LSVP.19

Indirect treatment comparison of three enzyme replacement treatments for late-onset Pompe disease: a network meta-analysis with patient-level and aggregate data

Shuai Fu,[1] Noemi Hummel,[1] Tahseen Mozaffar,[2] Jeff Castelli,[3] Brian Fox,[3] Ian Keyzor,[4] Syed Raza,[4] Sheela Sitaraman,[3] Simon Shohet[4]

[1]Certara GmbH, Germany; [2]Department of Neurology, University of California, Irvine, CA, USA; [3]Amicus Therapeutics, Inc., Philadelphia, PA, USA; [4]Amicus Therapeutics Ltd, UK

INTRODUCTION

- Pompe disease is a rare disorder caused by a lack or deficiency of the enzyme acid α-glucosidase (GAA) that hydrolyses lysosomal glycogen[1] and is characterised by progressive loss of muscular and respiratory function.[2]
- Pompe disease is a spectrum of phenotypes broadly classified into two clinical subtypes: infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD).[1]
- Enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA), alglucosidase alfa (Alglu) was the first approved treatment of Pompe disease.[3] More recently, Avalglucosidase alfa (Aval) was approved in 2021.[4]
- Cipaglucosidase alfa plus miglustat (Cipa+mig) is a novel enzyme and oral stabiliser combination currently undergoing Food and Drug Administration (FDA) and European Medicines Agency (EMA) review.

OBJECTIVE

- In the absence of head-to-head trials comparing Aval to Cipa+mig, an indirect treatment comparison (ITC) is a suitable approach to better understand clinical differentiation of the three treatments available or potentially forthcoming for LOPD. ITCs are widely requested by health technology assessment agencies (HTAs) to support comparative health economic evaluation.
- We performed an ITC providing relative effect estimates in the target population of interest (ie an LOPD population including a mix of ERT-naïve and ERT-experienced subjects as in the pivotal Phase III trial comparing Cipa+mig with Alglu [PROPEL]).

METHODS

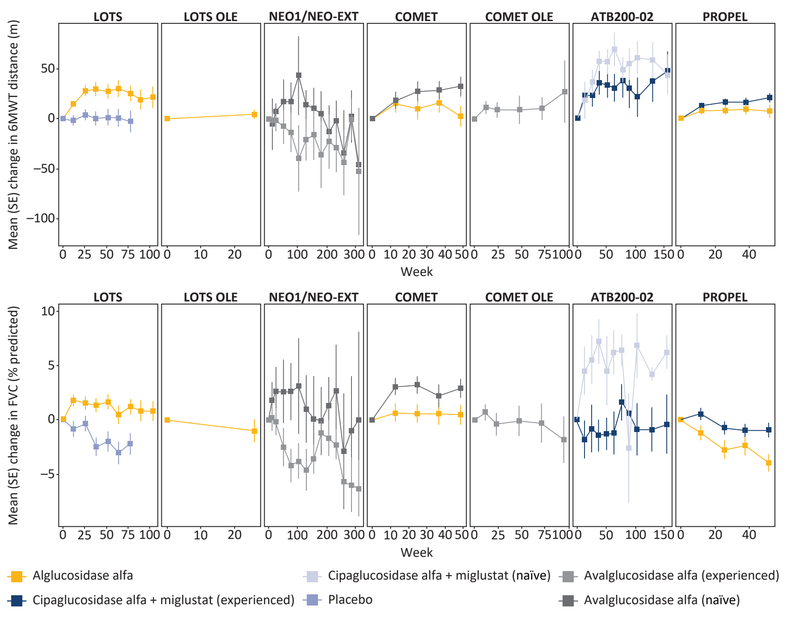
- A systematic literature review (SLR) was conducted to identify relevant published clinical studies of ERTs in LOPD.
- Outcomes assessed were change from baseline in 6-minute walking distance (6MWD) (m) and in forced vital capacity (FVC; % predicted) at week 52, acknowledged by clinicians, HTA agencies and payers as key LOPD trial endpoints.[5]
- Aggregate results on 6MWD and FVC change from baseline over time and baseline characteristics (age, gender, ethnicity, previous ERT duration, baseline 6MWD and baseline FVC) were extracted from included studies.
- A multi-level network meta regression (ML-NMR) was performed, which is an extension of standard network meta-analyses (NMAs) that take into account the effect of study-level covariates, and that can be applied to any connected network with any mixture of individual patient-level data (IPD) and aggregate data.[6]
- ML-NMR is an accepted method by the National Institute for Health and Care Excellence (NICE)[6,7] in support of cost effectiveness analysis.
- Single-arm study results were matched to appropriate comparator arms of the comparative studies to allow for inclusion into the network.[8]
- Mean treatment differences with associated 95% credible intervals (CrIs) were calculated for 6MWD and FVC change from baseline at week 52.
- A base-case scenario was evaluated in which all covariates were set to the target population of the PROPEL trial. To study the impact of previous ERT duration on relative effects, ERT duration value was varied, keeping remaining covariate values as in the base-case scenario.
- A sensitivity analysis was performed by excluding all matched single-arm evidence from the network to assess its impact on the results.
- Both fixed effects (FE) and random effects (RE) ML-NMR models were applied and the deviance information criteria (DIC) was used to assess goodness-of-fit of the models and to identify the appropriate model (FE or RE model) for the data.
- Models were implemented in a Bayesian framework using Stan with help of the R package multinma.[9]

RESULTS

Included studies

- The SLR identified seven clinical studies for which baseline characteristics are shown in **Supplementary Table 1**.
- These studies included but were not limited to three randomised clinical trials (LOTS: Alglu versus Placebo; COMET: Aval versus Alglu; PROPEL: Cipa+mig versus Alglu). Each share 6MWD and FVC as key primary or secondary endpoints (see **Figures 1** and **2**), but differ in their trial populations (PROPEL is the only randomised controlled trial [RCT] that comprised both ERT-naïve and -experienced subjects).
- Efficacy results of the included studies are shown in **Figure 1**.

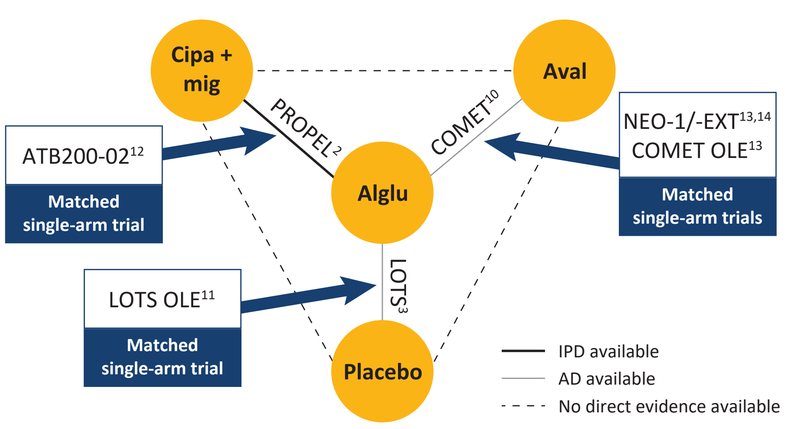
Figure 1. Longitudinal efficacy results versus trial: 6MWD (m) and FVC (% predicted) change from baseline



Network

- For both endpoints, the network is the same and shown in **Figure 2**.
- Evidence from the single-arm studies LOTS OLE, NEO-1/-EXT, COMET OLE and ATB200-02 was included into the network, as shown in the blue boxes, by matching the single-arm results to appropriate comparator results from the head-to-head trials.

Figure 2. Network for 6MWD (m) and sitting FVC (% predicted)



Main analysis

- In the base-case scenario, the covariates were set to the baseline characteristics of the target population (ie the PROPEL trial; see **Table 1**), and time was set to 52 weeks.

Table 1. Base-case scenario covariate setting

Age (years)	% Male	% White	ERT duration (years)	6MWD (m)	FVC (% predicted)
46.95	45.08	84.43	5.744	355.8	70.42

- Based on the DIC, an RE model was chosen for 6MWD and an FE model for FVC. For both endpoints (**Figures 3** and **4**):
  - Cipa+mig showed a statistically significant favourable effect versus Alglu and Aval
  - Cipa+mig showed a numerically favourable effect versus placebo.

Figure 3. Forest plot of relative effect estimates with 95% credible intervals for 6MWD in the base-case scenario (main analysis)

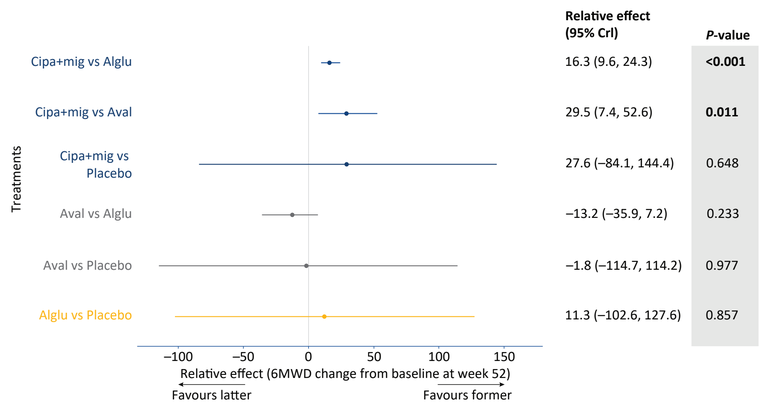
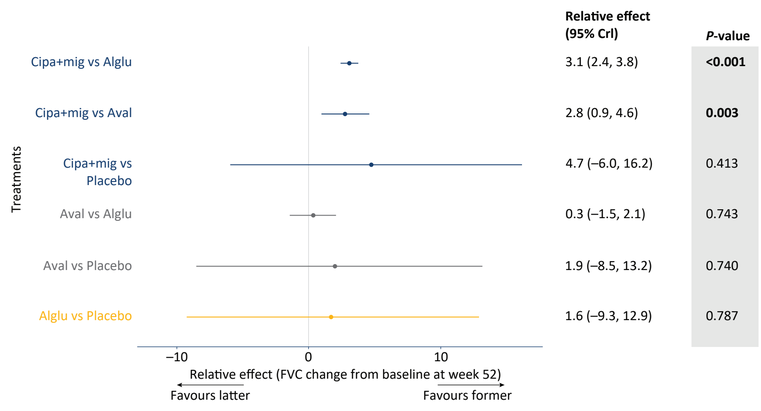


Figure 4. Forest plot of relative effect estimates with 95% credible intervals for FVC in the base-case scenario (main analysis)



- Note that the 95% CrIs of the relative effect estimates versus placebo are generally much wider than those versus Alglu or versus Aval. This reflects the larger uncertainty of those estimates, since data on placebo were only available for ERT-naïve subjects and previous ERT duration of the base-case scenario is relatively long (5.7 years).
- Relative effect estimates for different previous ERT durations (previous ERT duration = 0 years [ie naïve patients], 2.5 years, 5 years, and 9.2 years) are shown in **Figure 5** (6MWD) and **Figure 6** (FVC).

Figure 5. Forest plot of relative effect estimates with 95% credible intervals for 6MWD by ERT duration

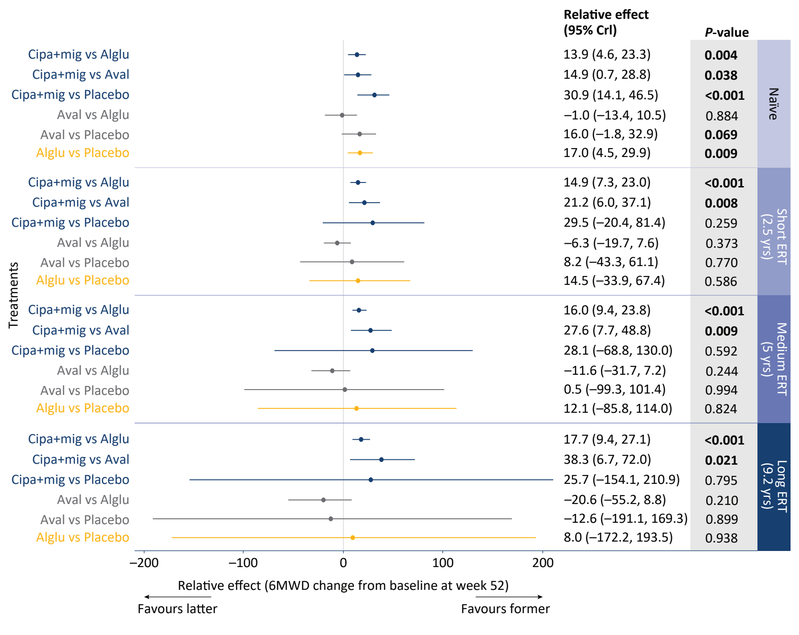
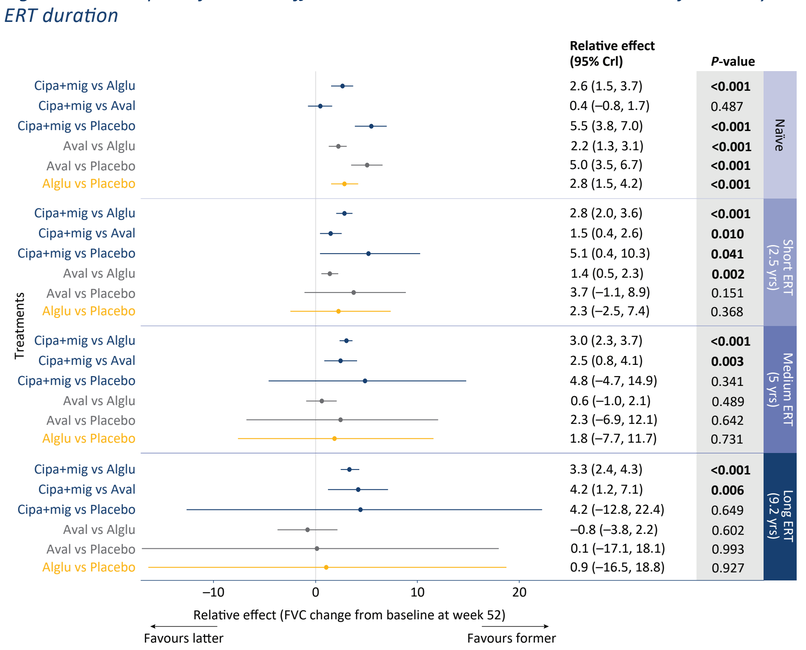


Figure 6. Forest plot of relative effect estimates with 95% credible intervals for FVC by ERT duration



Sensitivity analysis (only RCTs included in the network)

- RE models were chosen for both 6MWD and FVC based on the DIC.
- **Figures 7** and **8** provide an overview of the relative effect estimates with 95% CrIs for the base-case scenario using the sensitivity analysis and show:
  - Inclusion of matched single-arm evidence into the network for the main analysis reduces uncertainty of the relative effect estimates
  - Cipa+mig: statistically favourable versus Alglu; numerically unfavourable versus Aval; numerically favourable versus placebo (6MWT and FVC)
  - Aval: numerically favourable versus Alglu and placebo (6MWT and FVC)
  - Alglu: numerically favourable versus placebo.

Figure 7. Forest plot of relative effect estimates with 95% credible intervals for 6MWD in the base-case scenario (sensitivity analysis)

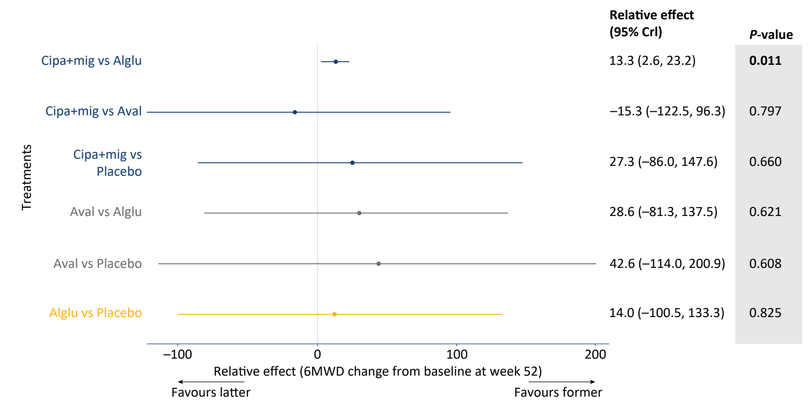
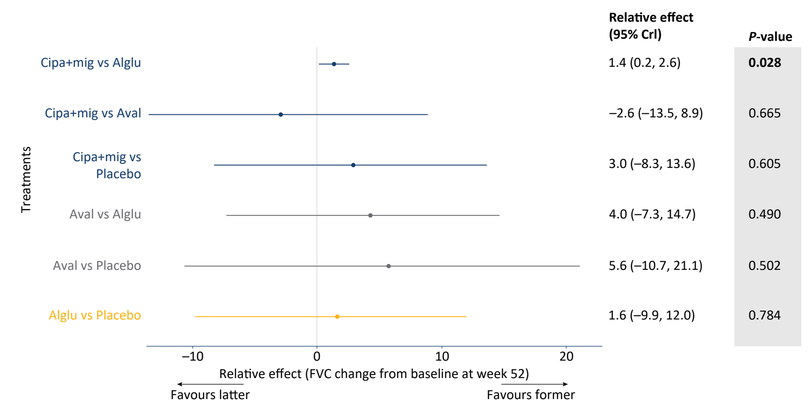


Figure 8. Forest plot of relative effect estimates with 95% credible intervals for FVC in the base-case scenario (sensitivity analysis)



Limitations

- Matching of single-arm trials can result in biased relative effect estimates when there is high heterogeneity between the single and the matched arm.
- The consequences of removing matched single-arm trials from the network were explored in the sensitivity analysis, yielding mainly an increase in uncertainty of the relative effect estimates since the single-arm trials contributed evidence on treatment effects in ERT-experienced patients who were part of the target population of interest.
- Hence, there is a trade-off between a potential bias in the relative effect estimates and an increase in uncertainty of those estimates.
- The ML-NMR method can adjust the relative effect estimates for any observed effect modifier available; unobserved effect modifiers or effect modifiers not available in the data cannot be accounted for.

CONCLUSIONS

- The ML-NMR comparison presented here showed that Cipa+mig was statistically significantly favourable versus Alglu and Aval for 6MWD and FVC in the base-case scenario of the main analysis.
- Cipa+mig was also statistically significantly favourable over Alglu and Aval for 6MWD and FVC for different ERT durations, with one exception: for FVC, Cipa+mig was only numerically favorable vs. Aval in the ERT-naïve setting.
- The sensitivity analysis (only including RCT data) demonstrates that the inclusion of matched single-arm evidence into the network for the main analysis reduces uncertainty of the relative effect estimates.
- Overall, these results point to Cipa+mig potentially having a differentiated clinical profile versus the other ERTs, particularly for individuals with some level of previous ERT treatment.
- Further analyses are anticipated to test and refine the findings, when additional longer-term data are published.

References

1. Kishnani PS *et al. Genet Med* 2006;8:267–88.
2. Schoser B *et al. Lancet Neurol* 2021;20:1027–37.
3. van der Ploeg AT *et al. N Engl J Med* 2010;362:1396–1406.
4. Sanofi. Nexviazyme™ prescribing information. Available at: https://products.sanofi.us/nexviazyme/nexviazyme.pdf (accessed August 2022).
5. Raza S *et al*. POSA283 *Value Health* 2022;25:S175.
6. Phillippo DM *et al. J R Stat Soc Ser A Stat Soc* 2020;183:1189–1210.
7. Welton NJ *et al*. NICE Decision Support Unit, 2020.
8. Leahy J *et al. Stat Med* 2019;38:2505–23.
9. Phillippo DM. *Zenodo*, 2022. Available at: https://doi.org/10.5281/zenodo.7033094 (accessed August 2022).
10. Diaz-Manera J *et al. Lancet Neurol* 2021;20:1012–26.
11. van der Ploeg AT *et al. Mol Genet Metab* 2012;107:456–61.
12. Byrne BJ *et al*. Poster presented at Muscular Dystrophy Association (MDA) Clinical & Scientific Conference, 2022;P92. https://www.mdaconference.org/abstract-library/long-term-follow-up-of-cipaglucosidase-alfa-miglustat-inambulatory-patients-with-pompe-disease-an-open-label-phase-i-ii-study-atb200-02/
13. Center for Drug Evaluation and Research. BLA integrated review 761194 Nexviazyme (Avalglucosidase Alfa-Ngpt), 2021.
14. Dimachkie MM *et al. Neurology* 2022;99:e536–48.

Poster PDF + Supplement

Please scan this QR code with your smartphone camera or app to obtain PDF copies of this poster and supplementary material.

This study was supported by Amicus Therapeutics, Inc.

Presented at the World Muscle Society (WMS) Annual Congress; Halifax, Nova Scotia, Canada; 11–15 October 2022.