests a gradual decline in both 6MWD and FVC % predicted over 10–15 years. However, these findings are constrained by small sample sizes and uncertainties regarding the impact of missing data.

Long-term evidence on BSC is extremely limited, with most of the evidence focused on characterising basic demographic information and support needs, such as the use of wheelchairs and ventilatory support. On the whole, studies were of limited duration, with follow-up limited to between 1 and 3 years. Further, there is very limited evidence on the 6MWD and FVC % predicted outcomes commonly reported in the trial evidence. Characterising long-term progression in the absence of ERT is therefore very difficult, and equally, it is not possible to construct non-randomised comparisons with observation data on ERT to evaluate the long-term benefits of ERT compared to BSC.

This lack of comparative evidence on the long-term effectiveness of ERT leaves critical questions unanswered. It remains unclear how ERTs perform relative to placebo (BSC) over extended periods or whether their initial benefits are sustained in the long term. Specifically, it is unclear whether early improvements with ERT translate into sustained clinical benefits relative to BSC, or whether the treatment effect wanes over time, leading to convergence in outcomes between treated and untreated patients. Likewise, the absence of robust comparative data prevents conclusions about the relative long-term effectiveness of different ERTs. This gap in evidence is a significant limitation, particularly given the chronic nature of the disease and the substantial costs associated with treatment.

Evidence on ERT-experienced populations is limited. However, available data suggest that switching from alglucosidase alfa to cipaglucosidase alfa with miglustat may offer short-term benefits. Nonetheless, whether these benefits are sustained over time or if switching ERT carries potential risks, such as antibody formation, remains unclear.

Limitations

A major limitation of the NMA was the inability to access IPD from the identified RCTs. This would have enabled the use of more advanced statistical synthesis methods and improved the ability to explore treatment–covariate interactions and heterogeneity across studies, potentially allowing for more nuanced conclusions. The lack of engagement from manufacturers, despite established data-sharing agreements, was particularly disappointing. Patient experts and stakeholders involved in the project found this lack of co-operation unacceptable and questioned the

commitment of the ERT manufacturers, Sanofi and Amicus Therapeutics, to improving patient outcomes.

An additional limitation of our work is that our searches were limited to only English language studies, meaning it is possible that relevant studies were missed. It is, however, unlikely that any additional studies that would have been identified would have meaningfully changed the review's conclusions, given the consistency of results across studies overall. It is also likely that was degree of overlap in the patients included in the identified registry studies. The reported patient numbers therefore do not represent unique samples.

Limitations and uncertainties in the identified evidence

Many of the limitations of this study reflect the limitations of the primary studies identified in the systematic review.

Two of the three RCTs, COMET and LOTS, included in the systematic review were found to be at high risk of bias. In both instances, this was because of the selective reporting of prespecified analyses. This raises concerns about the reliability of the estimates for 6MWD and FVC % predicted, as well as whether the treatment effects observed for these outcomes correspond with unreported results.

A further limitation of the RCT evidence is the significant heterogeneity observed in the effectiveness of alglucosidase alfa across the LOTS and COMET trials. In COMET, only small improvements in 6MWD were observed compared to baseline, contrasting sharply with the meaningful improvements seen in LOTS. The EMA highlighted this issue in its evaluation of avalglucosidase, expressing concerns about alglucosidase's apparent underperformance in COMET compared to LOTS. The sponsor (Sanofi) attributed these differences in the performance of alglucosidase alfa to the time gap between the trials, stating that LOTS was conducted when no other active treatments were available for the treatment of LOPD, potentially leading to significant variations in patient baseline characteristics between LOTS and COMET.[89] While post hoc analyses were conducted, they have not been fully reported, making further commentary difficult. The EMA, however, concluded that population differences likely influenced the COMET results, as suggested by the company.

A further important limitation of the COMET trial identified was the presence of outliers in the week 49 6MWD data for the alglucosidase alfa arm. The results suggest that at least one patient experienced a rapid decline in 6MWD. This appears to be a key factor contributing to the variability in alglucosidase alfa's effectiveness across published trials, which present results solely as mean values. As explored in scenario analysis, these outliers may also be an important driver of the reported differences between the effectiveness of alglucosidase alfa and avalglucosidase alfa.

Only a small number of outcomes were consistently collected across the primary studies, with FVC % predicted and 6MWD being the most common. However, other clinically meaningful measures such as individuals' ability to perform daily activities, reliance on supportive measures (e.g. mobility aids, respiratory support), and fatigue levels, were less frequently assessed. Members of the advisory group emphasised that these domains are key drivers of quality of life, raising concerns about the appropriateness of 6MWD and FVC % predicted as primary indicators of clinical benefit in LOPD.

Notably, several studies have highlighted the limitations of these measures in the LOPD context. 6MWD and FVC % predicted are susceptible to wide variation, outliers and external influences, such as motivation, test conditions and fatigue, as well as the impact of reference values that may not fully account for individual differences. Additionally, 6MWD primarily assesses lower limb endurance, failing to capture upper body weakness, respiratory decline and real-world daily activities like stair climbing or lifting. This narrow focus on 6MWD and FVC % predicted has important implications for the interpretation of the identified evidence, and the lack of information on other domains means that their impact cannot be evaluated.

Suggested research priorities

A key limitation of the current evidence base is the lack of comparative studies evaluating ERT against BSC. The available evidence is largely restricted to a single historical trial, which may not accurately reflect current clinical practice. Concerns have also been raised about the representativeness of the study population. While, ideally, future research studies would address these uncertainties, ethical and practical challenges make designing and conducting such a study unlikely. Retrospective data analysis may help bridge this gap, as could prospective studies in regions where ERT is not widely available. However, these approaches are unlikely to fully resolve the uncertainties surrounding the clinical effectiveness of ERT compared to BSC.

Researchers may therefore wish to consider further evaluations that focus on comparing the relative effectiveness of alternative ERT as current evidence is limited. An IPD systematic review, fully supported

by manufacturers, could help address some of these uncertainties. However, given the lack of manufacturer engagement in the current study and the inherent limitations of the existing RCT evidence, primary studies will likely be necessary to resolve these uncertainties. If future studies evaluating alternative ERTs are required, they should aim to address the methodological limitations of current evidence. While a RCT design would be preferable, prospective single-arm or switching designs could also be considered.

When designing evaluations in LOPD, careful consideration should be given to both baseline participant characteristics and outcome measures to ensure their relevance to LOPD patients, carers and decision-makers. Current studies have primarily focused on 6MWD and FVC % predicted. While future research should continue to collect data on these outcomes, consultations with LOPD patients and clinical experts indicate that these measures have limitations in capturing meaningful benefits and their practical relevance. Developing a standardised core outcome set would be highly beneficial in addressing these gaps.

The duration of follow-up in future studies of ERT for LOPD also requires careful consideration, given the substantial uncertainty surrounding the long-term durability of early benefits. Ideally, the longest possible follow-up period would be desirable. However, financial and logistical constraints often limit extended data collection. To address these uncertainties, alternative research approaches may be necessary, such as planned follow-ups of participants from existing RCTs or effectiveness studies, as well as prospective data collection through registries.

A further research priority is RCTs evaluating the benefits and risks associated with switching ERT. The PROPEL trial provides some limited evidence, but the PROPEL was not designed for the purpose, and therefore, the balance of benefits and risks is poorly understood. This will help inform clear clinical guidance on appropriate scenarios in which switching ERT should be considered.

Equality, diversity and inclusion

As this was a review project of existing trial data, we could not account for equality issues in this field beyond what was reported in the included publications or data. We note that reporting on potential equality areas such as ethnicity or socioeconomics was absent in trial publications and economic evaluations.

Late-onset Pompe disease does not show a strong prevalence difference based on sex, as it affects males and females equally. However, there are notable ethnic variations in its occurrence due to genetic factors. Specifically, LOPD is more common in higher rates observed in African Americans, Dutch populations and some East Asian populations. No trial publications reported outcomes specifically by ethnicity. Therefore, there is no current clear evidence as to whether ethnicity impacts the relative effectiveness of ERT compared with BSC.

Public and patient involvement

Patient involvement directed the project to focus on key issues that matter to patients and improve their quality of life, particularly in understanding how improvements in muscle function, respiratory capacity and other outcomes can translate into meaningful daily life benefits. For example, whether patients are more able to continue working, maintain mobility, perform daily activities, or care for children.

Upon reviewing all the evidence gathered in the systematic review, patient representatives highlighted several key areas of concern. Most critically, many clinical trials in Pompe disease use FVC or walking distance as primary outcomes, without sufficient consideration of how these measures impact patients' quality of life, ability to work, remain independent, or care for family members. Data on these patient-centred outcomes were only available in a limited way in the included trials. As a result, the available data were insufficient to fully evaluate the impact of ERT or other treatments on quality of life.

Additionally, due to the lack of evidence, concerns were raised about the benefits of switching and the relative effectiveness of alternative ERT treatments. There is significant uncertainty regarding the benefits of switching ERT, with only limited evidence available from a single trial. Similarly, current evidence does not demonstrate significant differences in the effectiveness of alternative ERTs.

Despite the lengthy meetings and the complexity of the information discussed, patient and public Advisory Focus Group participants generously contributed their time and input. Both during and after meetings, they reiterated their interest in the study and their continued motivation to take part, and several reported finding the experience rewarding, especially in view of the importance placed on their guidance and feedback.

Conclusions

The NMA indicates that ERT provides modest improvements in 6MWD and FVC % predicted after 1 year compared

to placebo (BSC without ERT) in ERT-naive populations. However, there is limited evidence to suggest meaningful differences in outcomes between alglucosidase alfa, avalglucosidase alfa and cipaglucosidase alfa with miglustat.

While longer-term observational data suggest gradual declines in 6MWD and FVC % predicted beyond 2–3 years, persisting for at least 15 years, there is a lack of long-term follow-up data on the comparative effectiveness of different ERTs. As a result, it remains unclear whether any initial benefits of ERT over BSC are sustained in the long term or whether ERT alters disease progression sufficiently to reduce the need for supportive care measures such as walking aids or ventilation. It is not possible to ascertain the benefits of switching, and sparse information on patient-centred outcomes limits the value of the available evidence to properly ascertain the impact of ERT or other treatments on quality of life.

Additional information

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Data-sharing statement

This is a report of a review and evidence synthesis of existing literature. All data collected in this review are contained in this manuscript. Any queries should be addressed to the corresponding author.

Ethics statement

This is a report of a review and evidence synthesis of existing literature. No ethical approval was required for this research.

Information governance statement

This is a systematic literature review and, therefore, the current research did not handle any personal information.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJRH0730.

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This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Study registration

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List of abbreviations

6MWD	6-minute walk test/distance
ACE	angiotensin-converting enzyme
BSC	best supportive care
COVID-19	coronavirus disease 2019
EMA	European Medicines Agency
ERT	enzyme replacement therapy
FVC	forced vital capacity
GAA	acid α-glucosidase
HHD	hand-held dynamometry
HRQoL	health-related quality of life
IOPD	infantile-onset Pompe disease
IPD	individual patient data
LFU	last follow-up
LOPD	late-onset Pompe disease
MCID	minimum clinically important differences
MIP	maximal inspiratory pressure
ML-NMR	multilevel network meta-regression
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	network meta-analysis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QMFT	Quick Motor Function Test
QMT	quantitative muscle testing
RCT	randomised controlled trial
SF-36	Short Form questionnaire-36 items

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Appendix 1 Search strategies

Every effort has been made to find and credit the original source/author(s) of the search strategies and to obtain permission from their copyright holders to reproduce this material; any further information related to the rightsholder if notified will be incorporated in any revisions or updates to this report/article.

Ovid MEDLINE(R) ALL

via Ovid http://ovidsp.ovid.com/

Date range searched: 1946–7 December 2023

Date searched: 12 December 2023

Records retrieved: 2198

1 glycogen storage disease type II/ (1973)
2 (pompe or pompe's or LOPD or LO-PD).ti,ab. (2476)
3 ((alpha glucosidase* or alpha-glucosidase* or alfa glucosidase* or alfa-glucosidase* or "4-glucosidase*" or "4 glucosidase*" or maltase or gaa) adj2 (deficien* or disease*)).ti,ab. (671)
4 (gsdii or gsd ii or gsd2 or "gsd 2" or gsdtwo or gsd two).ti,ab. (218)
5 generali?ed glycogenos?s.ti,ab. (58)
6 (glycogenos?s adj2 (ii or "2" or two)).ti,ab. (300)
7 (glycogen storage adj2 (disease* or disorder*) adj2 (ii or "2" or two)).ti,ab. (433)
8 or/1-7 (3348)
9 exp animals/ not humans.sh. (5176248)
10 8 not 9 (3177)
11 editorial/ or news/ or exp historical article/ (1288048)
12 10 not 11 (3122)
13 limit 12 to yr="2000-Current" (2384)
14 limit 13 to english language (2205)
15 remove duplicates from 14 (2198)

Key:

/or sh = indexing term (Medical Subject Heading: MeSH)

exp = exploded indexing term (MeSH)

* = truncation

? = wildcard for one additional letter

ti,ab = terms in either title or abstract fields

adj2 = terms within two words of each other (any order)

EMBASE

via Ovid http://ovidsp.ovid.com/

Date range searched: 1974–11 December 2023

Date searched: 12 December 2023

Records retrieved: 2997

1 glycogen storage disease type 2/ (5151)
2 (pompe or pompe's or LOPD or LO-PD).ti,ab. (4433)
3 ((alpha glucosidase* or alpha-glucosidase* or alfa glucosidase* or alfa-glucosidase* or "4-glucosidase*" or "4 glucosidase*" or maltase or gaa) adj2 (deficien* or disease*)).ti,ab. (1014)
4 (gsdii or gsd ii or gsd2 or "gsd 2" or gsdtwo or gsd two).ti,ab. (331)
5 generali?ed glycogenos?s.ti,ab. (36)
6 (glycogenos?s adj2 (ii or "2" or two)).ti,ab. (382)
7 (glycogen storage adj2 (disease* or disorder*) adj2 (ii or "2" or two)).ti,ab. (640)
8 or/1-7 (6230)
9 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (6871749)
10 8 not 9 (5847)
11 (letter or editorial or note).pt. (3055463)
12 10 not 11 (5518)
13 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5771584)
14 12 not 13 (3456)
15 limit 14 to yr="2000-Current" (2796)
16 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5771584)
17 12 and 16 (2062)
18 limit 17 to yr="2020-Current" (466)
19 15 or 18 (3262)
20 limit 19 to english language (3022)
21 remove duplicates from 20 (2997)

Key:

/or.sh. = indexing term (Emtree Subject Heading)

exp = exploded indexing term (Emtree)

* = truncation

? = wildcard for one additional letter

ti,ab = terms in either title or abstract fields

adj2 = terms within two words of each other (any order)

db = database field

su = source type

pt = publication type

EB health: KSR evidence

via Ovid http://ovidsp.ovid.com/

Date range searched: 2015–2023 Week 50

Date searched: 12 December 2023

Records retrieved: 20

1 (pompe or pompe's or LOPD or LO-PD).ti,ab. (19)
2 ((alpha glucosidase* or alpha-glucosidase* or alfa glucosidase* or alfa-glucosidase* or "4-glucosidase*" or "4 glucosidase*" or maltase or gaa) adj2 (deficien* or disease*)).ti,ab. (1)
3 (gsdii or gsd ii or gsd2 or "gsd 2" or gsdtwo or gsd two).ti,ab. (0)
4 generali?ed glycogenos?s.ti,ab. (0)
5 (glycogenos?s adj2 (ii or "2" or two)).ti,ab. (0)
6 (glycogen storage adj2 (disease* or disorder*) adj2 (ii or "2" or two)).ti,ab. (0)
7 or/1-6 (20)
8 limit 7 to yr="2000 -Current" (20)
9 remove duplicates from 8 (20)

Key:

* = truncation

? = wildcard for one additional letter

ti,ab = terms in either title or abstract fields

adj2 = terms within two words of each other (any order)

EconLit

via Ovid http://ovidsp.ovid.com/

Date range searched: 1886–23 November 2023

Date searched: 12 December 2023

Records retrieved: 4

1 (pompe or pompe's or LOPD or LO-PD).ti,ab. (5)
2 ((alpha glucosidase* or alpha-glucosidase* or alfa glucosidase* or alfa-glucosidase* or "4-glucosidase*" or "4 glucosidase*" or maltase or gaa) adj2 (deficien* or disease*)).ti,ab. (0)
3 (gsdii or gsd ii or gsd2 or "gsd 2" or gsdtwo or gsd two).ti,ab. (0)

This article should be referenced as follows:
Corbett M, Umemneku-Chikere C, Nevitt S, Deng NJ, Walton M, Fulbright H, *et al*. Enzyme replacement therapy compared with best supportive care for the treatment of Pompe Disease: a systematic review and network meta-analysis [published online ahead of print February 11 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GJRH0730

4 generali?ed glycogenos?s.ti,ab. (0)
5 (glycogenos?s adj2 (ii or "2" or two)).ti,ab. (0)
6 (glycogen storage adj2 (disease* or disorder*) adj2 (ii or "2" or two)).ti,ab. (0)
7 or/1-6 (5)
8 limit 7 to yr="2000 -Current" (4)
9 remove duplicates from 8 (4)

Key:

* = truncation

? = wildcard for one additional letter

ti,ab = terms in either title or abstract fields

adj2 = terms within two words of each other (any order)

National Health Service Economic Evaluations Database

via www.crd.york.ac.uk/CRDWeb/

Date range searched: Inception to 31 March 2015.

Date searched: 12 December 2023

Records retrieved: 10

1 MeSH DESCRIPTOR glycogen storage disease type II IN NHSEED 2
2 (pompe* or LOPD or LO-PD) IN NHSEED 12
3 ((alpha glucosidase* or alpha-glucosidase* or alfa glucosidase* or alfa-glucosidase* or "4-glucosidase*" or "4 glucosidase*" or maltase or gaa) NEAR2 (deficien* or disease*)) IN NHSEED 0
4 (gsdii or gsd ii or gsd2 or "gsd 2" or gsdtwo or gsd two) IN NHSEED 0
5 (generali* NEAR2 glycogenos*) IN NHSEED 0
6 (glycogenos* NEAR2 (ii or "2" or two)) IN NHSEED 0
7 (glycogen storage NEAR2 (disease* or disorder*) NEAR2 (ii or "2" or two)) IN NHSEED 2
8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 12
9 (#8) IN NHSEED FROM 2000 TO 2015 10

Key:

MeSH Description = indexing term (Medical Subject Heading: MeSH)

* = truncation

NEAR2 = terms within two words of each other

Cochrane Database of Systematic Reviews

via Wiley http://onlinelibrary.wiley.com/

Issue 12 of 12 December 2023

Date searched: 12 December 2023

Records retrieved: 65

#1 [mh ^"glycogen storage disease type II"]47
#2 (pompe or pompe's or LOPD or "LO-PD"):ti,ab213
#3 ((alpha NEXT glucosidase* or alfa NEXT glucosidase* or 4 NEXT glucosidase* or maltase or gaa) NEAR/2 (deficien* or disease*)):ti,ab21
#4 (gsdii or "gsd ii" or gsd2 or "gsd 2" or gsdtwo or "gsd two"):ti,ab11
#5 generali?ed glycogenos?s:ti,ab0
#6 (glycogenos?s NEAR/2 (ii or "2" or two)):ti,ab3
#7 (glycogen NEXT storage NEAR/2 (disease* or disorder*) NEAR/2 (ii or "2" or two)):ti,ab14
#8 1-#7 with Cochrane Library publication date Between Jan 2000 and Dec 2023, in Cochrane Reviews65

Key:

mh ^ = unexploded subject heading (MeSH heading)

* = truncation

? = wildcard for one additional letter

ti,ab = terms in title or abstract fields

near/3 = terms within three words of each other

next = terms are next to each other

Cochrane Central Register of Controlled Trials

via Wiley http://onlinelibrary.wiley.com/

Issue 11 of 12 November 2023

Date searched: 12 December 2023

Records retrieved: 153

#1 [mh ^"glycogen storage disease type II"]47
#2 (pompe or pompe's or LOPD or "LO-PD"):ti,ab213
#3 ((alpha NEXT glucosidase* or alfa NEXT glucosidase* or 4 NEXT glucosidase* or maltase or gaa) NEAR/2 (deficien* or disease*)):ti,ab21

#4 (gsdii or "gsd ii" or gsd2 or "gsd 2" or gsdtwo or "gsd two"):ti,ab11
#5 generali?ed glycogenos?s:ti,ab0
#6 (glycogenos?s NEAR/2 (ii or "2" or two)):ti,ab3
#7 (glycogen NEXT storage NEAR/2 (disease* or disorder*) NEAR/2 (ii or "2" or two)):ti,ab14
#8 1-#7 with Publication Year from 2000 to 2023, in Trials153

Key:

mh ^ = unexploded subject heading (MeSH heading)

* = truncation

? = wildcard for one additional letter

ti,ab = terms in title or abstract fields

near/3 = terms within three words of each other

next = terms are next to each other

International Health Technology Assessment database

via https://database.inahta.org/

Date range searched: Inception–12 December 2023

Date searched: 12 December 2023

Records retrieved: 11

((((glycogen storage and (disease* or disorder*) and (ii or "2" or two)))[Title] OR ((glycogen storage and (disease* or disorder*) and (ii or "2" or two)))[abs]) OR (((glycogenos* and (ii or "2" or two)))[Title] OR ((glycogenos* and (ii or "2" or two)))[abs]) OR ((generali* and glycogenos*)[Title] OR (generali* and glycogenos*)[abs]) OR ((((alpha glucosidase* or alpha-glucosidase* or alfa glucosidase* or alfa-glucosidase* or "4-glucosidase*" or "4 glucosidase*" or maltase or gaa) and (deficien* or disease*)))[Title] OR (((alpha glucosidase* or alpha-glucosidase* or alfa glucosidase* or alfa-glucosidase* or "4-glucosidase*" or "4 glucosidase*" or maltase or gaa) and (deficien* or disease*)))[abs]) OR (((pompe or pompe's or LOPD or LO-PD))[Title] OR ((pompe or pompe's or LOPD or LO-PD))[abs]) OR (("Glycogen Storage Disease Type II"[mh])))

FROM 2000 TO 2023 = 11

Key:

[mh] = indexing term: Medical Subject Heading (MeSH)

[abs] = search of abstract field

[Title] = search of title field

* = truncation

ClinicalTrials.gov

via https://clinicaltrials.gov/

Date searched: 12 December 2023

Records retrieved: 489

Condition or disease: pompe
= 140
Condition or disease: (glucosidase OR maltase OR gaa) AND (deficiency OR disease)
= 170
Condition or disease: ((glycogen OR GSD) AND (ii OR 2 OR two))
= 179

European Union Clinical Trials Register

via www.clinicaltrialsregister.eu/ctr-search/search

Date searched: 12 December 2023

Records retrieved: 280

Advanced Search: pompe*
= 83
Advanced Search: (glucosidase* OR maltase OR gaa) AND (deficien* OR disease*)
= 133
Advanced Search: ((glycogen* OR GSD) AND (ii OR 2 OR two))
= 64

World Health Organization International Clinical Trials Registry Platform

via https://trialsearch.who.int/

Date searched: 12 December 2023

Records retrieved: 262

Condition: pompe*

Recruitment Status: All = 154

Condition: (glucosidase* OR maltase OR gaa) AND (deficien* OR disease*)
Recruitment Status: All = 37
Condition: ((glycogen* OR GSD) AND (ii OR 2 OR two))
Recruitment Status: All = 71

Appendix 2 Randomised controlled trial, network meta-analyses and randomised controlled trial extension study details

Baseline characteristics such as age at disease onset, age at diagnosis, age at start of ERT, percentage of male patients, percentage of patients needing respiratory support (on ventilator), percentage of patients on wheelchair (ambulatory) were extracted from the studies where they were reported. The baseline characteristics of the population in each RCT is presented in *Table 2*. LOTS and COMET recruited ERT-naive patients in their studies but PROPEL recruited both ERT-experienced and ERT-naive patients. However, the NMA used results from the ERT-naive population.

The extracted outcomes used in the NMA were 6MWD (m) and percentage (%) FVC because these two outcomes were reported by all three RCTs (LOTS, COMET and PROPEL).

TABLE 2 Baseline characteristics of RCT cohorts

Study	Treatment group (*N*)	Mean age, mean (SD)	% Male	Mean age at onset[a] (SD)	% ERT-naive	Disease duration (years)	% c-32-13T > G, mutation	% Use of walking aid	Mean 6MWD, m (SD)	Mean 6MWD % predicted (SD)	Mean FVC % predicted (SD)
LOTS[12]	ALG (60)	45.3 (12.4)	57	30.3 (12.3)	100	9.0 (6.3)	NR	38	332.2 (126.7)	52.5 (19.0)	55.4 (14.4)
	PLB (30)	42.6 (11.6)	37	23.9 (11.0)	100	10.1 (8.4)	NR	53	317.9 (132.3)	50.3 (20.5)	53.0 (15.7)
	Total (90)	44.4 (16.98)[b]	50	28.2 (16.5)[b]	100	9.37 (10.5)[b]	NR	43	327.4 (183.2)[b]	51.8 (28.0)[b]	54.6 (21.3)[b]
COMET[22]	AVAL (51)	46 (14.5)	53	32.9 (16.6)[c]	100	NR	84	NR	399.3 (110.9)	57.3 (15.0)	62.5 (14.4)
	ALG (49)	50.3 (13.7)	51	37.7 (15.7)	100	NR	94	NR	378.1 (116.2)	55.3 (16.6)	61.6 (12.4)
	Total (100)	48.1 (14.2)	52	35.3 (16.3)[d]	100	NR	89	NR	388.9 (113.5)	56.3 (15.8)	62.1 (13.4)
PROPEL[21]	CM (85) Naive (20)[e]	47.6 (13.3)	42	NR	24	NR	89	20	357.9 (111.8) 393.6 (112.4)[e]	NR 61.9 (15.3)[e]	70.7 (19.6) 80.2 (18.7)[e]
	ALG (38) Naive (7)[e]	45.1 (13.3)	53	NR	21	NR	84	29	351.0 (121.3) 420.9 (135.7)[e]	NR 61.4 (17.1)[e]	69.7 (21.5) 79.1 (22.6)[e]
	Total (123)	46.8 (18.8)[b]	46	NR	23	NR	88	23	355.8 (165.0)[b]	NR	70.4 (29.1)[b]

ALG, alglucosidase; AVAL, avalglucosidase; CM, cipaglucosidase + miglustat; NR, not reported; PLB, placebo; SD, standard deviation.
a At first symptoms.
b Implies that the values were calculated assuming both treatment groups are independent.
c Based on 50 participants in AVAL.
d Based on 99 participants.
e ERT-naive population.

This article should be referenced as follows:
Corbett M, Umemneku-Chikere C, Nevitt S, Deng NJ, Walton M, Fulbright H, *et al.* Enzyme replacement therapy compared with best supportive care for the treatment of Pompe Disease: a systematic review and network meta-analysis [published online ahead of print February 11 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GJRH0730

DOI: 10.3310/GJRH0730

TABLE 3 Results of key review outcomes for the RCTs

	LOTS[12]			COMET[22,90]			PROPEL[21]		
	Change from baseline at week 78 (SD)			Change from baseline at week 49 (SE)			Change from baseline at week 52 (SE)		
Outcome	ALG	PLB	Difference in means (95% CI)	AVAL	ALG	Difference in means (95% CI)	CM; *N*	ALG + PLB; *N*	Difference in means (95% CI)
Motor function									
6MWD (m)	25.13 (7.68)[a]	−2.99 (10.80)[a]	28.12 (2.07 to 54.17)	32.21 (9.93)	2.19 (10.40)	30.01 (1.33 to 58.69)	20.8 (4.6); 85	7.2 (6.6); 37	13.7 (−1.2 to 28.5)
6MWD % predicted	NR	NR	NR	5.02 (1.54)	0.31 (1.62)	4.71 (0.25 to 9.17)	4.1 (0.8); 85	1.6 (1.0); 37	2.4 (−0.3 to 5.0)
Pulmonary function									
FVC % predicted	1.20 (0.70)[a]	−2.20 (0.98)[a]	3.40 (1.03 to 5.77)	2.89 (0.88)	0.46 (0.93)	2.43 (−0.13 to 4.99)	−0.9 (0.7); 84	−4.0 (0.8); 37	2.7 (0.4 to 5.0)
MIP % predicted	3.48 (1.31)[a]	−0.35 (1.84)[a]	3.83 (−0.60 to 8.26)	8.70 (2.09)	4.29 (2.19)	4.4 (−1.63 to 10.44)	2.1 (2.1); 84	−2.7 (2.8); 37	4.2 (−3.4 to 11.8)
Muscular function									
HHD lower	NR	NR	NR	260.69 (46.07)	153.72 (48.54)	106.97 (−26.56 to 240.5)	NR	NR	NR
HHD upper	NR	NR	NR	173.54 (38.04)	109.67 (38.98)	63.87 (−44.76 to 172.51)	NR	NR	NR
Quality-of-life measures									
EQ-5D-5L VAS	NR	NR	NR	7.49 (1.99)	2.20 (2.14)	5.29 (−0.55 to 11.2)	0.03 (SE 1.54); 84	3.61 (SE 2.40); 36	−3.58 (−4.29 to −2.87)[b]
EQ-VAS score				61.18 (SD = 15.90)	66.69 (SD = 18.28)	Total (*n* = 99) is 63.88 (SD = 17.24)			

ALG, alglucosidase alfa; AVAL, avalglucosidase alfa; CI, confidence interval; CM, cipaglucosidase + miglustat; EQ-5D, EuroQol-5 Dimensions; EQ-5D-5L, EuroQol-5 Dimensions, five-level version; m, metres; *N*, sample size; NR, not reported; PLB, placebo; SD, standard deviation; SE, standard error; VAS, visual analogue scale.

a SD calculated using the reported 95% CI.

b Difference in means and 95% CI calculated (not available to extract).

TABLE 4 Enzyme replacement therapy subgroup results in the PROPEL trial

	ERT-experienced					ERT-naive				
	CM		ALG + PLB		Mean difference (95% CI)	CM		ALG + PLB		Mean difference (95% CI)
Outcome	Baseline mean	CFBL week 52	Baseline mean	CFBL week 52		Baseline mean	CFBL week 52	Baseline mean	CFBL week 52	
6MWD, m	346.9 (110.2) *n* = 65	16.9 (40.4) *n* = 65	334.6 (114.0) *n* = 30	0.0 (39.3) *n* = 30	LS 16.8 (0.2 to 33.3)	393.6 (112.4) *n* = 20	33.4 (48.7) *n* = 20	420.9 (135.7) *n* = 7	38.3 (29.3) *n* = 7	LS − 9.0 (−46.5 to 35.0) −4.9 (SE = 19.7)
FVC % predicted	67.9 (19.1) *n* = 65	0.1 (5.8) *n* = 64	67.5 (21.0) *n* = 30	−4.0 (5.0) *n* = 30	LS 3.5 (1.0 to 6.0)	80.2 (18.7) *n* = 20	−4.1 (6.5) *n* = 20	79.1 (22.6) *n* = 7	−3.6 (4.7) *n* = 7	LS − 2.0 (−8.9 to 5.0) −0.5 (SE 2.7)
MIP % predicted	61.3 (27.9) *n* = 65	1.0 (20.1) *n* = 64	55.0 (16.9) *n* = 30	−1.7 (8.1) *n* = 30	LS 1.7 (−6.4 to 9.7)	63.5 (20.2) *n* = 20	5.6 (16.1) *n* = 20	80.7 (25.2) *n* = 7	−6.9 (37.0) *n* = 7	LS 5.3 (−22.6 to 33·1)

ALG, alglucosidase alfa; CFBL, change from baseline at randomisation; CM, cipaglucosidase + miglustat; LS, least squares; m, metres; PLB, placebo; SE, standard error.

Note
Numbers in brackets are standard deviations except where stated.

TABLE 5 Adverse events in RCTs

	LOTS *n/N* (%)		COMET *n/N* (%)		PROPEL *n/N* (%)	
Outcome	ALG	PLB	AVAL	ALG	C + M	ALG + PLB
TEAEs potentially related to treatment	32/60 (53)	17/30 (57)	23/51 (45)	24/49 (49)	26/85 (31)	14/38 (37)
IAR	17/60 (28)	7/30 (23)	13/51 (26)	16/49 (33)	21/85 (25)	10/38 (26)
STEAEs	13/60 (22)	6/30 (20)	8/51 (16)	12/49 (25)	8/85 (9)	1/38 (3)
Discontinuations due to AEs	2/60 (3)	1/30 (3)	0/51 (0)	4/49 (8)	3/85 (4)	1/38 (3)

AE, adverse events; ALG, alglucosidase; AVAL, avalglucosidase; C + M, cipaglucosidase + miglustat; IAR, infusion-associated reaction; PLB, placebo; STEAE, serious treatment emergent adverse events; TEAE, treatment emergent adverse events.

This article should be referenced as follows:
Corbett M, Umemneku-Chikere C, Nevitt S, Deng NJ, Walton M, Fulbright H, *et al.* Enzyme replacement therapy compared with best supportive care for the treatment of Pompe Disease: a systematic review and network meta-analysis [published online ahead of print February 11 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GJRH0730

DOI: 10.3310/GJRH0730

TABLE 6 Baseline characteristics of RCT extension cohorts

Study	Treatment (*N*)	Mean age (SD)	% Male	Ht	Wt	Mean age at diagnosis (SD)	% Use of walking aid	Mean 6MWT, m (SD)	Mean 6MWT % predicted (SD)	Mean FVC % predicted (SD)
LOTS[12]	ALG-ALG (55)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	PLB-ALG (26)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Total (81)	NR	NR	NR	NR	NR	NR	NR	NR	NR
COMET[22]	AVAL-AVAL (51)	47.0 (14.5)	52.9	NR	NR	NR	NR	433.4 (111.8)	62.6 (15.4)	65.3 (17.1)
	ALG-AVAL (44)	50.7 (13.9)	54.5	NR	NR	NR	NR	384.7 (139.6)	55.8 (19.1)	61.5 (13.5)
	Total (96[a])	48.3 (14.7)	53.1	NR	NR	NR	NR	410.8 (127.2)	59.4 (17.5)	63.6 (15.6)
[b]PROPEL[21]	CM-CM (81)	48.9 (13.5)	40.7	171.2 (9.7)	73.3 (15.3)	40.3 (13.8)	NR	NR	NR	NR
	ALG-CM (37)	46.0 (13.5)	51.4	171.2 (11.3)	78.9 (26.8)	37.2 (15.4)	NR	NR	NR	NR
	Total (118)	48.0 (13.5)	44.1	171.2 (10.2)	75.1 (19.7)	39.3 (14.4)	NR	NR	NR	NR

ALG, alglucosidase alfa; AVAL, avalglucosidase alfa; CM, cipaglucosidase + miglustat; Ht, height; m, metres; *N*, sample size; NR, not reported; PLB, placebo; SD, standard deviation; Wt, weight; %, percentage.

a A new patient entered the study during the extension period.

b Baseline outcome data only reported for subgroups based on previous ERT status.

Note

In the extension period, all patients crossed over to the intervention therapy.

TABLE 7 Results of RCT extension studies

	LOTS extension[24]		COMET extension[25,83]				PROPEL extension[23]	
	CFBL at week 104	CFBL at week 130 (US patients only)	CFBL at week 97[25,91]		CFBL at week 145[83,84]		CFBL week 104	
Outcomes	ALG-ALG, mean (SD); *N*		AVAL-AVAL, LS mean (SE); *N*	ALG-AVAL, LS mean (SE); *N*	AVAL-AVAL, LS mean (SE); *N*	ALG-AVAL, LS mean (SE); *N*	CM-CM, mean (SD); *N*	ALG-CM, mean (SD); *N*
Motor function								
6MWT (m)	21.3 (78); 53	22.9 (50.0); 27	18.60 (12.01); 42	4.56 (12.44); 41	20.65 (9.60)	0.29 (10.42)	381.54 (168.16); 74[a,b]	359.94 (177.81); 33 [a,b]
6MWT % predicted	NR	NR	3.27 (6.44); 42 (1.48, 5.22)[c]	0.83 (6.14); 41 (−0.98, 2.71)[c]	NR	NR	4.44 (11.81); 74[a]	1.49 (14.06); 33[a]
Pulmonary function								
FVC % predicted	0.8 (6.7); 53	0.2 (6.9); 27	2.65 (1.05); 43	0.36 (1.12); 35	1.43 (1.23)	1.26 (1.35)	−1.66 (9.92); 71[a]	−3.64 (9.13); 31[a]
MIP % predicted	5.1 (10.7); 53	NR	9.99 (5.72); 40 (8.09, 11.76)[c]	5.29 (5.68); 33 (3.31, 7.23)[c]	NR	NR	NR	NR
Quality of life								
EQ-5D VAS	NR	NR	72.02 (16.16)	67.88 (19.61)	NR	NR	NR	NR

ALG, alglucosidase alfa; AVAL, avalglucosidase alfa; CFBL, change from baseline at randomisation; CM, cipaglucosidase + miglustat; EQ-5D, EuroQol-5 Dimensions; LS, least squares; m, metres; *N*, group size; NR, not reported; SD, standard deviation; SE, standard error; VAS, visual analogue scale.

a Calculated using the values reported in the articles and in the subgroup results table.

b Mean at week 104 not CFBL.

c Calculated by digitising the published plot.

This article should be referenced as follows:
Corbett M, Umemneku-Chikere C, Nevitt S, Deng NJ, Walton M, Fulbright H, *et al.* Enzyme replacement therapy compared with best supportive care for the treatment of Pompe Disease: a systematic review and network meta-analysis [published online ahead of print February 11 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GJRH0730

Appendix 3 R-code for network meta-analysis

The NMA (Bayesian framework) was employed to estimate the indirect treatment effectiveness of the therapies evaluated in the RCTs. This was carried using the Rjags package in R Studio software.[19] The code is presented below:

```
### call up the packages needed

library(dplyr)

library(rjags)

library(coda)

library(R2jags)

## load the data set (called d_mwd in this analysis) and prepare data set to be used in the jags model

## nt = number of treatments; ns = number of studies; t1 = reference treatment in each RCT; t2 = interventional treatment in each RCT

d.jags<- list(ns=3, nt =4, y= d_mwd$y, se = d_mwd$se, t1 = d_mwd$t1, t2 = d_mwd$t2)

i.jags<- function(){list(d=c(NA,0,0,0))}

p.jags <- c("d","diff", "totresdev")

## Model adapted from the Technical Support Document (TSD) 2[21] written as nma_RE.txt

Model {

for(i in 1:ns) {

y[i] ~ dnorm(delta[i],prec[i])

prec[i]<- pow(se[i],-2)

dev[i] <- (y[i]-delta[i])*(y[i]-delta[i])*prec[i]

delta[i] ~ dnorm(md[i],tau)

md[i] <- d[t2[i]] - d[t1[i]] # mean of treat effects distributions

}

totresdev <- sum(dev[]) #Total Residual Deviance

d[1]<-0 # treatment effect is zero for reference treatment

for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects

sd ~ dunif(0,5) # vague prior for between-trial SD

tau <- pow(sd,-2) # between-trial precision = (1/ between-trial variance)

# All pairwise comparisons

for (c in 1:(nt-1)){for (k in (c+1):nt){diff[k,c]<- d[k] - d[c]}}

}

### run the analysis

m <- jags.model(d.jags, file = "nma_RE.txt",inits = i.jags,n.chains = 3)

update(m, 5000)

res <- coda.samples(m, variable.names = p.jags, n.iter = 500000, thin = 20)

summary(res)

## traceplot

Plot(res)
```

Appendix 4 Advisory group membership

Name	Role	Organisation
Chong Yew Tan	Clinical Academic	Cambridge University Hospitals NHS Foundation Trust
Robin Lachmann	Clinical Academic	University College London Hospitals NHS Foundation Trust
Allan Muir	Parent/Pompe Support Network representative	Pompe Support Network representative
Hülya Apaydin	Carer/Pompe Support Network representative	Pompe Support Network representative
Iqra Afzil	Representative with Pompe disease	N/A
Kevin Annesle	Representative with Pompe disease	N/A
Zoe Baillie	Representative with Pompe disease	N/A
Luke Fraser	Representative with Pompe disease	N/A
Deborah Havery	Representative with Pompe disease	N/A
Keith Jones	Representative with Pompe disease	N/A
Caroline Wilkinson	Representative with Pompe disease	N/A
Tony Wynne	Representative with Pompe disease	N/A

N/A, not applicable.

Appendix 5 Guidance for Reporting Involvement of Patients and the Public 2 (GRIPP2)

Section and topic	Item	Reported on page No
1: Aim	Report the aim of PPI in the study	14 – Stakeholder involvement
2: Methods	Provide a clear description of the methods used for PPI in the study	14 – Stakeholder involvement
3: Study results	Outcomes – Report the results of PPI in the study, including both positive and negative outcomes	26 – Discussion – Patient and public involvement
4: Discussion and conclusions	Outcomes – Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	4 – Abstract – Conclusions 8 – Plain language summary 14 – Stakeholder involvement 24 – Discussion – Limitations 24 Discussion – Limitations and uncertainties in the identified evidence 25 – Discussion – Suggested research priorities 26 – Discussion – Patient and public involvement 27 – Conclusions
5: Reflections/critical perspective	Comment critically on PPI input in the study, reflecting on the things that went well and those that did not, so others can learn from this experience	26 – Discussion – Patient and public involvement

PPI, patient and public involvement.

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Appendix 6 Enzyme replacement therapy registry studies and other prospective enzyme replacement therapy studies

TABLE 8 Baseline characteristics of ERT registry studies

Study, *N*, ERT	Age at ERT start (years)	Age at onset, years	% Male	% Using wheelchair	% Respiratory support	6MWT, m	6MWT % predicted	FVC % predicted
Pompe registry (Sanofi, Genzyme)								
Berger *et al.*,[26] *N* = 485, ALG	44.9[a]	34.3[a]	51	7	28 Non-invasive 0 invasive	380[a] *N* = 286	NR	67.1[a]
Stockton *et al.*,[27] *N* = 396, ALG	45[a]	33.7[a]	50	13 (*n* = 187)	16 (*n* = 188)	NR	NR	66.9[a]
Marcondes *et al.*,[28] *N* = 38 (LA), *N* = 1390 (RoW), ALG, CA	NR	LA 26.3 RoW 30.0	LA 47 RoW 50	NR	RoW 8% invasive	NR	NR	RoW 67% had an FVC < 80%
French Pompe registry								
Semplicini *et al.*,[29] *N* = 158, ALG	50.9	37	48	18	52	NR	57.0	64.4
Lefeuvre,[30] *N* = 177, ALG	49.6[a]	NR	49	NR	NR	431	NR	NR
Tard *et al.*,[31] ALG – AVAL (switching study) *N* = 177, ALG	45.3 56.2 at switch	NR	NR	NR	NR	213 (147) at switch	NR	NR
Spanish Pompe registry								
Martinez–Marin *et al.*,[32] *N* = 81, ERT	29.1	NR	NR	NR	NR	NR	NR	NR

ALG, alglucosidase alfa; AVAL, avalglucosidase alfa; CA, conference abstract; LA, Latin America; NR, not reported; RoW, rest of the world.
a Median.

TABLE 9 Results of ERT registry studies

Study, *N*	6MWT (m), *N* (if different from total)	6MWT % predicted	FVC % predicted, *N* (if different from total)	Muscle function outcomes	Other outcomes
Pompe registry (Sanofi, Genzyme)					
Berger *et al.*,[26] *N* = 485, ALG	NR	NR	Median FU 8.3 years 1.83 (0.66, 3.01) increase/year for first 6 months −0.54 (−0.79, −0.30) decrease/year from 6 months to 5 years −1.0 (−1.36, −0.63) decrease/year from 5–13 years	NR	34 patients (7%) died during FU at a median age of 60.3 years.
Stockton *et al.*,[27] *N* = 396, ALG	NR	NR	Median FU 4 years Change in FVC over time: −0.17 p/y	NR	26 patients (16.5%) began non-invasive respiratory support during the 5-year FU. This was nighttime only for 22 patients.

TABLE 9 Results of ERT registry studies (*continued*)

Study, *N*	6MWT (m), *N* (if different from total)	6MWT % predicted	FVC % predicted, *N* (if different from total)	Muscle function outcomes	Other outcomes
Marcondes *et al.*,[28] *N* = 38 (LA), *N* = 1390 (RoW), ALG, CA	RoW: At 2 years 8.7% had a > 20% decline	NR	RoW: At 2 years 22.7% had a > 10% decline	NR	NR
French Pompe Registry					
Semplicini *et al.*,[29] *N* = 158, ALG	NR	Median FU 5.3 years 1.4% increase p/y up to 2.2 years, followed by 2.3% decline	Median FU 5.3 years −0.9 decrease/year	MFM D2 sub-score: −1.0%/year, $p < 0.001$, D3 − 0.2%/year, $p < 0.05$	15 patients (9%) died at mean age 65.2 years and mean ERT duration 4.3 years
Lefeuvre,[30] *N* = 177, ALG	6MWD: Baseline: 431 10-year FU: slope = 0.85, 'mean progression of −1.00'; significant decrease over time ($p < 0.001$)	NR	Sitting FVC: mean change 'over time' 0.02 Supine FVC: mean change 'over time' 0.01	NR	Median time until walking ability progression (use of a walking stick, walker or wheelchair) = 9.4 years and time until respiratory function progression (use of any ventilation) = 14.8 years. 31 patients died at a mean age of around 66 years.
Tard *et al.*,[31] *N* = 29, ALG– ALG to AVAL (switching study)	Decrease of 63 m pre-switch vs. a decrease of 1 m 1 year post-switch.	NR	No statistically significant difference at 1 year when compared with pre-switch data.	NR	NR
Spanish Pompe Registry					
Martinez–Marin *et al.*,[32] *N* = 81, ERT	Estimated yearly decline (*n* = 58): < 5 years: −5.16 (−8.3 to −2.03) 5–10 years: −8.59 (−15.45 to −1.72) > 10 years: −8.74 (−237.2 to 219.7)	NR	Estimated yearly decline (*n* = 69): < 5 years: 0.46 (−1.48 to 0.57) 5–10 years: −1.03 (−1.75 to 3.81) > 10 years: −1.24 (−1.2 to 2.15)	NR	NR

ALG, alglucosidase alfa; AVAL, avalglucosidase alfa; CA, conference abstract; FU, follow up; LA, Latin America; m, metres; MFM, motor function measurement; *N*, sample size; NR, not reported; p/y, per year; RoW, rest of the world.
a Median.

TABLE 10 Registry studies reporting adverse event data

Authors	Adverse events					
	TEAE, *n*/*N* (%)	TEAE related to treatment *n*/*N* (%)	IAR, *n*/*N* (%)	Withdrawal due to TEAE *n*/*N* (%)	STEAE, *n*/*N* (%)	Discontinuation, *N* (%)
Semplicini *et al.*,[29] *N* = 158, ALG	NR	NR	14/158 (9)	NR	NR	26 (17.3) Median FU 5.3 years

ALG, alglucosidase alfa; FU, follow-up; IAR, infusion associated reaction; NR, not reported; STEAE, serious treatment emergent adverse event; TEAE, treatment emergent adverse events.

This article should be referenced as follows:
Corbett M, Umemeku-Chikere C, Nevitt S, Deng NJ, Walton M, Fulbright H, *et al.* Enzyme replacement therapy compared with best supportive care for the treatment of Pompe Disease: a systematic review and network meta-analysis [published online ahead of print February 11 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GJRH0730

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TABLE 11 Baseline characteristics of other prospective ERT studies

Study, *N*	Country	Age at ERT start years	Age at onset of disease	% Male	% Using wheelchair	% Respiratory support	6MWT, m (SD)	6MWT % predicted (SD)	Sitting FVC % predicted (SD)
Alglucosidase alfa studies									
Anderson *et al.* (2014),[33] *N* = 62	UK	45.5	NR	60	16	39	246	NR	59.6
Angelini *et al.* (2012),[34] *N* = 74	Italy	43	28.3	45	10	36	320 (161) (*n* = 58)	NR	65.2 (26.5) (*n* = 69)
Angelini *et al.* (2012),[35] *N* = 40 (subgroup of[34])	Italy	51	NR	45	0	35	319 (*n* = 32)	NR	NR
Bembi *et al.* (2010),[36] *N* = 24	Italy (juvenile, 7)	12	2.5	71	4	29	572.9[a]	NR	83 (45)
	Italy (adult, 17)	47.6	26.6	53		65	116.6[a]	NR	52 (26)
Claeys *et al.* (2022),[37] *N* = 12	Belgium	All on ERT before the study: mean of 8.8 years	32.8	42	0	33	451.9 (143.3)	NR	82.8 (24.89)
Clemens *et al.* (2017),[38] *N* = 68, CA	Same setting as LOTS	45.8	28.7	53	50	38	NR	NR	Estimated annual decline 1.3% per year
De Vries *et al.* (2012),[39] *N* = 69	The Netherlands	52.1[a]	30.8[a]	52	40	37	NR	NR	68.3[a]
Ditters *et al.* (2023),[40] *N* = 121	The Netherlands	52.2[a]	33.5[a]	49	NR	NR	NR	NR	NR
Ditters *et al.* (2023),[78] *N* = 100	The Netherlands	50.1[a] adult 10.5[a] childhood onset	NR	42 adult 60 childhood onset	NR	NR	NR	NR	NR
Gungor *et al.* (2013),[10] *N* = 204[b]/283	The Netherlands, UK, USA, Germany, Australia and Canada	51[a]	NR	49	18	14	NR	NR	NR
Gungor *et al.* (2016),[11,92] *N* = 174	The Netherlands, UK, USA, Germany, Australia and Canada	50[a]	NR	47	52	48	NR	NR	NR
Hahn *et al.* (2018),[41] *N* = 26	USA	6.0	NR	73	NR	NR	NR	NR	NR
Harlaar *et al.* (2019),[42] (94–96) *N* = 30 LOTS trial patients	The Netherlands and France	49[a]	NR	47	23	23	NR	49[a]	54[a]

TABLE 11 Baseline characteristics of other prospective ERT studies (*continued*)

Study, *N*	Country	Age at ERT start years	Age at onset of disease	% Male	% Using wheelchair	% Respiratory support	6MWT, m (SD)	6MWT % predicted (SD)	Sitting FVC % predicted (SD)
Hartung *et al.* (2007),[43] *N* = 11, CA	Germany	NR	NR	NR	NR	NR	336 (215)	NR	2.35 (1.06)
Kuperus *et al.* (2017),[44] *N* = 102 (88 on ERT)	The Netherlands	52[a]	33[a]	52	36	29	376,[a] 53	NR	NR
Kuperus *et al.* (2018),[45] *N* = 112	The Netherlands	49[a]	31[a]	50	31	22	417	NR	57
Ravaglia *et al.* (2022),[46] *N* = 18	Italy	53[a]	36[a]	39	17	44	367	67 (23), *n* = 12	73.8 (21.3), *n* = 12
Ravaglia *et al.* (2012),[47] *N* = 16	Italy	NR	31	44	0	44	339 for non-responders *n* = 7	NR	59 (27.5)
Regnery *et al.* (2012),[48] *N* = 38	Germany	50.7	36.2	47	16	34	312 (165.5); *n* = 21	NR	80.27 (14.1); *n* = 28
Strothotte *et al.* (2010),[49] *N* = 44	Germany	48.9	NR	55	18.9	43.2	341 (149.5); *n* = 22	NR	69.9 (28.1); *n* = 33
van der Meijden *et al.* (2018),[50] *N* = 319; 126 at risk of wheelchair, 125 at risk of respiratory support	Canada, Germany, the Netherlands, USA, France and UK	48[a] – WC 49[a] – RS	39[a] (based on *n* = 189 at risk of using wheelchair including those who started ERT and NH) 39[a] (based on *n* = 177 at risk of using RS including those who started ERT and NH)	48[a] (ERT and non-ERT) 38[a] (ERT and non-ERT)	0	0	NR	NR	NR
van der Meijden *et al.* (2018);[51] *N* = 17	The Netherlands, Belgium, UK, USA and Germany.	11.9[a]	2.5[a] (on text) and 3[a] (on the table).	65	18	18	NR	79[a]	87[a]
Van der Ploeg (2016)[52] Thurberg *et al.* (2015),[93] *N* = 16	USA, UK, Germany and the Netherlands	51.6 (13.69)	40 (11.58)	44	0%	0%	449.9 (208.0); *n* = 15	NR	Upright: 76.4 (15.63); *n* = 15
Van Kooten *et al.* (2020),[53] *N* = 111	The Netherlands	42.7[a] (G1) 56.6[a] (G2A) 66[a] (G2B)	NR	50 (G1) 100 (G2A) 50 (G2B)	60 (G1) 90 (G2A) 75 (G2B)	20 (G1) 90 (G2A) 50 (G2B)	NR	NR	NR

continued

This article should be referenced as follows: Corbett M, Umemneku-Chikere C, Nevitt S, Deng NJ, Walton M, Fulbright H, *et al.* Enzyme replacement therapy compared with best supportive care for the treatment of Pompe Disease: a systematic review and network meta-analysis [published online ahead of print February 11 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GJRH0730

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TABLE 11 Baseline characteristics of other prospective ERT studies (*continued*)

Study, *N*	Country	Age at ERT start years	Age at onset of disease	% Male	% Using wheelchair	% Respiratory support	6MWT, m (SD)	6MWT % predicted (SD)	Sitting FVC % predicted (SD)
Avalglucosidase alfa studies									
NEO1 and NEO-EXT, Dimachkie *et al.* (2022),[54,94–96] Schoser *et al.* (2020)[97–99] Mozaffar *et al.* (2023),[100] *N* = 24	USA, France, Germany, Belgium, Denmark, the Netherlands, UK Naive, 10	NR	43.3 (23.79), 8	50	0	0	449 (118)	< 45 years: 71.6 (9.9) ≥ 45 years: 56.2 (19.2)	69.2 (19.3)
	USA, France, Germany, Belgium, Denmark, the Netherlands, UK Experienced (ALG), 14	NR	36.3 (16.39), 9	64	0	0	440 (141)	< 45 years: 70.3 (13.4) ≥ 45 years: 54.2 (18.5)	77.3 (16.4)
Cipaglucosidase + miglustat studies									
Byrne *et al.* (2023),[55] *N* = 29	Australia, UK, USA, the Netherlands, New Zealand and Germany: Cohort 1, 11	NR	NR	82	NR	NR	397.2 (96.8)	61 (13.4)	52.6 (13.9)
	Cohort 2, 6	NR	NR	67	100	NR	NA	NA	42.3 (28.2)
	Cohort 4, 6	NR	NR	33	NR	NR	387.3 (161.3)	59 (21.4)	65.3 (21.1)
	Experienced	NR			NR	NR		60.2 (16.2), *n* = 16	57.4 (17.4), *n* = 16
	Naive (Cohort 3)	NR	NR	20	NR	NR	396 (75.2)	67.8 (12.6), *n* = 6	57.2 (20.8), *n* = 6

CA, conference abstract; *N*, sample size; NR, not reported; RS, respiratory support; SD, standard deviation; WC, wheelchair.
a Medians.
b Indicate ERT patients out of the total number (*N*) in the study.

Note
Continuous data are means (SD) unless otherwise indicated.
Cohort 1 indicates 2–6 years ERT-experienced patients; Cohort 2 indicates ≥ 2 years ERT-experienced non-ambulatory patients; Cohort 3 indicates ERT-naive patients; Cohort 4 indicates ≥ 7 years ERT-experienced patients; NR, not reported; *N*, sample size; USA, United States of America; UK, United Kingdom; G1 is group 1 which is made up of patients that discontinue ERT for personal reasons, G2A is group 2A which are deceased patients related to Pompe disease and G2B is group 2B which are deceased patients non-related to Pompe disease.

TABLE 12 Results of other prospective ERT studies

Study, *N*	Subgroups	6MWT (m)	6MWT % predicted	FVC % predicted	Muscle function or strength outcomes	Other outcomes
Alglucosidase studies						
Anderson *et al.* (2014),[33] *N* = 62 (59 on ERT)		CFB with 95% CI, *n* = 20: < 12 months: 43.7 (13.8 to 73.6) 1–3 years: 51.3 (29.1 to 73.5) > 3 years: 16.1 (−21.4 to 53.6)	NR	CFB 95% CI, *n* = 57: < 12 months: 1.77 (−0.75 to 4.29) 1–3 years: −0.21 (−2.55 to 2.14) > 3 years: −2.11 (−5.68 to 1.46)	MRC, CFB 95% CI, *n* = 53: < 12 months: 3.53 (1.39 to 5.66) 1–3 years: 4.04 (2.26 to 5.83) > 3 years: 1.30 (−1.92 to 4.52)	Safety data – see table below.
Angelini *et al.* (2012),[34] 74		Baseline: 320 End of follow-up: 383, $p < 0.001$, $n = 58$ Follow-up ranged from 12 to 54 months.	NR	Baseline: 65.2 4 years: 66.5, $p = 0.22$, $n = 69$	NR	6 patients stopped ventilatory support and 2 started NIV. Of 21 patients continuing with NIV mean hours dropped from 15.6 to 12.1 hours/day.
Angelini *et al.* (2012),[35] *N* = 40 (subgroup of[34])		Baseline: 319 1 year: 371, $p < 0.001$, $n = 32$	NR	NR	NR	NR
Bembi *et al.* (2010),[36] *N* = 24	Juvenile, 7	Baseline: 572.9[a] 1 year: 589,[a] $p < 0.03$ 2 years: 630,[a] $p < 0.03$ 3 years: 664,[a] $p = 0.01$	NR	Baseline: 54[a] 1 year: 56[a] 2 years: 60[a] 3 years: 59.5[a] not ss across time points	NR	Of the 13 patients needing ventilatory support at baseline, this dropped to 8 patients at the end of the study. The median daily ventilation for the remaining 8 patients reduced from 14 to 8 at year 1, 2, 3.
	Adult, 17	Baseline: 116.6[a] 1 year: 213.1,[a] $p < 0.001$ 2 years: 206,[a] $p < 0.001$ 3 years: 265,[a] $p < 0.001$	NR		NR	
Claeys *et al.* (2022),[37] *N* = 12		CFB with 95% CI 6 months: −19.1 (−58.8 to 20.6) 1 year: −41.3 (−86.9 to 4.3) 18 months: −28.5 (−63.9 to 6.9) 2 years: −60.6 (−92.0 to −29.1)	NR	Sitting (*n* = 12): Baseline: 82.8 (24.89) 2 years: 80.3 (25.08) Supine (*n* = 11): Baseline: 65.6 (21.97) 2 years: 65.10 (25.77) Neither result was ss.	MRC: Baseline: 67.2 (8.2) 6 months: 70.4 (7.7) 1 year: 71.1 (8.3) 18 months: 70.4 (8.3) 2 years: 71.3 (8.1) Not ss for all time points	NR
Clemens *et al.* (2017),[38] *N* = 68, CA		NR	Increased for first 2–3 years, then a modest decline over the next 3 years and a decrease of 6.4% over the first 6 years.	% predicted FVC declined by 0.78% (after having received up to 9 years of ERT).	NR	71% of 42 patients who were ventilator free at baseline remained ventilator free. 53% of non-ambulatory at baseline remain non-ambulatory.

continued

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TABLE 12 Results of other prospective ERT studies (*continued*)

Study, *N*	Subgroups	6MWT (m)	6MWT % predicted	FVC % predicted	Muscle function or strength outcomes	Other outcomes
De Vries *et al.* (2012),[39] *N* = 69		NR	NR	Median FU 23 months: Upright: increased by 0.1%/y, *p* = 0.92, *n* = 62	Median FU 23 months: MRC: 1.4%/y, *p* < 0.001, *n* = 69 HHD: 4%/y, *p* < 0.001, *n* = 64 QMFT: 0.7%/y, *p* = 0.14, *n* = 69	No change in median No. of hours of ventilation per day. Also see safety data table
Ditters *et al.* (2023),[40,78] *N* = 121;100		NR	NR	NR	NR	IAR (see safety data table)
Gungor *et al.* (2013),[10] *N* = 283 204 recieved ERT		NR	NR	NR	NR	ERT positively associated with survival: HR = 0.41 (0.19 to 0.87)
Gungor *et al.* (2016),[11,92] *N* = 174		NR	NR	NR	NR	Change in points per year SF-36 PCS, 0–2 years: 1.49 (0.76 to 2.21) > 2 years: −0.15 (−0.43 to 0.13) SF-36 MCS, 0–2 years: 1.03 (−0.07 to 2.13) > 2 years: 0.02 (−0.41 to 0.46)
Hahn *et al.* (2018),[41] *N* = 26 (22 patients were analysed)		NR	NR	Upright FVC decreased ≥ 15% predicted at 1 year: 11.1% (95% CI 0.3% to 48.2%)	GMFM-88: Baseline: 70.9%[a] 1 Year: 85.9%[a] CFB: 0.2%[a]	At 1 year: Invasive ventilator-free survival: 88.7% (61.4% to 97.1%). No deaths.
Harlaar *et al.* (2019)[42,101–103] *N* = 30 LOTS trial patients		NR	10 years FU (*n* = 7): −22.2%, *p* < 0.001	Upright at 10 years FU (*n* = 11): −10.98%, *p* < 0.001 Supine at 10 years FU (*n* = 8): −9.21%, *p* < 0.001	MRC scores were significantly lower after 10 years (graph only, split by sex)	At end of FU 13 (43%) were partially or fully wheelchair dependent compared to 7 at ERT start. 24 (80%) needed NIV compared to 7 (23%) at ERT start. MIP: −1.79% at 10 years MEP: −2.50% at 10 years
Hartung *et al.* (2007),[43] *N* = 11, CA		Baseline: 336 (215) 6 months: 383 (220) CFB: 47 Statistical significance NR	NR	Only FVC reported (not % predicted)	NR	NR

TABLE 12 Results of other prospective ERT studies (*continued*)

Study, *N*	Subgroups	6MWT (m)	6MWT % predicted	FVC % predicted	Muscle function or strength outcomes	Other outcomes
Kuperus *et al.* (2017),[44] *N* = 88	ERT	Baseline: 376[a] 5 years: 416,[a] *n* = 53 CFB: 40.9, *p* = 0.03	NR	Upright: 5 years: CFB: −0.1, *p* = 0.84, *n* = 84 Supine: 5 years: CFB: −2.9, *p* = 0.005, *n* = 74	CFBL at 5 years: MRC score: 0.7, *p* = 0.25, *n* = 88 HHD score: 8.4, *p* < 0.001, *n* = 84 QFMT score: −0.2, *p* = 0.87 R-Pact: 3.6, *p* = 0.004	8 and 9 additional patients needed a ventilator or wheelchair, respectively, at study end. MIP: CFB: −0.5%, *p* = 0.81, *n* = 83 MEP: CFB: 2.6%, *p* = 0.18, *n* = 83
Kuperus *et al.* (2018)[45] *N* = 112 *Values were digitised from plots*	II ACE genotype *N* = 32	Baseline: 424 1 year: 433, 2 years: 434, 3 years: 427, 4 years: 417, 5 years: 406	NR	Baseline: 80 1 year: 80, 2 years: 80, 3 years: 79, 4 years: 78, 5 years: 78	NR	NR
	DD ACE genotype *N* = 41	Baseline: 365 1 year: 368, 2 years: 371, 3 years: 371, 4 years: 365, 5 years: 354	NR	Baseline: 66 1 year: 68, 2 years: 68, 3 years: 67, 4 years: 66, 5 years: 65	NR	
	ID ACE genotype *N* = 58	Baseline: 399 1 year: 428, 2 years: 441, 3 years: 441, 4 years: 430, 5 years: 415	NR	Baseline: 64 1 year: 65, 2 years: 65, 3 years: 65, 4 years: 66, 5 years: 65	NR	
Ravaglia *et al.* (2022),[46] *N* = 18		Baseline: 367 1 year: 424, *p* = 0.01, *n* = 12 3 years: 377 CFB (*digitised from plot*): 6 years FU: −17 (107.98) 15 years FU: −58 (192.73)	NR	NR	NR	NR
Ravaglia *et al.* (2012),[47] *N* = 16		24 months (*digitised from plot):* Mean % change in 6MWT 38.35 (51.7)	NR	NR	NR	Muscle strength, endurance and mass improved in 14 (87%), 13 (81%) and 11 (69%) of patients respectively.
Regnery *et al.* (2012),[48] *N* = 38		All *n* = 21, baseline: 312 (165.5) 1 year: 344 (*p* = 0.006) 2 years: 356.4 (*p* = 0.03) 3 years: 325.6 (*p* = 0.49)	NR	All *n* = 28, baseline: 80.27, 1 year: 79.19, 2 years: 78.62, 3 years: 77.19 All results were not ss.	MRC, all *n* = 38, baseline: 42.29, 1 year: 41.92, 2 years: 43.89, 3 years: 41.19 All results were not ss.	NR
Strothotte *et al.* (2010),[49] *N* = 44		Baseline: 342[a] (mean 341) 12 months: 412[a] (mean 393); 22 *p* < 0.03 for comparison of means	NR	Baseline: 69.9 (SD: 28.1) 12 months: 70 (SD: 26.9); 33	MRC: *n* = 34 Baseline: 41.5 12 months: 42, *p* = 0.31	NR

continued

This article should be referenced as follows: Corbett M, Umemneku-Chikere C, Nevitt S, Deng NJ, Walton M, Fulbright H, *et al.* Enzyme replacement therapy compared with best supportive care for the treatment of Pompe Disease: a systematic review and network meta-analysis [published online ahead of print February 11 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GJRH0730

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TABLE 12 Results of other prospective ERT studies (*continued*)

Study, *N*	Subgroups	6MWT (m)	6MWT % predicted	FVC % predicted	Muscle function or strength outcomes	Other outcomes
van der Meijden *et al.* (2018),[50] *N* = 319 126 at risk of wheelchair, 125 at risk of respiratory support		NR	NR	NR	NR	16 ERT patients started using wheelchair and 28 ERT patients started respiratory support during the follow-up. The hazard ratios for WC and RS comparing patients treated with ERT and untreated patients are 0.36 (0.17 to 0.75) and 1.23 (0.61 to 2.47), respectively.
van der Meijden *et al.* (2018),[51] *N* = 17		NR	7 years: increased by 7.4% (95% CI 2.4 to 12.3); 14	Sitting position Baseline: 87[a] (16–104%) 7 years: −5.2[a]% (95% CI 0.05 to 10.4) Supine position Baseline: 85[a] (39–109%) 7 years: −4.7[a]% (95% CI −4.5 to 13.9)	QMFT *n* = (15): Baseline: 92[a] 7 years: increased by 9.2% (95% CI 1.8 to 16.6) HHD (14 patients): Baseline: 57[a] 7 years: increased by 17.8% (95% CI −3.4 to 39) MRC (17 patients): Baseline: 91.7[a] 7 years: decreased by 1.3% (95% CI −0.7 to 3.28)	NR
Van der Ploeg (2016);[52] Thurberg *et al.* (2015),[93] *N* = 16		6 months: 471.2 CFB: 37.3, *p* = 0.02	NR	Upright, 6 months: 77.6 CFB: 1.8, *p* = 0.67 Supine: 6 months: 60.8 CFBL: 2.9, *p* = 0.41	HHD (*n* = 15), 6 months Upper body: CFB: 43.2, *p* = 0.55 Lower body: CFB: 188.3, *p* = 0.09	PedsQoL Fatigue scale (*n* = 15), 6 months, CFB: 8.1 MIP% (*n* = 13 for upright; *n* = 6 for supine): Upright: CFB: 1.6 Supine: CFB: −8.2 MEP% (*n* = 13 for upright; *n* = 6 for supine): Upright: CFB: 2.4 Supine: CFB: – 11.6 Other measures are GSGMC, GMFS, QMT
Van Kooten *et al.* (2020),[53] *N* = 111		NR	NR	NR	NR	Discontinuation reported in AE table below

TABLE 12 Results of other prospective ERT studies (*continued*)

Study, *N*	Subgroups	6MWT (m)	6MWT % predicted	FVC % predicted	Muscle function or strength outcomes	Other outcomes
Avalglucosidase alfa studies						
NEO1 and NEO-EXT, Dimachkie *et al.* (2022),[54,94–96] *N* = 24 Schoser *et al.* (2020);[98,99] Mozaffar *et al.* (2023);[100] Schoser *et al.* (2020),[97] *N* = 24, CA	Naive	Note Baseline: 449 CFB 12 weeks: −46.5, *n* = 2	Over up to 6 years: −0.70%/year (95% CI −1.57 to 0.17)[b]	Over up to 6 years: −0.47%/year (95% CI −1.19 to 0.24)[b]	NR	MIP % predicted of 1.51 per year (−1.04 to 1.34) and MEP% predicted of 0.73 per year (−0.49 to 1.95)
	Experienced	Baseline: 440 CFB 12 weeks: −53.0, *n* = 3	−0.846%/year (95% CI −1.57 to −0.13)[b]	Baseline: 77.3 (16.4) −0.648%/year (95% CI −1.06 to −0.24)[b]	NR	MIP % predicted of −0.63 per year (−1.56 to 0.30) and MEP% predicted of 0.95 per year (−0.27 to 2.17)
	Naive 5.5 years	NR	−0.965 (−1.89 to −0.04)	Slope: 0.396 (−0.35 to 1.14)	NR	MIP%: 0.74 (−0.61 to 2.10) MEP%: 0.70 (−0.69 to 2.09)
	Switch 5.5 years	NR	−1.216 (−2.03 to −0.41)	Slope: −0.331 (−0.78 to 0.12)	NR	MIP%; −0.95 (−2.00 to 0.11) MEP%: 1.19 (−0.15 to 2.53)
Cipaglucosidase + miglustat studies						
Byrne *et al.* (2023),[55] *N* = 29	ERT Experienced (excludingnon-ambulatory)	CFB 4 years: 20.7, *n* = 9	4 years: 66.2, 9 CFB 4 years: 5.9, *n* = 9	4 years: 55.7, 6 CFB 4 years: 1.0, *n* = 6	MMT LES: Baseline: 30; 15 4 years: 35; 8	NR
	ERT-naive	CFB 4 years: 52.2, *n* = 4	4 years: 82.8, 4 CFB 4 years: 11.7, *n* = 4	4 years: 37, 4 CFB 4 years: 8.3, *n* = 4	MMT LES: Baseline: 29, 5 4 years: 30, 4	NR

AE, adverse event; CA, conference abstract; CFB, change from baseline; CFBL, change from baseline at randomisation; FU, follow-up; GMFCS, Gross Motor Functional Classification System; GMFM = Gross Motor Function Measure; IAR, infusion-associated reaction; LES, lower extremities score; MMT, manual muscle test; NIV, non-invasive ventilation; NR, not reported; ss, statistically significant.

a Indicates median.

b Indicates slope.

Note

Continuous data are means unless otherwise indicated.

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TABLE 13 Adverse events reported in other prospective ERT studies of alglucosidase

Authors	Deaths	Adverse events					
		TEAE, *n*/*N* (%)	TEAE related to treatment *n*/*N* (%)	IAR, *n*/*N* (%)	Withdrawal due to TEAE *n*/*N* (%)	SAE, *n*/*N* (%)	Discontinuation, *n*
Anderson *et al.* (2014)[33]							
Angelini *et al.* (2012)[35]							4
Clemens *et al.* (2017),[38]	4						
De Vries *et al.* (2012)[39]				12/69 (17)			3
Ditters *et al.* (2023)[78]				32/121 (26.4) (home and hospital)			
Hahn *et al.* (2018)[41]							
Harlaar *et al.* (2019)[42]					2		2
Kuperus *et al.* (2017)[44]				19/88 (26)			
Regnery *et al.* (2012)[48]					1		2
Strothotte *et al.* (2009)[49]							0
Van der Ploeg (2016)[52]		6/16 (35.5)		4/16 (25)	0	1	
Van Kooten *et al.* (2020)[53]	14 (10 were Pompe related)						10

IAR, infusion-associated reactions; SAE, serious adverse event; TEAE, treatment emergent adverse event.

TABLE 14 Adverse events reported in other prospective ERT studies of avalglucosidase alfa and cipaglucosidase plus miglustat

Authors	Subgroup	Adverse events					
		TEAE, *n*/*N* (%)	TEAE related to treatment *n*/*N* (%)	IAR, *n*/*N* (%)	Withdrawal due to TEAE *n*/*N* (%)	SAEs, *n*/*N* (%)	Discontinuation, *n*
Avalglucosidase alfa studies							
Dimachkie *et al.* (2022)[54]	Total	24 (100)	18 (75)	6 (25)	1 (4)	9 (38)	3
	Naive	10 (100)	8 (80)	3 (30)	1 (10)	5 (50)	
	Experienced	14 (100)	10 (71)	3 (21)	0 (0)	4 (29)	
Cipaglucosidase + miglustat studies							
Byrne *et al.* (2023)[104]	Experienced, 23	23 (100)	16 (70)	10 (43)	2 (9)	8 (35)	3
	Naive, 6	6 (100)	4 (67)	3 (50)	0 (0)	4 (67)	

IAR, infusion-associated reactions; SAE, serious adverse event; TEAE, treatment emergent adverse event.

Appendix 7 Digitisation of Kaplan–Meier from randomised controlled trials included in the network meta-analyses

The changes from baseline values (mean and 95% CI) for 6MWD and FVC of the treatments evaluated in each RCT at varying time points were extracted by digitising the change in baseline curves using the plotDiogitizer software on the website (https://plotdigitizer.com/). The digitised values are reported in *Tables 15* and *16*. The digitised values were used in the NMA primary, sensitivity and explorative analysis.

TABLE 15 Digitised values from the change in baseline 6MWD

6MWD (m)	LOTS			COMET			PROPEL		
	Alglu	Placebo	Difference	Aval	Alglu	Difference	Cipa + Mig	Algu	Difference
12/13 weeks	14.42 (8.59 to 20.26)	−1.79 (−11.13 to 7.54)	16.22 (5.2 to 27.23)	18.06 (1.06 to 35.07)	15.03 (−2.73 to 32.8)	3.03 (−21.56 to 27.63)	17.16 (7.69 to 26.63)	20.48 (4.23 to 36.74)	−3.32 (−22.13 to 15.5)
25/26 weeks	27.88 (17.42 to 38.34)	3.64 (−7.09 to 14.37)	24.24 (9.26 to 39.22)	27.23 (8.01 to 46.45)	9.55 (−10.81 to 29.91)	17.68 (−10.32 to 45.68)	32.16 (14.5 to 49.83)	30.43 (16.3 to 44.57)	1.73 (−20.9 to 24.36)
37/38 weeks	29.3 (15.9 to 42.7)	−0.04 (−13.31 to 13.23)	29.34 (10.48 to 48.2)	28.52 (11 to 46.03)	15.42 (−2.85 to 33.69)	13.1 (−12.21 to 38.41)	25.24 (4.89 to 45.59)	38.65 (24.38 to 52.93)	−13.41 (−38.27 to 11.45)
49/52 weeks	27.04 (12.97 to 41.12)	1.22 (−13.86 to 16.29)	25.83 (5.21 to 46.45)	32.13 (12.85 to 51.41)	2.06 (−16.52 to 20.65)	30.06 (3.28 to 56.85)	33.44 (12 to 54.89)	38.3 (16.53 to 60.07)	−4.86 (−35.41 to 25.7)
LFU	28.13 (10.36 to 45.91)	−2.38 (−21.87 to 17.12)	30.51 (4.13 to 56.89)	32.13 (12.85 to 51.41)	2.06 (−16.52 to 20.65)	30.06 (3.28 to 56.85)	33.44 (12 to 54.89)	38.3 (16.53 to 60.07)	−4.86 (−35.41 to 25.7)

Note
Last follow-up during the double-blind phase of the RCT; week 78 in LOTS trial, week 49 in the COMET trial and week 52 in the PROPEL trial.

TABLE 16 Digitised values from the change in baseline FVC

FVC (% predicted)	LOTS			COMET			PROPEL		
	Alglu	Placebo	Difference	Aval	Alglu	Difference	Cipa + Mig	Algu	Difference
12/13 weeks	1.8 (0.83 to 2.77)	−0.82 (−2.25 to 0.62)	2.61 (0.86 to 4.37)	3.04 (1.54 to 4.53)	0.64 (−0.91 to 2.19)	2.4 (0.24 to 4.55)	0.27 (−2.01 to 2.55)	−0.95 (−4.11 to 2.21)	1.22 (−2.68 to 5.12)
25/26 weeks	1.59 (0.47 to 2.7)	−0.33 (−1.59 to 0.94)	1.91 (0.21 to 3.62)	3.21 (1.67 to 4.74)	0.57 (−1.04 to 2.19)	2.63 (0.41 to 4.86)	−1.51 (−4.17 to 1.14)	−4.4 (−8.3 to −0.49)	2.89 (−1.84 to 7.61)
37/38 weeks	1.35 (0.09 to 2.6)	−2.45 (−4.08 to −0.82)	3.8 (1.7 to 5.91)	2.2 (0.25 to 4.15)	0.55 (−1.45 to 2.55)	1.65 (−1.14 to 4.44)	−4.08 (−6.33 to -1.83)	−0.58 (−7.1 to 5.93)	−3.5 (−10.39 to 3.4)
49/52 weeks	1.65 (0.35 to 2.96)	−1.95 (−3.7 to −0.2)	3.6 (1.4 to 5.8)	2.89 (1.19 to 4.58)	0.46 (−1.33 to 2.24)	2.43 (−0.03 to 4.89)	−4.1 (−7 to −1.21)	−3.64 (−7.14 to −0.14)	−0.46 (−5.01 to 4.08)
LFU	1.32 (−0.2 to 2.85)	−2.61 (−4.41 to −0.81)	3.93 (1.55 to 6.32)	2.89 (1.19 to 4.58)	0.46 (−1.33 to 2.24)	2.43 (−0.03 to 4.89)	−4.1 (−7 to −1.21)	−3.64 (−7.14 to −0.14)	−0.46 (−5.01 to 4.08)

Note
Last follow-up during the double-blind phase of the RCT; week 78 in LOTS trial, week 49 in the COMET trial and week 52 in the PROPEL trial.

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Appendix 8 Risk-of-bias assessments

TABLE 17 Randomised controlled trials risk-of-bias assessment results (using August 2019 template)

Bias domains and signalling questions	Responses, supporting text and judgements		
	LOTS[12]	COMET[22,90]	PROPEL[21]
Randomisation process			
1.1 Was the allocation sequence random?	Y: Randomisation was performed using a centralised Interactive Voice Response System	Y: A centralised treatment allocation system (interactive response technology) was used.	Y: Patients were randomly assigned using proprietary and validated interactive response technology software
1.2 Was the allocation sequence concealed?	Y: See 1.1	Y: See 1.1	Y: See 1.1
1.3 Were there baseline imbalances that suggest a problem with the randomisation process?	No: although there were notable imbalances in age at onset, sex and use of a walking device which were likely due to chance	No: although chance imbalances in age and age at onset	*N*
Risk-of-bias judgement	LOW (although chance imbalances exist in sex, age at symptom onset and use of walking device)	LOW	LOW
Deviations from the intended interventions			
2.1. Were participants aware of their assigned intervention during the trial?	PN: The trial was placebo-controlled, though details of blinding were not reported. EMA assessment report was reassuring on this issue.	PN: The two treatments have the same dosing schedule and administration method. EMA assessment report states that 'The plans described in relation to blinding measures are generally considered adequate'	PN: Cipaglucosidase alfa and alglucosidase were both administered intravenously and at the same frequency. A matching placebo for miglustat was used with alglucosidase alfa, and black or dark covering over cipaglucosidase alfa and alglucosidase alfa reconstituted solution were used during infusion.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN: see 2.1	PN: see 2.1	PN: See 2.1
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended interventions that arose because of the trial context?	N/A	N/A	N/A
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	N/A	N/A	N/A
2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	N/A	N/A
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	N/A	N/A	N/A

TABLE 17 Randomised controlled trials risk-of-bias assessment results (using August 2019 template) (*continued*)

Bias domains and signalling questions	Responses, supporting text and judgements		
	LOTS[12]	COMET[22,90]	PROPEL[21]
2.7 If *N*/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	N/A	N/A	N/A
Risk-of-bias judgement	LOW	LOW	LOW
Missing outcome data			
3.1 Were outcome data available for all, or nearly all, participants randomised?	*N*: 90% completed the study	Y: 95% of participants completed the primary analysis period	Y: 5% discontinued treatment. 2 Alg + placebo patients were not dosed due to absence of genotype confirmation
3.2 If *N*/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N	N/A	N/A
3.3 If *N*/PN to 3.2: Could missingness in the outcome depend on its true value?	Y	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	*N*: 5% difference in dropouts between groups. Reasons for missing data were similar.	NA	NA
Risk-of-bias judgement	SOME CONCERNS	LOW	LOW
Measurement of the outcome			
4.1 Was the method of measuring the outcome inappropriate?	N	N	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	N	Y: COVID-19 resulted in some patients experiencing missed infusions, missed assessments or delayed visits. Delayed visits and makeup assessments were allowed, and the data were assigned to a specified visit time point (for the analyses) when appropriate, i.e. data from the delayed visits were remapped to the earlier planned study visits. The EMA noted that using an analysis model based on *actual* (rather than remapped) time points is expected to lead to a more reliable estimation of the treatment difference. The EMA reported that there were 17 subjects (13 vs. 4) with a delayed visit of at least 4 weeks after the target day, 8 of these 17 subjects (8 vs. 0) had a delay of at least 6 weeks after the target day.[79] See 5.3 below.
4.3 If *N*/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N	N	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N/A	N/A	N/A

continued

TABLE 17 Randomised controlled trials risk-of-bias assessment results (using August 2019 template) (*continued*)

Bias domains and signalling questions	Responses, supporting text and judgements		
	LOTS[12]	**COMET**[22,90]	**PROPEL**[21]
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	N/A	N/A	N/A
Risk-of-bias judgement	LOW	LOW	LOW
Selection of the reported result			
5.1 Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalised before unblinded outcome data were available for analysis?	Y, though not all results were reported (see below)	Y: Analyses were planned using a mixed model for repeated measures (MMRM) using change from baseline; treatment difference estimated based on least square means at week 49. The EMA considered this to be adequate.	Y: Primary end-point analysis (6MWD) used a mixed-effect model with repeated measures using observed values. Secondary end points were analysed using an ANCOVA model. For sensitivity analyses, ANCOVA was used for 6MWD and MMRM was used for all key secondary efficacy end points.
Is the numerical result being assessed likely to have been selected, on the basis of the results, from... 5.2.... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	N	N
5.3... multiple eligible analyses of the data?	Y: From EMA report – Analyses were planned using a LME model. Sensitivity analyses were performed with WMW test and with analysis of covariance. The data did not fit the model assumptions of the LME model. The EMA stated that the ANCOVA model could not be considered as valid since the analysis of the residuals distribution was lacking, but that the WMW results could be assessed since its validity was less questionable.[80]The published paper presented results based on the ANCOVA analyses.	N (see 5.1)	Y: The paper did not report all the analyses (see 5.1 above) for all key secondary outcomes, nor for all the key outcomes for the ERT-naive/experienced subgroups. The company thought that the normality assumption for the predefined MMRM analysis was significantly violated and the non-parametric ANCOVA results were more appropriate. The EMA disagreed, noting that (1) visual inspection of the residuals from both the original and the (EMA) requested MMRM analyses did not suggest violation of the normality assumption, and (2) the ANCOVA analyses used LOCF for handling missing data and was performed based on remapping of visit time points (not the actual time points – see 4.2 above); EMA thought that both could introduce bias in the estimated efficacy treatment difference.[79]
Risk-of-bias judgement	HIGH	LOW	HIGH
Overall risk of bias	HIGH	LOW	HIGH

ANCOVA, analysis of covariance; LME, linear mixed effects; LOCF, last observation carried forward; N, no; N/A, not applicable; WMW, Wilcoxon–Mann–Whitney; Y, yes.

Appendix 9 Additional network meta-analyses results

This appendix section presents all the estimates obtained from the NMA (both random-effects and fixed-effects models). The estimates are presented as mean difference (95% CrI).

Results of primary analysis

The primary analysis evaluated the treatment effectiveness of AVAL, ALG, CM and placebo using digitised data from 49/52 weeks for all the RCTS (LOTS, PROPEL and COMET) in ERT-naive population. NMA was carried out using FE and RE models. The results for the RE are presented in the main article and the result from the FE is presented *Table 18*.

TABLE 18 Primary analysis – relative treatment effects of FVC and 6MWD (RE and FE models)

	PBO	ALG	AVAL	CM
Mean differences (95% CrI) from random-effects NMA				
Outcome: FVC				
PBO		3.58 (−2.95 to 10.13)	6.01 (−3.40 to 15.33)	3.11 (−6.79 to 13.00)
ALG	−3.58 (−10.13 to 2.95)		2.43 (−4.22 to 9.07)	−0.48 (−7.97 to 6.98)
AVAL	−6.01 (−15.33 to 3.40)	−2.43 (−9.07 to 4.22)		−2.90 (−12.91 to 7.07)
CM	−3.11 (−13.00 to 6.79)	0.48 (−6.98 to 7.97)	2.90 (−7.07 to 12.91)	
DIC: 26.76				
Outcome: 6MWD				
PBO		24.68 (3.97, 45.65)	53.55 (19.66 to 87.31)	19.29 (−17.43 to 56.09)
ALG	−24.68 (−45.65 to −3.97)		28.87 (1.74 to 55.66)	−5.39 (−35.72 to 25.58)
AVAL	−53.55 (−87.31 to −19.66)	−28.87 (−55.66 to −1.74)		−34.26 (−74.80 to 6.96)
CM	−19.29 (−56.09 to 17.43)	5.39 (−25.58 to 35.72)	34.26 (−6.96 to 74.80)	
DIC: 13.94				
Mean differences (95% CrI) from fixed-effects NMA				
Outcome: FVC				
PBO		3.60 (1.40 to 5.80)	6.03 (2.74 to 9.35)	3.11 (−1.94 to 8.16)
ALG	−3.60 (−5.80 to −1.40)		2.43 (−0.02 to 4.87)	−0.49 (−5.04 to 4.03)
AVAL	−6.03 (−9.35 to −2.74)	−2.43 (−4.87 to 0.02)		−2.92 (−8.07 to 2.21)
CM	−3.11 (−8.16 to 1.94)	0.49 (−4.03 to 5.04)	2.92 (−2.21 to 8.07)	
DIC: 26.81				
Outcome: 6MWD				
PBO		24.74 (4.59 to 44.93)	53.71 (20.50 to 86.93)	19.43 (−16.68 to 55.44)
ALG	−24.74 (−44.93 to −4.59)		28.97 (2.33 to 55.67)	−5.31 (−35.29 to 24.81)
AVAL	−53.71 (−86.93 to −20.50)	−28.97 (−55.67 to −2.33)		−34.28 (−74.37 to 5.97)
CM	−19.43 (−55.44 to 16.68)	−5.31 (−24.81 to 35.29)	34.28 (-5.97 to 74.37)	
DIC: 13.85				

ALG, alphaglucosidase; AVAL, avalglucosidase; CM, cipaglucosidase + miglustat; PBO, placebo.

Note
Column treatment vs. row treatment.

Results of sensitivity analysis

The sensitivity analysis evaluated the treatment effectiveness of AVAL, ALG, CM and placebo using digitised data from 49/52 weeks for LOTS and PROPEL, and 37/38 weeks for COMET in ERT-naive population.

The sensitivity analysis was carried out using 37/38 weeks from COMET because of an outlier in the 6MWD which skewed the data making a substantial difference between the means and medians values. The relative treatment effectiveness is reported in *Table 19*.

TABLE 19 Sensitivity analysis – relative treatment effects of FVC and 6MWD (RE and FE models)

	PBO	ALG	AVAL	CM
Mean differences (95% CrI) from random-effects NMA				
Outcome: FVC				
PBO		3.59 (−3.00 to 10.17)	5.24 (−4.18 to 14.64)	3.14 (−6.77 to 13.10)
ALG	−3.59 (−10.17 to 3.00)		1.64 (−5.09 to 8.35)	−0.46 (−7.94 to 7.04)
AVAL	−5.24 (−14.64 to 4.18)	−1.64 (−8.35 to 5.09)		−2.10 (−12.17 to 7.95)
CM	−3.14 (−13.10 to 6.77)	0.46 (−7.04 to 7.94)	2.10 (−7.95 to 12.17)	
DIC: 14.14				
Outcome: 6MWD				
PBO		24.79 (3.65 to 45.62)	37.22 (4.08 to 70.10)	19.38 (−17.51 to 56.78)
ALG	−24.79 (−45.62 to −3.65)		12.43 (−13.18 to 38.07)	−5.41 (−36.06 to 25.24)
AVAL	−37.22 (−70.10 to −4.08)	−12.43 (−38.07 to 13.18)		−17.84 (−57.83 to 22.31)
CM	−19.38 (−56.78 to 17.51)	5.41 (−25.24 to −36.06)	17.84 (−22.31 to 57.83)	
DIC: 26.78				
Mean differences (95% CrI) from fixed-effects NMA				
Outcome: FVC				
PBO		3.59 (1.37 to 5.82)	5.24 (1.69 to 8.79)	3.12 (−1.93 to 8.17)
ALG	−3.59(−5.82 to −1.37)		1.65 (−1.12 to 4.43)	−0.47 (−4.98 to 4.08)
AVAL	−5.24 (−8.79 to −1.69)	−1.65 (−4.43 to 1.12)		−2.12 (−7.41 to 3.22)
CM	−3.12 (−8.17 to 1.93)	0.47 (−4.08 to 4.98)	2.12 (−3.22 to 7.41)	
DIC: 14.17				
Outcome: 6MWD				
PBO		24.89 (4.67 to 45.13)	37.32 (5.52 to 69.21)	19.55 (−16.65 to 55.82)
ALG	−24.89 (−45.13 to −4.67)		12.43 (−12.29 to 37.47)	−5.34 (−35.67 to 24.86)
AVAL	−37.32 (−69.21 to −5.52)	−12.43 (−37.47 to 12.29)		−17.77 (−57.14 to 21.25)
CM	−19.55 (−55.82 to 16.65)	5.34 (−24.86 to 35.67)	17.77 (−21.25 to 57.14)	
DIC: 26.73				

ALG, alphaglucosidase; AVAL, avalglucosidase; CM, cipaglucosidase + miglustat; PBO, placebo.

Note
Column treatment vs. row treatment

Results of other explorative analysis using various time points of the digitised data set

In addition to the primary and sensitivity analysis carried out using the ERT-naive population, NMA was conducted using the digitised data set from four time points (12/13 weeks, 24/26 weeks, 37/38 weeks and LFU) for all the RCTs. The LFU are 49 weeks, 78 weeks and 52 weeks for COMET, LOTS and PROPEL, respectively. These are presented in *Tables 20* and *21*.

TABLE 20 Relative treatment effects of FVC and 6MWD (RE models) for varying time points

	PBO	ALG	AVAL	CM
12/13 weeks, mean differences (95% CrI)				
Outcome: FVC				
PBO		1.91 (−4.54 to 8.32)	4.30 (−4.86 to 13.47)	3.12 (−6.52 to 12.67)
ALG	−1.91 (−8.32 to 4.54)		2.39 (−4.11 to 8.93)	1.21 (−5.99 to 8.32)
AVAL	−4.30 (−13.47 to 4.86)	−2.39 (−8.93 to 4.11)		−1.18 (−11.00 to 8.42)
CM	−3.12 (−12.67 to 6.52)	−1.21 (−8.32 to 5.99)	1.18 (−8.42 to 11.00)	
DIC: 12.85				
Outcome: 6MWD				
PBO		16.00 (3.65 to 28.35)	18.76 (−8.94 to 46.44)	12.49 (−10.62 to 35.48)
ALG	−16.00 (−28.35 to −3.65)		2.76 (−22.24 to 27.82)	−3.51 (−23.15 to 16.01)
AVAL	−18.76 (−46.44 to 8.94)	−2.76 (−27.82 to 22.24)		−6.27 (−37.98 to 25.51)
CM	−12.49 (−35.48 to 10.62)	3.51 (−16.01 to 23.15)	6.27 (−25.51 to 37.98)	
DIC: 24.20				
24/26 weeks, mean differences (95% CrI)				
Outcome: FVC				
PBO		3.80 (−2.75 to 10.28)	6.42 (−2.84 to 15.52)	6.67 (−3.24 to 16.57)
ALG	−3.80 (−10.28 to 2.75)		2.62 (−3.98 to 9.18)	2.87 (−4.66 to 10.41)
AVAL	−6.42 (−15.52 to 2.84)	−2.62 (-9.18 to 3.98)		0.25 (−9.74 to 10.22)
CM	−6.67 (−16.57 to 3.24)	−2.87 (−10.41 to 4.66)	−0.25 (10.22 to 9.74)	
DIC: 13.69				
Outcome: 6MWD				
PBO		23.60 (7.64 to 39.43)	40.34 (7.78 to 72.39)	24.96 (−2.88 to 52.99)
ALG	−23.60 (−39.43 to −7.64)		16.74 (−11.76 to 44.95)	1.36 (−21.82 to 24.37)
AVAL	−40.34 (−72.39 to −7.78)	−16.74 (−44.95 to 11.76)		−15.39 (−51.64 to 21.33)
CM	−24.96 (−52.99 to 2.88)	−1.36 (−24.37 to 21.82)	15.39 (−21.33 to 51.64)	
DIC: 25.60				

continued

TABLE 20 Relative treatment effects of FVC and 6MWD (RE models) for varying time points (*continued*)

	PBO	ALG	AVAL	CM
37/38 weeks, mean differences (95% CrI)				
Outcome: FVC				
PBO		3.60 (−3.02 to 10.15)	5.25 (−4.22 to 14.70)	0.10 (−10.86 to 11.18)
ALG	−3.60 (−10.15 to 3.02)		1.65 (−5.12 to 8.40)	−3.50 (−12.50 to 5.51)
AVAL	−5.25 (−14.70 to 4.22)	−1.65 (−8.40 to 5.12)		−5.15 (−16.33 to 6.07)
CM	−0.10 (−11.18 to 10.86)	3.50 (−5.51 to 12.50)	5.15 (−6.07 to 16.33)	
DIC: 14.87				
Outcome: 6MWD				
PBO		28.60 (9.30 to 47.83)	41.10 (9.26 to 72.88)	14.98 (−16.72 to 46.71)
ALG	−28.60 (−47.83 to −9.30)		12.50 (−13.31 to 38.09)	−13.62 (−39.01 to 11.87)
AVAL	−41.10 (−72.88 to −9.26)	−12.50 (−38.09 to 13.31)		−26.12 (−62.14 to 10.13)
CM	−14.98 (−46.71 to 16.72)	13.62 (−11.87 to 39.01)	26.12 (−10.13 to 62.14)	
DIC: 25.95				
LFU, mean differences (95% CrI)				
Outcome: FVC				
PBO		3.38 (−3.27 to 9.97)	5.80 (−3.55 to 15.03)	2.86 (−7.41 to 13.18)
ALG	−3.38 (−9.97 to 3.27)		2.42 (−4.27 to 9.06)	−0.52 (−8.43 to 7.38)
AVAL	−5.80 (−15.03 to 3.55)	−2.42 (−9.06 to 4.27)		−2.94 (−13.28 to 7.36)
CM	−2.86 (−13.18 to 7.41)	0.52 (−7.38 to 8.43)	2.94 (−7.36 to 13.28)	
DIC: 14.37				
Outcome: 6MWD				
PBO		26.41 (0.36 to 52.51)	55.12 (16.65 to 94.05)	20.63 (−24.03 to 66.00)
ALG	−26.41 (−52.51 to −0.36)		28.72 (−0.13 to 57.91)	−5.78 (−43.84 to 32.42)
AVAL	−55.12 (−94.05 to −16.65)	−28.72 (−57.91 to 0.13)		−34.49 (−82.72 to 13.33)
CM	−20.63 (−66.00 to 24.03)	5.78 (−32.42 to 43.84)	34.49 (−13.33 to 82.72)	
DIC: 27.34				

ALG, alphaglucosidase; AVAL, avalglucosidase; CM, cipaglucosidase + miglustat; PBO, placebo.

Note
Column treatment vs. row treatment.

TABLE 21 Relative treatment effects of FVC and 6MWD (FE models) for varying time points

	PBO	ALG	AVAL	CM
12/13 weeks, mean differences (95% CrI)				
Outcome: FVC				
PBO		1.92 (0.20 to 3.62)	4.30 (1.54 to 7.04)	3.14 (−1.13 to 7.41)
ALG	−1.92 (−6.62 to −0.20)		2.86 (0.24 to 4.54)	1.22 (−2.69 to 5.13)
AVAL	−4.30 (−7.04 to −1.54)	−2.86 (−4.54 to −0.24)		−1.16 (−5.63 to 3.31)
CM	−3.14 (−7.41 to 1.13)	−1.22 (−5.13 to 2.69)	1.16 (−3.31 to 5.63)	
DIC: 12.73				
Outcome: 6MWD				
PBO		16.06 (5.05 to 26.99)	18.79 (−7.75 to 45.45)	12.63 (−9.02 to 34.10)
ALG	−16.06 (−26.99 to −5.05)		2.73 (−21.60 to 27.18)	−3.44 (−22.22 to 15.19)
AVAL	−18.79 (−45.45 to 7.75)	−2.73 (−27.18 to 21.60)		−6.17 (−37.12 to 24.48)
CM	−12.63 (−34.10 to 9.02)	3.44 (−15.19 to 22.22)	6.17 (−24.48 to 37.12)	
DIC: 24.45				
24/26 weeks, mean differences (95% CrI)				
Outcome: FVC				
PBO		3.80 (1.71 to 5.91)	6.44 (3.38 to 9.49)	6.68 (1.52 to 11.81)
ALG	−3.80 (−5.91 to −1.71)		2.63 (0.42 to 4.85)	2.87 (−1.84 to 7.58)
AVAL	−6.44 (−9.49 to −3.38)	−2.63 (−4.85 to −0.42)		0.24 (−4.94 to 5.45)
CM	−6.68 (−11.81 to −1.52)	−2.87 (−7.58 to 1.84)	−0.24 (−5.45 to 4.94)	
DIC: 13.67				
Outcome: 6MWD				
PBO		23.73 (8.91 to 38.61)	40.64 (9.40 to 71.87)	25.17 (−1.41 to 52.00)
ALG	−23.73 (−38.61 to −8.91)		16.91 (−10.87 to 44.72)	1.44 (−20.83 to 23.86)
AVAL	−40.64 (−71.87 to −9.40)	−16.91 (−44.72 to 10.87)		−15.46 (−50.73 to 20.08)
CM	−25.17 (−52.00 to 1.410	−1.44 (−23.86 to 20.23)	15.46 (−20.08 to 50.73)	
DIC: 25.68				
37/38 weeks, mean differences (95% CrI)				
Outcome: FVC				
PBO		3.60 (1.42 to 5.80)	5.25 (1.71 to 8.83)	0.11 (−7.13 to 7.35)
ALG	−3.60 (−5.80 to −1.42)		1.65 (−1.14 to 4.46)	−3.50 (−10.42 to 3.43)
AVAL	−5.25 (−8.83 to −1.71)	−1.65 (−4.46 to 1.14)		−5.15 (−12.61 to 2.32)
CM	−0.11 (−7.35 to 7.13)	3.50 (−3.43 to 10.42)	5.15 (−2.32 to 12.61)	
DIC: 14.92				

TABLE 21 Relative treatment effects of FVC and 6MWD (FE models) for varying time points (*continued*)

	PBO	ALG	AVAL	CM
Outcome: 6MWD				
PBO		28.55 (9.85 to 47.11)	41.00 (10.14 to 71.99)	14.83 (−15.95 to 45.58)
ALG	−28.55 (−47.11 to −9.85)		12.45 (−12.39 to 37.65)	−13.72 (−38.40 to 10.88)
AVAL	−41.00 (−71.99 to 10.14)	−12.45 (37.65. 12.39)		−26.17 (−61.61 to 9.08)
CM	−14.83 (−45.58 to 15.95)	13.72 (−10.88 to 38.40)	26.17 (9.08 to 61.61)	
DIC: 26.12				
LFU, mean differences (95% CrI)				
Outcome: FVC				
PBO		3.39 (1.03 to 5.77)	5.82 (2.35 to 9.33)	2.89 (−2.85 to 8.70)
ALG	−3.39 (−5.77 to −1.03)		2.43 (−0.12 to 4.99)	−0.51 (−5.78 to 4.77)
AVAL	−5.82 (−9.33 to −2.35)	−2.43 (−4.99 to 0.12)		−2.93 (−8.75 to 2.96)
CM	−2.89 (−8.70 to 2.85)	0.51 (−4.77 to 5.78)	2.93 (−2.96 to 8.75)	
DIC: 14.40				
Outcome: 6MWD				
PBO		26.27 (0.85 to 51.70)	55.09 (17.44 to 92.78)	20.48 (−24.27 to 65.57)
ALG	−26.27 (−51.70 to −0.85)		28.82 (0.48 to 57.23)	−5.79 (−43.35 to 32.11)
AVAL	−55.09 (−92.78 to −17.44)	−28.82 (−57.23 to −0.48)		−34.61 (−81.60 to 12.43)
CM	−20.48 (−65.57 to 24.27)	5.79 (−32.11 to 43.35)	34.61 (−12.43 to 81.60)	
DIC: 27.67				

ALG, alphaglucosidase; AVAL, avalglucosidase; CM, cipaglucosidase + miglustat; PBO, placebo.

Note
Column treatment vs. row treatment.

TABLE 22 Relative treatment effects of FVC and 6MWD (RE and FE model) of all ERT vs. placebo at time varying time points

	Treatments comparison	FVC % predicted	DIC	6MWD	DIC
Mean differences (95% CrI); FE model					
12/13 weeks	ERT vs. PBO	2.21 (1.22 to 3.21)	18.51	18.19 (11.47 to 31.47)	33.20
25/26 weeks	ERT vs. PBO	1.38 (0.40 to 2.37)	28.1	22.91 (14.48 to 31.47)	36.99
37/38 weeks	ERT vs. PBO	2.74 (1.54 to 3.95)	28.31	28.29 (18.76 to 37.79)	37.60
49/52 weeks	ERT vs. PBO	2.40 (1.20 to 3.61)	30.92	24.62 (13.9 to 35.39)	41.38
LFU	ERT vs. PBO	2.91 (1.67 to 4.16)	30.24	28.50 (16.08 to 40.90)	42.09
Mean differences (95% CrI); RE model					
12/13 weeks	ERT vs. PBO	2.04 (−0.01 to 3.83)	19.20	18.28 (10.99 to 25.28)	32.59
25/26 weeks	ERT vs. PBO	0.63 (−2.45 to 3.35)	21.83	22.83 (13.94 to 31.66)	36.76
37/38 weeks	ERT vs. PBO	2.48 (−0.58 to 5.42)	22.78	28.23 (18.45 to 38.05)	37.50
49/52 weeks	ERT vs. PBO	1.69 (−1.57 to 4.69)	22.82	24.66 (13.76 to 35.61)	41.56
LFU	ERT vs. PBO	2.27 (−0.97 to 5.23)	23.27	28.52 (15.92 to 41.02)	41.89

DIC, deviance information criteria; FE, fixed effect; PBO, placebo; RE, random effects.

Appendix 10 Natural history studies

TABLE 23 Baseline characteristics of longitudinal natural history studies of Pompe disease

Study, *N*	Setting	Age at onset years (SD)	Age at diagnosis (SD)	% Male	% Using wheelchair	% Respiratory support	Notes
Berger (2016),[56] *N* = 22	USA	29 (13)	NR	41	19	32	VC% predicted: 69
Gungor (2011),[57]	International	NR	38[a]	47	38	40	Overlapping cohorts
Gungor (2011),[58] *N* = 110, CA	The Netherlands	NR	36[a]	NR	NR	NR	
Hagemans (2004),[59] *N* = 210	International	NR	NR	46	46	45	
Hagemans (2006),[60] *N* = 52	The Netherlands	NR	35 (14)	40	46	37	
Lefeuvre *et al.* (2023),[30] *N* = 33	France	37.5 (16)	44 (16)	52	NR	NR	
Kanters (2011),[61] *N* = 80	The Netherlands	NR	NR	51	48.8	30	
Muller-Felber (2007),[62] *N* = 18	Germany	30.7	40.9	34	47	32	
Pellegrini (2005),[63] *N* = 29	France	41 (11)	NR	38	NR	55	FVC % predicted: 57.0
Slonim (2007),[64] *N* = 34	USA, Spain, Canada	32.4 (11)	NR	53	NR	NR	
van der Beek (2009),[65] *N* = 16	The Netherlands	24 (11)	27 (12)	38	50	25	Overlapping cohorts
van der Beek (2011),[66] *N* = 92	The Netherlands	30[a]	36[a]	44	29	28	
van der Beek (2012),[67] *N* = 66	The Netherlands	32[a]	40.2[a]	51	32	29	
Wokke (2008),[68] *N* = 61 (58 completed the study)	USA, France and the Netherlands, Europe	29.2 (11.5)	36.3 (11)	38	NR	7	

CA, conference abstract; CS, cross-sectional; FU, follow-up; MMT, manual muscle test; N/A, not applicable; RHS, Rotterdam Handicap Scale.
a Median.

TABLE 24 Results of longitudinal natural history studies (some cohorts may overlap)

Study, *N*, setting	Motor function	Pulmonary function	Muscle function	Other outcomes
Berger (2016),[56] *N* = 22, Prospective United States	NR	FVC % predicted: Baseline: 69 FU: digitised and calculated from graph 5–9 months: 73.22; *n* = 15 10–14 months: 75.9; *n* = 12 15–19 months: 59.8; *n* = 4 20–30 months: 77.1; *n* = 3	NR	NR
Gungor (2011),[57] *N* = 268, Prospective International	NR	NR	NR	Median FU of 3.5 years 34 out of 268 patients died during FU. Median age at death was 56 years. Median survival after diagnosis without ERT was 27 years. Estimated 5-year survival after diagnosis was 95%.
Gungor (2011),[58] *N* = 110, Prospective Netherlands	NR	NR	NR	Median FU of 2.3 years 23 patients died during FU. Median survival after diagnosis was 27 years. 5-year survival for patients without wheelchair or ventilations was 96%, and was 74% for patients who were wheelchair-bound and had respiratory support.
Hagemans (2004),[59] *N* = 210, Prospective International	NR	NR	NR	No significant differences for any SF-36 scale between baseline and 1-year FU (*n* = 38)
Hagemans (2006),[60] *N* = 52, Prospective Netherlands	NR	NR	NR	At 2 years: 4 patients had died, 2 patients had started using wheelchair, 2 patients went from partial to full wheelchair use. 3 patients started using respiratory support (8–9 hours a day) 5 patients increased the number of hours of ventilation per day. RHS Score – Baseline: 25.5, 2-year FU: 24.3 *p* = 0.035
Lefeuvre 2023,[30] *N* = 33, Prospective France	NR	Sitting FVC: 'Over time' mean change: −0.07 (*p* < 0.001) Supine FVC: 'Over time' mean change: −0.07 (*p* < 0.001)	NR	27 (82%) needed no technical walking assistance at last FU (median 12 years FU)
Kanters (2011),[61] *N* = 80, Prospective Netherlands	NR	NR	NR	EQ-5D utility mean score: Overall population: 0.72, *n* = 72 ≤ 5 years of disease: 0.74, *n* = 31 6–15 years of disease: 0.70, *n* = 18 > 15 years of disease: 0.69, *n* = 22 Ambulatory support: 0.67, *n* = 37 Respiratory support: 0.61, *n* = 20
Muller-Felber (2007),[62] *N* = 18 Appears retrospective Germany	NR	NR	NR	Mean FU 14.8 years: 6 patients lost ambulation. 10 patients initiated MV – the mean time between diagnosis and start of ventilation was 4.6 years.

TABLE 24 Results of longitudinal natural history studies (some cohorts may overlap) (*continued*)

Study, *N*, setting	Motor function	Pulmonary function	Muscle function	Other outcomes
Pellegrini (2005),[63] *N* = 29, Retrospective France	NR	Patients with MV, FVC 39.2% Patients without MV, FVC 78.9%, $p < 0.0001$	NR	NR
Slonim (2007),[64] *N* = 34, Prospective evaluation of a nutrition and exercise therapy USA	NR	Annual % change in mean FVC in the 26 compliant patients was −0.21, and in the 8 non-compliant patients was −1.70; $p = 0.14$	Walton score, *n* = 26 compliant: mean difference between pre–post therapy −0.29 (95% CI −0.36 to −0.19). For the 8 non-compliant patients: −0.01 (95% CI −0.36 to 0.34).	NR
van der Beek (2009),[65] *N* = 16, Retrospective Netherlands	NR	At FU (mean of 9 years): mean upright FVC% = 61.9, *n* = 13. Mean rate of decline= 1.6% per year ($p = 0.002$)	At FU (mean of 8 years): mean MRC score= 29.1 Decreased by 0.5 points per year ($p < 0.001$)	During FU, 50% became wheelchair dependent and 19% needed respiratory support. 2 patients died.
van der Beek (2011),[66] *N* = 53, Prospective Netherlands, Belgium	NR	FU for median of 1.6 years upright FVC predicted decreased by 0.9% per year ($p = 0.094$) and supine FVC reduced by 1.2% per year ($p = 0.049$). MIP reduced by 3.2% per year ($p = 0.02$), MEP reduced by 3.8% per year ($p < 0.01$).	NR	During FU: 3 patients started MV 5 patients increased the number of hours of ventilation per day. One patient died.
van der Beek (2012),[67] *N* = 66, Prospective Netherlands, Belgium	NR	FU for median of 1.6 years Mean yearly change in FVC upright was −1% ($p = 0.02$) and in the supine position it was −1.3% ($p = 0.06$).	MRC score FU: deteriorated by 1.3% per year ($p < 0.001$) HHD: deteriorated 2.6% per year ($p < 0.001$).	One patient became wheelchair-bound, MV initiated in four patients, and eight patients increased their number of hours of ventilation per day. One patient died.
Wokke (2008),[68] *N* = 61, Prospective USA, France, the Netherlands, Europe	6MWT, *n* = 47 At 1 year: 340.6 m 6MWT % predicted at 1 year: 53.7 No changes from baseline reported except *mean variability between the first and second test was 7%.*	FVC % predicted, *n* = 58: Upright: At 1 year: a decline of 4.6% ($p < 0.01$) Supine: At 1 year: a decline of 5.5% ($p < 0.01$) MIP, *n* = 58: No significant change at 1 year MEP, *n* = 58: At 1 year: a decline of 7.3% ($p < 0.01$)	QMT, *n* = 54 At 1 year: mean leg score: 44.6%. Declined by 7.1% ($p < 0.01$) Mean arm score 72.7%. Declined by 4% ($p < 0.01$)	SF-36: PCS and MCS: No clinically meaningful changes in PCS or MCS were seen from baseline to 1 year.

CA, conference abstract; FU, follow-up; MCS, mental component summary; MMT, manual muscle test; MEP, maximal expiratory pressure; MV, mechanical ventilation; NR, not reported; PCS physical component summary; RHS, Rotterdam Handicap Scale.

TABLE 25 Cross-sectional studies reporting natural history data of Pompe disease patients

Study, *N*	Setting	Age at onset	Age at diagnosis	Results (and other outcomes reported)
De Filippi (2014),[69] *N* = 126, Patients have been described by Angelini *et al.* (2012)[34]	Italy	NR	NR	Compared FVC, 6MWT and Walton score for different polymorphisms. Polymorphisms did not demonstrate significant associations with vital capacity (compared to controls), Walton score and 6MWT. Disease-free life is presented via subgroup (based on gene/allele).
Hagemans (2005),[70] *N* = 54[a]	The Netherlands	28.1 (14.3)	35.4 (13.9)	WC use = 48%, ventilation = 37%; median number of hours of ventilation was 11.5 hours per day.
Hagemans (2005),[71] *N* = 255[a]	International	NR	NR	WC use = 44%, RS = 45%; median number of hours of ventilation per day is 10.5.
Hagemans (2007),[72] *N* = 257[a]	International	NR	37 (14)	WC use: 42%; RS: 46% HRQoL (RHS) based on ± wheelchair use and respiratory support. RHS correlation with SF-36 subscales. RHS score: mean 25.9 (scale 0–36) Mean score for patient with RS was 22.9 and for patients without RS was 28.5 ($p < 0.001$). The mean score for patients on WC compared to patients without WC was 20.9 vs. 29.5 ($p < 0.001$).
Haley (2003),[85] *N* = 30 (including 3 with infantile disease)	International (mostly USA)	NR	NR	Ventilator use = 77%; WC= 83% Mobility and self-care using the Paediatric Evaluation of Disability Inventory (PEDI): mean functional scores for mobility = 43.7 and self-care = 51.9.
Rigter (2012),[74] *N* = 42 (13 children and 29 adults)	The Netherlands	NR	Children: 10[b] Adult: 43[b]	At diagnosis, median sitting position FVC was 92%, while median supine position FVC was 77%. At diagnosis, 2 adults were using a wheelchair, and 4 adults were using non-invasive ventilation
van Capelle (2016),[75] *N* = 31	The Netherlands	2.6[b]	4[b]	14 of 29 patients (48%) had decreased FVC indicated by z-score below −1.64 (i.e. considered abnormal). 13 patients had a percentage of predicted below 80%. FVC sitting: 82%. FVC supine: 79% HHD sum score 55% (*n* = 24) WC use= 26%, RS= 19%
Winkel (2005),[76] (Review of *N* = 225 published cases)	International	24[b], *n* = 172	33[b], *n* = 206	28% artificial ventilation, 8% wheelchair use Muscular and respiratory symptoms by age at onset.

CA, conference abstract; MMT, manual muscle test; NR, not reported; RHS, Rotterdam Handicap Scale; RS use of respiratory support; WC, wheelchair use.
a Patient cohorts substantially overlap in these studies.
b Median.