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Comparing the efficacy of cipaglucosidase alfa plus miglustat with other enzyme replacement therapies for late-onset Pompe disease: a network meta-analysis utilizing patient-level and aggregate data

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Aim: Late-onset Pompe disease is characterized by progressive loss of muscular and respiratory function. Until recently, standard of care was enzyme replacement therapy (ERT) with alglucosidase alfa. Second-generation ERTs avalglucosidase alfa (aval) and cipaglucosidase alfa with miglustat (cipa+mig) are now available. Without head-to-head trials comparing aval with cipa+mig, an indirect treatment comparison is informative and timely for understanding potential clinical differentiation. **Materials & methods:** A systematic literature review was performed to identify relevant studies on cipa+mig and aval. Using patient-level and aggregate published data from randomized controlled trials (RCTs) and phase I/II and open-label extension (OLE) trials, a multi-level network meta-regression was conducted, adjusting for various baseline covariates, including previous ERT duration, to obtain relative effect estimates on 6-minute walk distance (6MWD, meters [m]) and forced vital capacity (FVC, % predicted [pp]). Analyses of two networks were conducted: Network A, including only RCTs, and network B, additionally including single-arm OLE and phase I/II studies. **Results:** Network B (full evidence analysis) showed that cipa+mig was associated with a relative increase in 6MWD (mean difference 28.93 m, 95% credible interval [8.26–50.11 m]; Bayesian probability 99.7%) and FVC (2.88 pp [1.07–4.71 pp]; >99.9%) compared with aval. The comparison between cipa+mig and aval became more favorable for cipa+mig with increasing previous ERT duration for both end points. Analysis of network A showed that cipa+mig was associated with a relative decrease in 6MWD (-10.02 m [-23.62 to 4.00 m]; 91.8%) and FVC (-1.45 pp [-3.01 to 0.07 pp]; 96.8%) compared with aval. **Conclusion:** Cipa+mig showed a favorable effect versus aval when all available evidence was used in the analysis.

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Keywords: cipaglucosidase alfa • indirect treatment comparison • miglustat • Pompe disease

Pompe disease

Pompe disease is a rare disorder caused by a lack or deficiency of the enzyme acid α-glucosidase that hydrolyzes lysosomal glycogen [1]. It is characterized by progressive loss of muscular and respiratory function [2]. Two forms of

Pompe disease exist: fast-progressing infantile-onset Pompe disease, which presents in the first months of life and is often fatal within 1 year of age without treatment, and late-onset Pompe disease (LOPD), which is progressive and can present at variable ages [1,3]. The combined frequency of infantile- and late-onset Pompe disease is estimated as 1 in 23,000 [4].

Treatments for Pompe disease

Pharmacologic treatment for Pompe disease consists of enzyme replacement therapy (ERT) to slow disease progression. ERT with recombinant human acid α-glucosidase (rhGAA) alglucosidase alfa (alglu) was the first approved treatment of LOPD [5]. Recently, advances have been made with the approvals of second-generation ERTs using rhGAA, such as avalglucosidase alfa (aval) [6,7] and cipaglucosidase alfa in combination with the small molecule stabilizer miglustat (cipa+mig) [8–12].

Need for an indirect treatment comparison

No head-to-head trials are currently available comparing aval with cipa+mig in patients with LOPD. Instead, the two novel ERTs have been studied in two pivotal, phase III randomized controlled trials (RCTs): the COMET trial comparing aval (n = 51) with alglu (n = 49) in ERT-naive patients [13], and the PROPEL trial comparing cipa+mig (n = 85) with alglu (n = 38) in primarily ERT-experienced patients with a smaller cohort of ERT-naive patients (77% ERT experienced, 23% ERT naive). Therefore, an indirect treatment comparison (ITC) is required to obtain estimates on their relative effect. This comparison may help us to better understand whether eligible patients with LOPD may benefit from one or another treatment, and potentially inform health technology assessment, cost effectiveness and reimbursement decisions.

ITC methods & multi-level network meta-regression (ML-NMR): ensuring populations are comparable

A standard network meta-analysis (NMA) collects aggregate data from multiple studies on multiple treatments in order to produce consistent estimates of relative treatment effects between each pair of treatments in the network [14,15]. It combines direct evidence (from head-to-head RCTs) and indirect evidence (via a common comparator) in a coherent manner from studies that form a connected network of treatment comparisons. Patient populations included in the RCTs forming a network can differ with respect to prognostic factors (i.e., factors that have an influence on the prognosis of the disease or condition) or with respect to effect modifiers (i.e., factors that lead to a differential effect of the intervention). While differences in prognostic factors across the RCTs included in the network should not impact the NMA results due to randomization and control, an imbalance of effect modifiers can lead to biased results [16].

Data from PROPEL and other clinical studies (e.g., ATB200-02 [17], NEO-1/-EXT [18]) suggest previous ERT treatment is a treatment effect modifier. Thus, a standard NMA might not be suitable to study the indirect treatment effect of cipa+mig versus aval, since the two RCTs (PROPEL and COMET) forming the network via the common comparator alglu differ with respect to previous treatment of the respective study populations at baseline.

Anchored population-adjustment indirect comparison methods such as matching-adjusted indirect comparison [16,19] or simulated treatment comparison (STC) [16,20] would allow a comparison to be made between cipa+mig and aval in similar populations, but since the COMET trial included only ERT-naive patients, results would be similar to an NMA of COMET and the ERT-naive subgroup from PROPEL.

Single-arm studies, which are common in rare diseases, can contribute valuable evidence on the effect of treatment in the trial population included. Unanchored matching-adjusted indirect comparison or unanchored STC (i.e., not linked via a common comparator) can be performed to derive relative effects adjusted to the comparator trial population, but they are applicable only to the simple pairwise scenario.

Another population-adjustment indirect comparison method, multi-level network meta-regression (ML-NMR) [21], can provide relative effect estimates for any target population of interest, accounting for various treatment effect modifiers such as a mix of ERT-naive and ERT-experienced patients with LOPD [22,23]. ML-NMR can be applied to any connected network with any mixture of individual patient-level data (IPD) and aggregate data, and is a generalization of network meta-regression, which is usually based on aggregate data only. Single-arm studies can be included into the network by matching them to comparator arms of the existing RCTs [24,25]. ML-NMR is specified as a valid method for population-adjusted ITC by the National Institute for Health and Care Excellence [21,26].

Objective

The aim of this study was to provide relative effect estimates for cipa+mig versus aval for a patient population such as in the PROPEL study (i.e., including both ERT-naive [23%] and ERT-experienced [77%] patients with LOPD), reflective of the real-world LOPD population, as demonstrated by ongoing registry studies, in which 78–80% of patients have received ERT previously [19,20]. We accomplish this objective through an ML-NMR.

Methods

Systematic literature review

A systematic literature review (SLR) was conducted identifying relevant RCTs and non-RCTs including single-arm phase I/II and open-label extension (OLE) trials in adult patients with LOPD of the following ERTs: alglu, aval and cipa+mig. Development of the search strategy and eligibility criteria for studies were based on the Population, Intervention, Comparator, Outcome, Study design (PICOS[+]) framework, as presented in Supplementary Table 1.

The SLR followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [27], and the search was conducted on 7–15 September 2022, to identify hits that were available until 31 May 2022. An update of the SLR was performed in August 2023 to retrieve additional hits from 31 May 2022 to 31 July 2023.

Search strategy

The search was run through the Ovid SP® platform. A manual clinical trial registries search was conducted to ensure that ongoing studies and completed third-party studies were exhaustively identified. To complement the search for published trials, abstracts published between 2020 and 2023 from key international conferences were searched. In addition, the grey literature sources Google Scholar and Center for Drug Evaluation and Research were searched. Details on the search strategies can be found in Supplementary Tables 2–16.

Study selection

Each of the records identified during the search was assessed for relevance against the PICOS(+) scheme. For the 2022 SLR, double independent record selection was performed. Discrepancies concerning inclusion or exclusion criteria were resolved through reconciliation by a third reviewer. For the 2023 SLR update, a single reviewer selected the records. Records selected during the SLR were then further assessed for eligibility into the ITC.

Data extraction

All data (trial details, patient characteristics, treatments and outcomes) were extracted by one investigator.

Quality assessment

The critical appraisal of all included RCTs was done using the revised Risk Of Bias tool for randomized trials [28], focusing on the primary and key secondary end points, and the quality of included interventional non-RCTs was assessed using the Risk Of Bias In Non-randomized Studies – of Interventions tool (if full-text publications were available) [29].

ML-NMR approach

The ML-NMR method is described in detail in Phillippo *et al.* [21]. In short, an individual-level regression is fitted to IPD studies and a (numeric) integration of this regression is performed over the aggregate data studies. The 'multinma' package of the R statistical software provides a Bayesian implementation through the Stan software [30–33]. The Bayesian framework enables informative priors, which reflect a prior belief of the possible values of the pooled relative effect and effects of covariates, to be chosen to alleviate the limitations of small numbers of studies and low sample sizes, a common issue in rare diseases such as Pompe disease.

Matching of single-arm studies

Single-arm phase I/II and OLE trials were included into the network by matching them to a comparator arm of the comparative studies. The choice of the appropriate comparator arm was based on a matching criterion summing the distances between the (aggregate) baseline characteristics of the single-arm trial and the potential comparator arm (Supplementary Material) [24].

Outcomes

Outcomes assessed were changes from baseline in 6-minute walk distance (6MWD, m) and forced vital capacity (FVC, % predicted). These two outcomes capture the key Pompe disease manifestations of impaired motor and pulmonary function and served as either the primary or key secondary end point in the recent pivotal RCTs for LOPD treatments, COMET and PROPEL. The primary timepoint of assessment was week 52, but outcome values at timepoints other than week 52 were also included in the analysis.

Models

The linear regression models that were part of the ML-NMR aimed to include all baseline covariates that were considered potential treatment effect modifiers affecting the outcomes of interest, if reported in the studies. Literature and review of LOPD RCTs suggested the following baseline covariates: age [2,13,34,35], sex, baseline outcome values [2,13], height, weight [2], previous ERT duration or ERT status [2,36], angiotensin-converting enzyme genotype [37], cross-reactive immunological material status and severity of muscular damage [34]. In addition, the models included the timepoints of visit (weeks) for each study.

Suitable marginal distributions were chosen for the covariates from which to draw the points for numerical integration over aggregate studies (Supplement Material).

Covariates were included in the model as main effects (prognostic factor) and interacting with treatment (treatment effect modifier). Covariates were estimated for each treatment independently by specifying a separate regression model for each treatment, if data permitted, and for treatment classes with a regression model per treatment class; the latter approach assumed shared effect modifiers for treatments of the same class.

For 6MWD and FVC, mean difference (MD) between treatments with associated 95% credible intervals (CrIs) were calculated. The Bayesian probability that the treatment was superior (MD >0) or inferior (MD <0) to the reference treatment was also derived. These probabilities are the Bayesian equivalent of one-sided p-values. In line with the recommendations of the American Statistical Association [38], no strict threshold for interpreting these Bayesian probabilities was adopted. Instead, the probability itself was reported. Probabilities were interpreted to suggest strong evidence (probability $<0.1\%$ or $>99.9\%$), evidence (probability between 0.1% and 5% or between 95% and 99.9%), weak evidence (probability between 5% and 10% or 90% and 95%) and no evidence [39].

Both fixed-effects (FE) and random-effects (RE) ML-NMR models were evaluated. In RE models, an informative prior was chosen for the between-study heterogeneity parameter τ, as recommended by ISPOR (details in Supplementary Figures 4 & 5) [40,41].

The deviance information criterion (DIC) and the heterogeneity standard deviation τ (the latter for RE models only) were used to assess goodness-of-fit of the models and to select the final model [42]. A decrease of at least 5 points in the DIC of the RE model in comparison with the DIC of the FE model was considered as an indicator of heterogeneity in the network of evidence [43].

Scenarios

A base case scenario was evaluated in which all included covariates were set to the target population of the PROPEL trial (which included a mix of ERT-naive and ERT-experienced patients with LOPD reflective of the real-world population). To study the impact of covariates on relative effects, the covariate values were varied one by one, keeping the remaining covariate values as in the base case scenario.

Ranking of treatments

The surface under the cumulative ranking curve (SUCRA) is a metric to evaluate which treatment in a network is likely to be the most efficacious [44]. The posterior SUCRA ranking was calculated for each analysis (details in the Supplement).

Results

SLR results

A total of 1262 records were identified in the specified databases, and a total of 44 publications representing nine studies and three systematic reviews were included in the SLR (Supplementary Figure 1). A list of included publications can be found in Supplementary Table 17.

Quality assessment of the studies revealed low (for the included RCTs) to moderate (for the included single-arm/extension/observational studies for which full-text publications were available) risk of bias (Supplementary Tables 18 & 19).

Three of the nine studies included in the SLR and their corresponding records were excluded from the ITC: two studies had neither cipa+mig nor aval as an intervention or comparator [5,45] and one study was not an RCT [46]. Also, three systematic reviews were excluded from the ITC [35,47,48]. This resulted in a total of 34 records/six studies included in the ITC (Supplementary Table 17) [2,13,18,49–51]. All included studies were prospectively planned sponsor-initiated studies of high-quality standard.

Trial & patient characteristics

The trial and baseline characteristics of the included studies are shown in Table 1.

In the OLE trials, patients switching to the investigational treatment (aval in COMET OLE, cipa+mig in PROPEL OLE) after the double-blind period were re-baselined in our analysis, and a previous ERT duration of the length of the double-blind period (0.9 years for COMET OLE, 1 additional year for PROPEL OLE) was assigned to them.

The analysis used patient-level data from the PROPEL trial and aggregate-level data from the other five studies.

Efficacy data

Efficacy results of the included studies are shown in Supplementary Table 20, Supplementary Figures 2 & 3.

Networks

Two different networks were considered in this study: a network including only the phase III RCTs PROPEL and COMET, forming a connected network via the common comparator alglu (network A – RCTs only, Figure 1), and a network also including the single-arm and OLE studies for cipa+mig and aval (network B – full evidence, Figure 1).

Matching of single-arm studies

The cipa+mig arms from ATB200-02 and PROPEL OLE were matched to the alglu arm from PROPEL, the aval arm from COMET OLE was matched to the alglu arm from COMET, and the aval arm from NEO-1/-EXT was matched to the alglu arm from PROPEL and, as a sensitivity analysis, to the alglu arm from COMET, since the matching criterion revealed similar results (Supplementary Table 21).

Estimation of covariate effect

The baseline covariates included in the models were age (years), sex (% male), previous ERT duration (years), and 6MWD (m; for analysis of 6MWD) or FVC (% predicted; for analysis of FVC). For the analysis of network A, cipa+mig and aval were grouped into the same treatment class due to limited data from only two RCTs, and the effect of covariates was estimated separately for {cipa+mig, aval} and for {alglu}. For the analysis of network B, the evidence base allowed the effect of covariates to be estimated separately for {cipa+mig}, {aval} and {alglu}, but also the grouping {cipa+mig, aval}, {alglu} was explored.

Model evaluation

Assessment of the ML-NMR models is shown in Table 2, providing the DIC for all models, and the estimated between-study heterogeneity standard deviation τ for RE models.

As can be seen, the between-study standard deviation τ was high in comparison to estimated treatment effects when covariates were estimated for two treatment classes, suggesting more significant between-study heterogeneity. This was confirmed by the improved model fit for 6MWD of the RE model over the FE model (DIC decreased >5 points), but not for FVC (similar DICs).

In contrast, between-study heterogeneity seemed low or accounted for in the models where the covariate effect was estimated separately for the three ERTs: τ was low, and the DICs were similar for both FE and RE models. Based on those considerations, we chose B-FE-3 as the final model to analyze network B for both outcomes.

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Table 1. Trial and patient baseline characteristics of included trials.

Trial name	NCT	Trial design	Follow-up time (weeks)	Population	Intervention	n	Age, mean (SD)	Male (%)	ERT duration in years, mean (SD)	6MWD in meters, mean (SD)	FVC (predicted, %), mean (SD)	Ref.
NEO-1/-EXT	NCT01898364/ NCT02032524	Phase I/II, single arm	312	ERT-N	Aval	10	44.8 (20.3)	30.0	0.0 (0.0)	449.2 (118.4)	69.2 (19.3)	[17,52]
				ERT-E		14	46.7 (14.1)	64.3	4.0 (2.0)†	440.4 (141.0)	77.3 (16.5)	
COMET	NCT02782741	Phase III RCT	49	ERT-N	Aval	51	46.0 (14.5)	52.9	0.0 (0.0)	399.3 (110.9)	62.5 (14.4)	[12]
					Alglu	49	50.3 (13.7)	51.0	0.0 (0.0)	378.1 (116.2)	61.6 (12.4)	
COMET OLE	NCT02782741	Phase III OLE	96‡	ERT-E‡	Aval	44	50.7 (13.9)	54.5	0.9 (0)‡	384.7 (139.6)	61.5 (13.5)	[49,53]
ATB200-02	NCT02675465	Phase I/II, single arm	208	ERT-E	Cipa+mig	17	46.4 (11.7)§	64.7	7.0 (1.6)¶	393.5 (119.7)	57.1 (17.9)	[48]
				ERT-N	Cipa+mig	6	47.2 (12.0)#	16.7	0.0 (0.0)	396.0 (75.2)	57.2 (20.8)	
PROPEL	NCT03729362	Phase III RCT	52	ERT-E	Cipa+mig	65	48.1 (12.6)††	43.1††	7.5 (3.4)††	346.9 (110.2)	67.9 (19.1)	[2]
				ERT-N		20	46.0 (15.3)††	40.0††	0.0 (0.0)	393.6 (112.4)	80.2 (18.7)	
				ERT-E	Alglu‡‡	30	45.9 (13.5)††	46.7††	7.1 (3.6)††	334.6 (114.0)	67.5 (21.0)	
				ERT-N		7	43.0 (13.5)††	71.4††	0.0 (0.0)	420.9 (135.7)	79.1 (22.6)	
PROPEL OLE	NCT04138277	Phase III OLE	52	ERT-E	Cipa+mig	37	46.0 (12.7)§§	51.4	6.7 (4.3)††	359.7 (137.4)††	62.8 (20.5)††	[50,54]

†This was derived from the range of 0.9 to 7.9 years provided in Pena *et al.* [55], using formulas from Wan *et al.* [56] and assuming a median of (7.9–0.9)/2 = 3.5.
‡Patients who switched from alglu to aval after the double-blinded primary analysis period in COMET were re-baselined at week 49; therefore, those patients were followed for 96 weeks and considered ERT experienced with a previous ERT duration of the length of the double-blinded primary analysis period (i.e., 49 weeks = 0.9 years).
§This was derived as follows: Median and range of Cohort 1 and 4 provided by Mozaffar *et al.* [17] were converted to mean and SD using formulas from Wan *et al.* [56]. Then, a weighted mean and pooled SD was calculated to obtain mean and SD of the pooled Cohort 1 and 4.
¶A weighted mean and pooled SD was calculated from mean and SD values for Cohort 1 and 4 provided by Mozaffar *et al.* [17] to obtain mean and SD of the pooled Cohort 1 and 4.
#This was derived as follows: Median and range provided in Schoser *et al.* 2022 [57] were converted to mean and SD using formulas from Wan *et al.* [56].
††From individual patient-level data.
‡‡Excluding one patient who deliberately underperformed on baseline assessments to meet inclusion criteria as described in Schoser *et al.* [2].
§§This was derived as follows: Median and range were converted to mean and SD using formulas from Wan *et al.* [56].
6MWD: 6-minute walk distance; alglu: Alglucosidase alfa; aval: Avalglucosidase alfa; cipa+mig: cipaglucosidase alfa plus miglustat; ERT: Enzyme replacement therapy; ERT-E: ERT experienced; ERT-N: ERT naive; FVC: Forced vital capacity; OLE: Open-label extension; RCT: Randomized controlled trial; SD: Standard deviation.

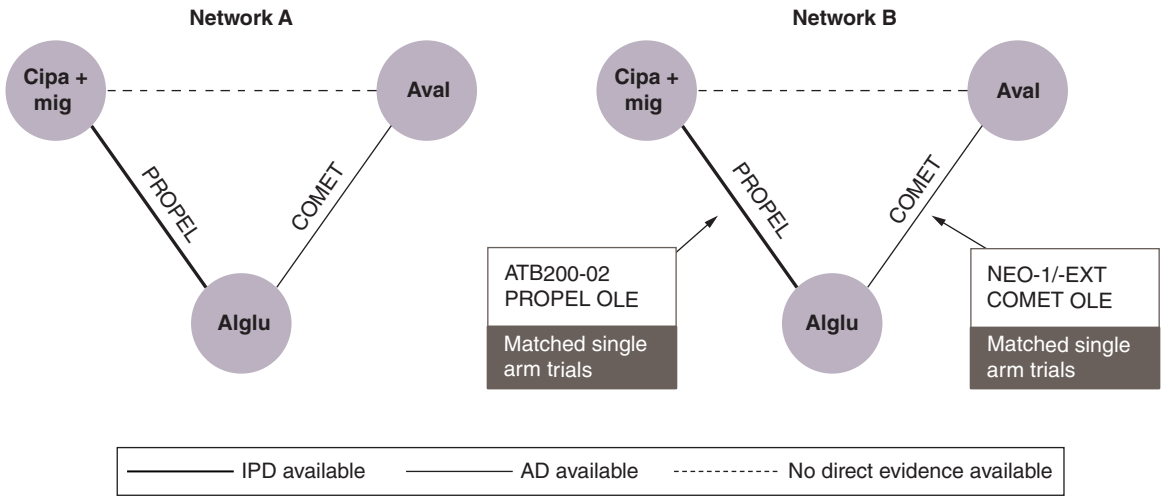

Figure 1. Networks for six-minute walk distance (m) and forced vital capacity (% predicted). Network A: RCTs-only network, network B: full evidence network.
AD: Aggregate data; alglu: Alglucosidase alfa; aval: Avalglucosidase alfa; cipa: Cipaglucosidase alfa; IPD: Individual patient-level data; mig: Miglustat; OLE: Open-label extension.

Table 2. Goodness-of-fit of ML-NMR models.

Model	Network	Treatment classes	Matching	6MWD (m)		FVC (% predicted)	
				DIC	τ [95% CrI]	DIC	τ [95% CrI]
A-FE-2	A	{cipa+mig, aval}, {alglu}	NA	543.0	NA	634.3	NA
B-FE-2	B	{cipa+mig, aval}, {alglu}	aval from NEO-1/-EXT to alglu from PROPEL	642.3	NA	731.7	NA
B-RE-2	B	{cipa+mig, aval}, {alglu}	aval from NEO-1/-EXT to alglu from PROPEL	615.8	12.3 [7.6 to 17.5]	734.9	3.0 [0.0 to 11.9]
B-FE-3	B	{cipa+mig}, {aval}, {alglu}	aval from NEO-1/-EXT to alglu from PROPEL	631.0	NA	715.3	NA
B-RE-3	B	{cipa+mig}, {aval}, {alglu}	aval from NEO-1/-EXT to alglu from PROPEL	631.8	0.3 [0.0 to 2.8]	715.3	0.4 [0.0 to 5.1]
SB-FE-2	B	{cipa+mig, aval}, {alglu}	aval from NEO-1/-EXT to alglu from COMET	637.2	NA	741.3	NA
SB-RE-2	B	{cipa+mig, aval}, {alglu}	aval from NEO-1/-EXT to alglu from COMET	611.8	12.2 [7.3 to 17.4]	736.4	6.4 [0.0 to 14.4]
SB-FE-3	B	{cipa+mig}, {aval}, {alglu}	aval from NEO-1/-EXT to alglu from COMET	630.3	NA	716.0	NA
SB-RE-3	B	{cipa+mig}, {aval}, {alglu}	aval from NEO-1/-EXT to alglu from COMET	632.2	0.4 [0.0 to 4.0]	721.3	0.4 [0.0 to 5.4]

A-FE-2: Analysis of network A (RCTs only) with FE model and estimating the covariate effect separately for {cipa+mig, aval} and {alglu}; B-FE-2: Analysis of network B (full evidence) with FE model and estimating the covariate effect separately for {cipa+mig, aval} and {alglu}; B-RE-2: Analysis of network B (full evidence) with RE model and estimating the covariate effect separately for {cipa+mig, aval} and {alglu}; B-FE-3: Analysis of network B (full evidence) with FE model and estimating the covariate effect separately for {cipa+mig}, {aval} and {alglu}; B-RE-3: Analysis of network B (full evidence) with RE model and estimating the covariate effect separately for {cipa+mig}, {aval} and {alglu}; SB-FE-2: Analysis of network B (full evidence) with FE model and estimating the covariate effect separately for {cipa+mig, aval} and {alglu}, with aval from NEO-1/-EXT matched to alglu from COMET; SB-RE-2: Analysis of network B (full evidence) with RE model and estimating the covariate effect separately for {cipa+mig, aval} and {alglu}, with aval from NEO-1/-EXT matched to alglu from COMET; SB-FE-3: Analysis of network B (full evidence) with FE model and estimating the covariate effect separately for {cipa+mig}, {aval} and {alglu}, with aval from NEO-1/-EXT matched to alglu from COMET; SB-RE-3: Analysis of network B (full evidence) with RE model and estimating the covariate effect separately for {cipa+mig}, {aval} and {alglu}, with aval from NEO-1/-EXT matched to alglu from COMET.
6MWD: 6-minute walk distance; alglu: Alglucosidase alfa; aval: Avalglucosidase alfa; cipa+mig: cipaglucosidase alfa with miglustat; CrI: Credible interval; DIC: Deviance information criterion; FE: Fixed effect; FVC: Forced vital capacity; NA: Not applicable; RE: Random effect.

Relative effects estimation based on ML-NMR

Base case scenario results

Base case covariate settings were the same as in PROPEL with age = 46.95 years, % male = 45.08, ERT duration = 5.744 years, 6MWD (m) = 355.8, FVC (% predicted) = 70.42, time = 52 weeks.

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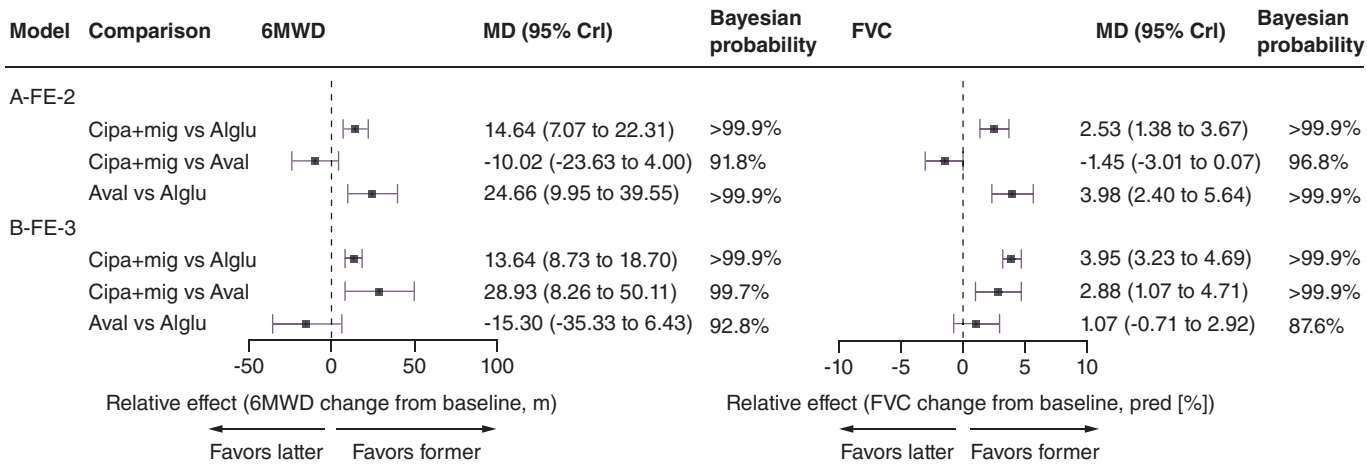

Figure 2. Forest plots for six-minute walk distance (m) and forced vital capacity (% predicted), base case scenario.
A-FE-2: Analysis of network A (RCTs only) with fixed-effects model and estimating the covariate effect separately for {cip+mig, aval} and {alglu}; B-FE-3: Analysis of network B (full evidence) with fixed-effects model and estimating the covariate effect separately for {cipa+mig}, {aval} and {alglu}.
6MWD: 6-minute walk distance; alglu: Alglucosidase alfa; aval: Avalglucosidase alfa; cipa+mig: Cipaglucosidase alfa plus miglustat; CrI: Credible interval; FVC: Forced vital capacity; MD: Mean difference; RCT: Randomized controlled trial.

Relative effects under the base case scenario at week 52 are shown in Figure 2 for the selected ML-NMR models.

The analysis of network A (RCTs only; Model A-FE-2), driven primarily by the subset of matched ERT-naive patients in the RCT network (PROPEL: 27 ERT-naive patients), showed that cipa+mig was associated with an increase in 6MWD (m) (MD 14.64 m, 95% CrI [7.07 to 22.31]; Bayesian probability >99.9%) and FVC (% predicted; 2.53 [1.38 to 3.67]; >99.9%) as compared with alglu, with a reduction in 6MWD (-10.02, [-23.62 to 4.00]; 91.8%) and FVC (-1.45 [-3.01 to 0.07]; 96.8%) compared with aval, and aval was associated with an increase in 6MWD (24.66 [9.95 to 39.55]; >99.9%) and FVC (3.98 [2.40 to 5.64]; >99.9%) compared with alglu.

The analysis of network B (full evidence; Model B-FE-3) revealed that cipa+mig was associated with an increase in 6MWD and FVC compared with alglu and aval (6MWD: 13.64 [8.73 to 18.70]; >99.9% and 28.93 [8.26 to 50.11]; 99.7%, respectively; FVC: 3.95 [3.23 to 4.69]; >99.9% and 2.88 [1.07 to 4.71]; >99.9%, respectively), and aval was associated with a reduction in 6MWD (-15.30 [-35.33 to 6.43]; 92.8%), but not different in FVC (1.07 [-0.71 to 2.92]; 87.6%) compared with alglu.

Results of other models evaluated for network B were directionally consistent with those of Model B-FE-3, with evidence – or strong evidence – of a favorable effect of cipa+mig versus aval for both end points across all models (Supplementary Figure 4).

Ranking of treatments

The SUCRA scores for 6MWD and FVC for the base case scenario are shown in Figure 3.

For the analysis of network A and both end points, the SUCRA score was highest for aval, with the posterior probability of ranking the best close to 1. Cipa+mig had the second-best SUCRA score, with the posterior probability of ranking the best of approximately 0.5.

For the analysis of network B (full evidence), cipa+mig always had the highest SUCRA score, with the posterior probability of ranking the best being 1. For 6MWD, the second-best treatment option according to the SUCRA score was alglu, while for FVC it was aval. Results were generally consistent for the other models evaluated (Supplementary Figure 5).

Impact of covariates on relative effects

Relative effects for different previous ERT durations (previous ERT duration = 0 years [i.e., naive patients], 2.5 years, 5 years and 9.2 years) are shown in Supplementary Figure 6.

The comparison between cipa+mig and alglu became more favorable for cipa+mig with increasing previous ERT duration for both end points in the analysis of both networks.

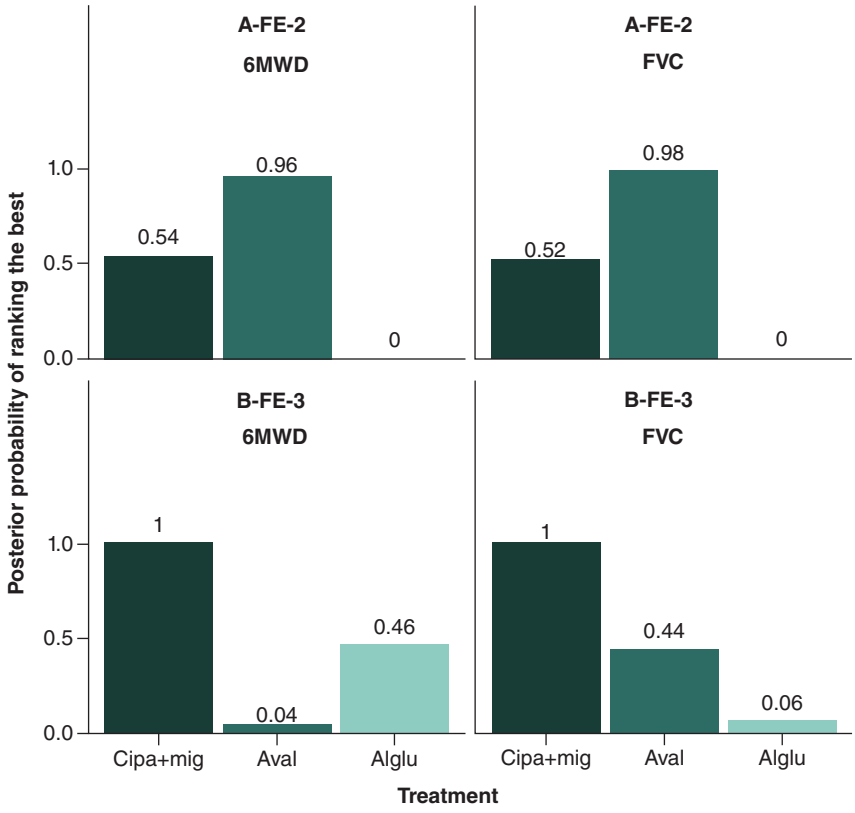

Figure 3. SUCRA scores, base case scenario.
A-FE-2: Analysis of network A (RCTs only) with fixed-effects model and estimating the covariate effect separately for {cipa+mig, aval} and {alglu}; B-FE-3: Analysis of network B (full evidence) with fixed-effects model and estimating the covariate effect separately for {cipa+mig}, {aval} and {alglu}.
6MWD: 6-minute walking distance; alglu: Alglucosidase alfa; aval: Avalglucosidase alfa; cipa+mig: Cipaglucosidase alfa plus miglustat; FVC: Forced vital capacity; RCT, Randomized controlled trial; SUCRA, Surface under the cumulative ranking curve.

It should be noted that, for Model A-FE-2, the effect of previous ERT duration was canceled out in the comparison between cipa+mig and aval, as the same regression model was estimated for cipa+mig and aval (shared effect modifier). For Model B-FE-3, the comparison between cipa+mig and aval became more favorable for cipa+mig with increasing previous ERT duration for both end points, but also the width of the CrIs increased due to less evidence informing those scenarios.

The comparison between aval and alglu became less favorable for aval with increasing previous ERT duration for both end points in the analysis of network B, but when the network A was analyzed, it became more favorable for aval with increasing previous ERT duration. The key driver of this discrepancy was the NEO-1/-EXT trial, where a decrease of 6MWD and FVC was clearly observed with aval at later timepoints.

In addition to previous ERT duration, the impact of time on the relative effects was tested (Supplementary Figure 7). Results regarding the impact of the other baseline variables included in the regression models (i.e., age, sex, 6MWD and FVC) on the relative effect estimates are not shown because none of the covariates was significant.

Discussion

No head-to-head trials are currently available comparing aval and cipa+mig in patients with LOPD. After exploring various indirect comparison methodologies, an ML-NMR was chosen as the most appropriate and robust method to make this comparison. We used patient-level data from PROPEL and publicly available data from other studies on aval and cipa+mig (identified through an SLR) to obtain indirect estimates of relative effects and to evaluate how those treatments rank among each other. End points assessed were 6MWD and FVC changes from baseline

at week 52, which are standard end points in clinical trials in Pompe disease, and are well accepted by clinicians, health technology assessment agencies and payers [58].

Analyses of two networks were conducted: network A, which included only RCTs, and network B, which also included single-arm OLE and phase I/II studies, to enhance the evidence base for the relative effects and, specifically, the effect of aval in ERT-experienced patients.

The results from the analysis of network A under the base case scenario (i.e., covariates set to PROPEL values) provided evidence of a less favorable effect of cipa+mig versus aval for both outcomes (6MWD: weak evidence), with the SUCRA score indicating aval as the most efficacious treatment for both end points, followed by cipa+mig. The results from the analysis of network B provided evidence of a favorable effect of cipa+mig versus aval for both outcomes (FVC: strong evidence) that was further supported by the results of other models explored in the analysis of network B. The SUCRA score indicated cipa+mig as the most efficacious treatment option for both end points, followed by aval (FVC) or alglu (6MWD), that led to a mean increase in 6MWD of 28.93 (8.26 to 50.11) m and in FVC of 2.88 (1.07 to 4.71) pp compared with aval. These results show that the positioning of cipa+mig compared with aval changes to superiority when additional evidence on the effect of aval in patients with LOPD previously treated with ERT is included in the analysis. These additional trial data on aval indicated reduced performance of aval in ERT-experienced patients, which explains why the analysis of network B revealed less favorable results for aval in an ERT-experienced LOPD population, which was the dominant population of the PROPEL trial. Exploring the impact of previous ERT duration revealed that the comparison between cipa+mig and aval became more favorable for cipa+mig with increasing previous ERT duration for both end points in the analysis of network B.

We can speculate that the reasons for the observed difference in efficacy between cipa-mig and aval (that is most notable for the patients previously treated with alglu) is most likely due to differences in their chemistry and modes of action, though this is a matter of ongoing debate [52–54]. Cipa is biologically synthesized with high levels of bis-phosphorylated mannose-6-phosphate and retained endolysosomal glycan processing, which, together with the addition of miglustat, may enable more active enzyme into target tissues. For patients who have been undergoing therapy for an extended period of time, cipa+mig may be able to clear accumulated, and more highly complexed, glycogen in skeletal muscles. This would lead to the differentiation seen between enzymes in the results of network B in terms of functional measures of 6MWD and FVC.

To our knowledge, there exists only one other ITC approach comparing cipa+mig and aval. It applied an anchored STC in ERT-naive and an unanchored STC in ERT-experienced patients with LOPD, using data from COMET and PROPEL (ERT-naive subgroup only) for the anchored STC and data from COMET OLE, NEO-1/-EXT, PROPEL and ATB200-02 for the unanchored STC [59]. Results of the anchored STC were directionally consistent with the ML-NMR results for network A, but the results of the unanchored STC differed from the ML-NMR results for network B, showing favorable results for aval compared with cipa+mig. This was presumably due to data and analysis limitations such as STC estimates extrapolated from a regression model based on data from few participants (e.g., only 18 patients on aval with previous ERT duration of $\geq$3 years, whereas >90% of the patients in PROPEL [n = 61] had previous ERT duration $\geq$3 years) and assumptions made on baseline characteristics not reported separately for ERT-naive and -experienced patients in PROPEL.

Our ML-NMR made optimal use of the available data (i.e., individual patient-level data of the PROPEL trial and aggregate data of the other trials included). It is a method recommended by the National Institute for Health and Care Excellence's Decision Support Unit [26].

Limitations

Due to network A being formed only by two studies, the effect of covariates was not estimated separately for cipa+mig and aval, and shared effect modifiers were assumed. Since COMET did not include any ERT-experienced patients, the impact of previous ERT duration on the treatment effect of aval had to be extrapolated from that on cipa+mig where both ERT-naive and ERT-experienced patients were available, which is a strong assumption.

To overcome this deficiency, network B was analyzed, which included evidence on aval in ERT-experienced patients from single-arm phase I/II and OLE studies. Single-arm trials were matched to an appropriate comparator arm of the head-to-head clinical trials. This can result in biased relative effect estimates when there is still high heterogeneity between the single and the matched arm, despite the optimal choice minimizing the relative differences between the two arms [24,25]. Another limitation of that approach is that evidence of the comparator arms is used

multiple times in the network. Hence, there is a trade-off between a potential bias in the relative effect estimates in the analysis of network B and the improper accounting for previous ERT duration in the analysis of network A.

Another limitation of the ML-NMR method is that it can only adjust the relative effect estimates for any observed effect modifier available in the data, but cannot adjust for unobserved or unobservable effect modifiers. In the present analysis, a significant number of potential treatment effect modifiers were included in the analysis: age, sex, previous ERT duration, time, baseline 6MWD and/or baseline FVC, while others such as weight, height, muscle damage and angiotensin-converting enzyme genotype could not be included due to lack of reporting.

Finally, inconsistency could not be assessed as there were no closed loops in the network.

Conclusion

In the absence of head-to-head trials, the results of this ITC provide clinically important results and inform decision-making on the optimal choice of treatment in patients with LOPD, with cipa+mig being the treatment option with the highest probability of ranking best among all treatments compared when all available evidence was used in the analysis. We suggest that the differences in chemistry and mode of action between cipa+mig and aval can help explain why cipa+mig appears to be more efficacious in the analysis of network B, and why pre-treated patients are more responsive.

The chosen method, ML-NMR, made optimal use of the available evidence, and enabled incorporation of evidence from trials whose included patient populations differed with respect to an important treatment effect modifier, namely previous ERT duration.

Clinical evidence will continue to evolve as longer-term data on the effect of Pompe disease treatments become available. This will allow for more robust, long-term relative effect estimates, as well as insights into modes of action that may better explain the underlying clinical differences.

Summary points

- Both recently approved enzyme replacement therapies (ERTs), cipaglucosidase alfa with miglustat (cipa+mig) and avalglucosidase alfa (aval), show numerical superiority over alglucosidase alfa (alglu) in 6-minute walk distance (6MWD) and forced vital capacity (FVC) in the pivotal trials PROPEL and COMET, but there exist no head-to-head trials comparing cipa+mig and aval directly.
- PROPEL and COMET differ with respect to the included trial population: PROPEL includes 77% of late-onset Pompe disease (LOPD) patients previously treated with ERT, whereas COMET includes 100% ERT-naive patients.
- Previous ERT duration is considered as an effect modifier for cipa+mig; therefore, a standard network meta-analysis including PROPEL and COMET with their common comparator alglu is not considered appropriate to derive relative effect estimates between the two new ERTs.
- Also, standard population-adjustment methods, such as matching-adjusted indirect comparison and simulated treatment comparison, are not suitable to obtain a relative effect estimate between cipa+mig and aval in the target population of interest, particularly in an LOPD population that includes mainly ERT-experienced patients, such as in PROPEL, since they only adjust for the comparator trial population.
- In this study, an indirect treatment comparison applying a multi-level network meta-regression was conducted, adjusting for previous ERT duration as the effect modifier.
- Two networks were studied: network A, including only the two randomized controlled trials (RCTs) COMET and PROPEL, and network B, additionally including – via matching to comparator arms – single-arm evidence from phase I/II and open-label extension trials that were the only source providing information on the effect of aval in ERT-experienced patients.
- Results from network B adjusted to reflect a real-world LOPD population, such as in PROPEL, revealed that cipa+mig was associated with an increase in 6MWD and FVC at week 52 compared with aval, and that the comparison between cipa+mig and aval became more favorable for cipa+mig with increasing previous ERT duration for both end points.
- Analysis of network A showed that cipa+mig was associated with a decrease in 6MWD and FVC at week 52 compared with aval.
- The chosen network of evidence greatly impacts the conclusions drawn about the favorability of one ERT over another, and decision-makers should consider several networks of evidence when evaluating indirect treatment comparison results, rather than the most conservative methods (i.e., networks of RCTs).
- Research should continue as new evidence on cipa+mig and aval for LOPD continues to evolve in the real-world setting.

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Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://bpl-prod.literatumonline.com/doi/10.57264/cer-2024-0045

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