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Indirect Treatment Comparison (ITC) of Avalglucosidase Alfa (AVA) vs Cipaglucosidase Alfa Plus Miglustat (Cipa+mig) in Late-Onset Pompe Disease (LOPD): An Updated Analysis Using Mixed-Model Repeated Measures (MMRM) Data

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Background

- Late-onset Pompe disease (LOPD) is a rare, debilitating genetic disorder with progressive neuromuscular degeneration caused by the deficiency of the enzyme acid α-glucosidase, leading to glycogen accumulation within cells.[1–3]
- Enzyme replacement therapy (ERT) has been the standard of care since 2006 for patients with Pompe disease.[4,5]
- A previous indirect treatment comparison (ITC) using simulated treatment comparison (STC) evaluated the comparative efficacy of avalglucosidase alfa (AVA) vs cipaglucosidase alfa plus miglustat (Cipa+mig) in patients with LOPD using data from comparative and single-arm trials.[6]
- In the previous ITC, changes from baseline (CFB) for AVA were estimated using mixed model repeated measures (MMRM), while for Cipa+mig, the published results included estimated CFB from the ANCOVA model at the time of the analyses or just an observed data. The study demonstrated more favourable outcomes with AVA than with Cipa+mig.
- Additional data from the PROPEL trial on CFB, derived using MMRM, are now available.

Objectives

- To conduct an STC between AVA and Cipa+mig in patients with LOPD who were either ERT-naïve or ERT-experienced using MMRM estimates from clinical trials for both products and compare results with the previous STC.

Methods

Study design

- Separate ITCs using STC were conducted in two populations of patients with LOPD: ERT-naïve and ERT-experienced.
- In the ERT-naïve population, individual patient data (IPD) for AVA (20 mg/kg intravenous infusion [IV] every 2 weeks [Q2W]) were obtained from the Phase 3 COMET trial (AVA, *n* = 51; alglucosidase alfa [ALG], *n* = 49)[7] and aggregate data for Cipa (20 mg/kg IV Q2W)+mig were obtained from the Phase 3 PROPEL trial (Cipa+mig, *n* = 20; ALG, *n* = 7).[8]
- In the ERT-experienced population, IPD for AVA (*n* = 59) were obtained from the COMET-open-label extension (OLE; *n* = 44)[9] and the NEO-1 (NCT01898364; Phase 1)/NEO-EXT (NCT02032524; Phase 2) studies (NEO-1/NEO-EXT; *n* = 15).[10] These data were compared with the aggregate data of Cipa+mig (*n* = 81) from the PROPEL (treatment-experienced; *n* = 65) + ATB200-02 (NCT02675465, *n* = 16; Phase 1/2, Cohorts 1 and 4) studies after adjusting for differences in population characteristics through regression adjustment.[11]
- For AVA vs Cipa+mig, CFB in forced vital capacity percent predicted (FVCpp) and the 6-minute walk test (6MWT) were assessed as outcomes and compared at Weeks 49–52 and Weeks 48–52 in treatment-naïve and treatment-experienced patients, respectively.

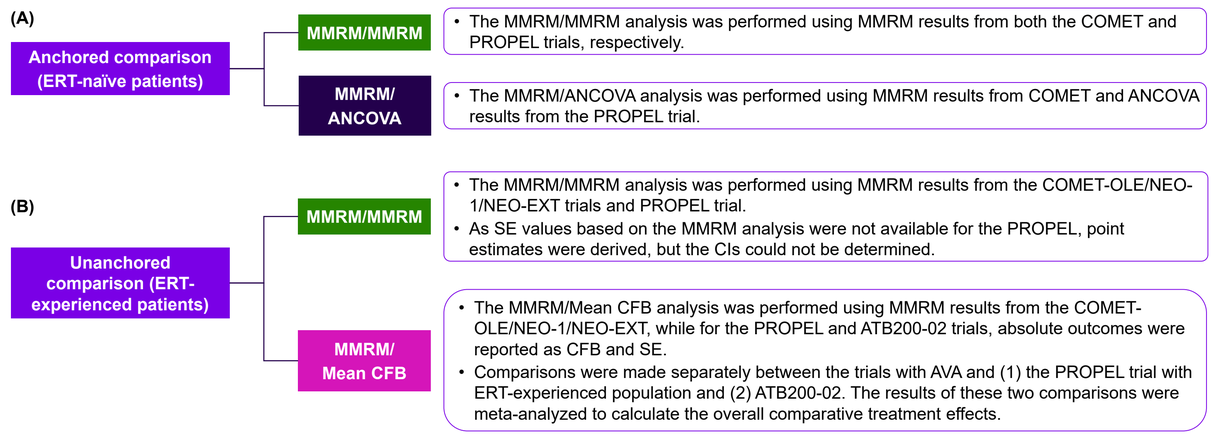
Statistical analysis

- The mean age at baseline, sex and baseline values of each outcome as well as ERT duration (for the ERT-experienced population) were selected as effect modifiers for the adjustment in STC analyses. In addition, region (the United States vs others) was included as a prognostic variable.
- The CFB for AVA were analysed using MMRM, while various results from PROPEL were analysed using ANCOVA, Mean CFB and/or MMRM. Each comparison between AVA and Cipa+mig was therefore categorised according to the statistical methods used, such as MMRM/ANCOVA, MMRM/Mean CFB or MMRM/MMRM. Details of these analyses are depicted in **Figure 1**.
- For the ERT-naïve population, an anchored STC was conducted between AVA and Cipa+mig using ALG as the common comparator (**Figure 2**). A linear MMRM was fitted to the IPD from the primary analysis period of the COMET. The model included sex, baseline age, baseline values for outcomes of interest (FVCpp and 6MWT), treatment group, visit, region and interaction terms between treatment groups and each of the variables (visit, age, sex and baseline endpoint value).

Methods (contd.)

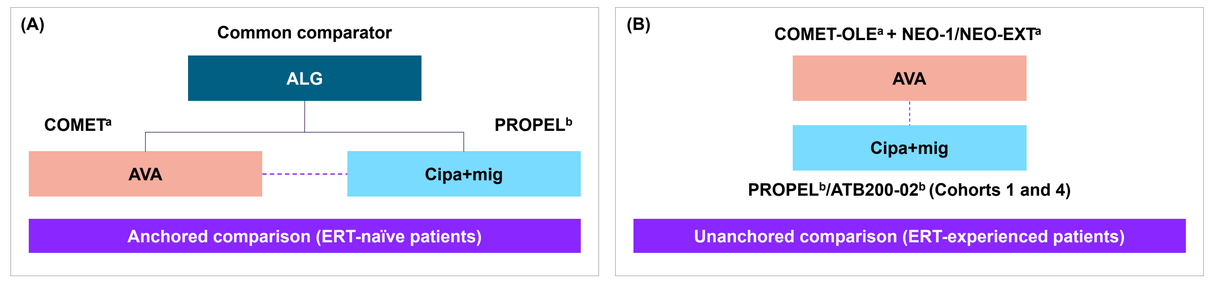
- For the ERT-experienced population, unanchored STCs were conducted between AVA and Cipa+mig due to the lack of a common comparator. A linear MMRM was fitted to the IPD from the COMET-OLE and NEO-1/NEO-EXT. The unanchored STC included the following variables: sex, baseline age, ERT duration, baseline values for outcomes of interest (FVCpp and 6MWT), visit and region (**Figure 1**).
- All STCs were conducted according to the NICE Decision Support Unit guidelines.[12]

Figure 1: (A) Anchored comparison for ERT-naïve patients with MMRM/MMRM and MMRM/ANCOVA analyses and (B) unanchored comparison for ERT-experienced patients with MMRM/MMRM and MMRM/Mean CFB analysis



CFB, changes from baseline; CI, confidence interval; ERT, enzyme replacement therapy; MMRM, mixed-model repeated measures; SE, standard error.

Figure 2: Design of the model used for the (A) anchored (ERT-naïve patients) and (B) unanchored comparison (ERT-experienced patients)



Solid line: data available; dashed line: data based on estimates. [a]Trials for which individual patient data were available. [b]Trials for which aggregate data were available.
NOTE: For those patients who switched to AVA during the COMET-OLE or NEO-EXT, baseline was redefined at the time of switching. ALG, alglucosidase alfa; AVA, avalglucosidase alfa; Cipa+mig, cipaglucosidase alfa plus miglustat; ERT, enzyme replacement therapy; OLE, open-label extension.

Results

Baseline characteristics

- Baseline characteristics across the ERT-naïve and ERT-experienced populations are summarised in **Table 1** and **Table 2**, respectively.

Table 1: Baseline characteristics of the ERT-naïve population

Characteristics	COMET[7]			PROPEL-naïve[8]		
	AVA (*N* = 51)	ALG (*N* = 49)	Overall (*N* = 100)	Cipa+mig (*N* = 20)	ALG (*N* = 8)*	Overall (*N* = 27)
Age at enrolment (years)	46.0 (14.5)	50.3 (13.7)	48.1 (14.2)	47.6 (13.3)[a]	45.1 (13.3)[a]	46.8 (13.3)[a]
Male, *n* (%)	27 (52.9)	25 (51.0)	52 (52.0)	36 (42.4)[a]	20 (52.6)[a]	56 (45.5)[a]
Region, *n* (%)						
APAC+EU	35 (68.6)	22 (44.9)	57 (57.0)	59 (69.4)[a]	23 (60.5)[a]	82 (66.7)[a]
North/South America	16 (31.4)	27 (55.1)	43 (43.0)	26 (30.6)[a]	15 (39.5)[a]	41 (33.3)[a]
FVCpp (%)	62.6 (14.4)	61.6 (12.4)	62.1 (13.4)	80.2 (18.7)	79.1 (22.6)	80.0 (19.5)
6MWT (m)	399.3 (110.9)	378.1 (116.2)	388.9 (113.5)	393.6 (112.4)	420.9 (135.7)	398.9 (117.3)

All data are presented as mean (SD) unless specified otherwise. [a]These baseline patient characteristics were not available in the ERT-naïve population; therefore, an assumption was made that the average baseline characteristics of the ERT-naïve population were similar to that of the overall population. *n = 1 excluded for patient baseline values in FVCpp and 6MWT, due to suspected deliberate underperformance. 6MWT, 6-minute walk test; ALG, alglucosidase alfa; APAC, Asia Pacific; AVA, avalglucosidase alfa; Cipa+mig, cipaglucosidase alfa plus miglustat; ERT, enzyme replacement therapy; EU, European Union; FVCpp, forced vital capacity percent predicted; m, metre; *N*, total number of patients; *n*, number of patients; SD, standard deviation.

Table 2: Baseline characteristics of the ERT-experienced population

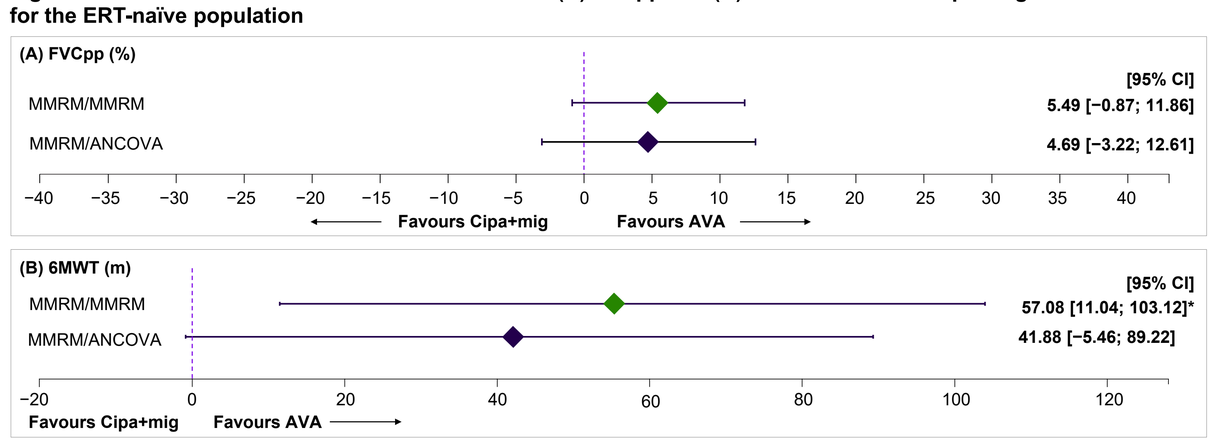
Characteristics	AVA (at the time of switching therapy)			Cipa+mig (baseline)	
	COMET-OLE[9] (*N* = 44)[a]	NEO-1/NEO-EXT[10] (*N* = 15)	Overall (*N* = 59)	PROPEL-experienced[8] (*N* = 65)[b]	ATB200-02[11,13] (*N* = 16)*
Age (years)	50.7 (13.9)	46.9 (16.5)	49.7 (14.6)	47.6 (13.3)[b,c]	46.4 (NR)
Male, *n* (%)	24 (54.5)	7 (46.7)	31 (52.5)	36 (42.4)[b,c]	11 (64.7)
Region, *n* (%)					
APAC+EU	21 (47.7)	8 (53.3)	29 (49.1)	59 (69.4)[b,c]	NA
North/South America	23 (52.3)	7 (46.7)	30 (50.8)	26 (30.6)[b,c]	NA
Use of walking aid, *n* (%)	9 (20.5)	2 (13.3)	11 (18.6)	17 (20.0)[b,c]	NA
Previous ERT duration, *n* (%)					
<3 years	44 (100.0)	6 (40.0)	50 (84.7)	4 (6.2)	NA
3–5 years	0	4 (26.7)	4 (6.8)	16 (24.6)	NA
>5 years	0	5 (33.3)	5 (8.5)	45 (69.2)	NA
Previous ERT duration (years)	0.92 (0.0)	4.67 (2.7)	1.87 (2.1)	7.50 (3.4)	6.64 (1.5)
Age at the first ERT dose (years)	49.7 (13.9)	41.30 (17.0)	47.6 (15.1)	40.8 (12.7)	NA
FVCpp (%)	61.5 (13.5)[d]	73.3 (21.9)	64.5 (16.7)	67.9 (19.1)	56.9 (16.3)[e]
6MWT (m)	384.7 (139.6)[d]	419.3 (151.7)	393.5 (142.3)	346.9 (110.2)	390.3 (120.4)[e]

Data presented as mean (SD) unless specified otherwise. [a]Data for eight patients from the COMET trial were reported only at baseline; thus, only 36 patients from the COMET were included in the STC. [b]Age and sex are reported only for the overall population. For the analyses, an assumption was made that the average baseline characteristics of the ERT-experienced population were similar to that of the overall population. [c]Data reported for the overall study population (*n* = 85). [d]One patient for each outcome had a rebaseline defined at Week 37 for 6MWT and FVCpp instead of Week 49. To align with other patients and how the baseline was defined for other outcomes, the baseline was assumed to be Week 49 for this patient. [e]Data reported for 16 patients with available baseline data. **n* = 16 with available baseline data
6MWT, 6-minute walk test; APAC, Asia Pacific; AVA, avalglucosidase alfa; Cipa+mig, cipaglucosidase alfa plus miglustat; ERT, enzyme replacement therapy; EU, European Union; EXT, extension; FVCpp, forced vital capacity percent predicted; m, metre; *N*, total number of patients; *n*, number of patients; NA, not available; NR, not reported; OLE, open-label extension; SD, standard deviation; STC, simulated treatment comparison.

Comparative efficacy

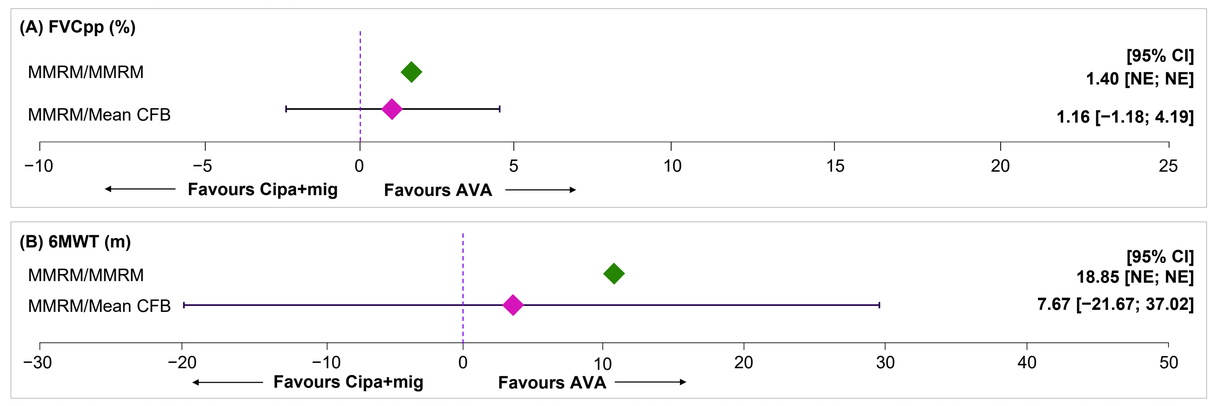
- **ERT-naïve population**: Using the anchored STC estimates, the treatment differences in FVCpp at Weeks 49–52 for AVA vs Cipa+mig were 5.49% (95% confidence interval [CI]: −0.87, 11.86; $p<0.09$) with MMRM/MMRM and 4.69% (95% CI: −3.22, 12.61; $p<0.25$) with MMRM/ANCOVA, both methods numerically favouring AVA over Cipa+mig. In 6MWT, the differences for AVA vs Cipa+mig were 57.08 m (95% CI: 11.04, 103.12; $p<0.02$) with MMRM/MMRM and 41.88 m (95% CI: –5.46, 89.22; $p<0.08$) with MMRM/ANCOVA, both methods favouring AVA over Cipa+mig, with the former being statistically significant (**Figure 3**).
- **ERT-experienced population**: Using the unanchored STC estimates, the treatment differences in FVCpp at Weeks 48–52 for AVA vs Cipa+mig were 1.40% (CI and *p*-value could not be determined) with MMRM/MMRM and 1.16% (95% CI: –1.88, 4.19; $p = 0.45$) with MMRM/Mean CFB. In 6MWT, the differences were 18.85 m (CI and *p*-value could not be determined) with MMRM/MMRM and 7.67 m (95% CI: –21.67, 37.02; $p = 0.61$) with MMRM/Mean CFB. Both analyses numerically favoured AVA over Cipa+mig in FVCpp and 6MWT (**Figure 4**).

Figure 3: STC estimates for the differences in CFB in (A) FVCpp and (B) 6MWT for AVA vs Cipa+mig at Weeks 49–52 for the ERT-naïve population



The number of patients for FVCpp (AVA [*n* = 98]; Cipa+mig [*n* = 27]) and 6MWT (AVA [*n* = 98]; Cipa+mig [*n* = 27]). *Significantly ($p<0.02$) favours AVA vs Cipa+mig for 6MWT in MMRM/MMRM analysis; MMRM/ANCOVA for 6MWT and both MMRM/MMRM and MMRM/ANCOVA for FVCpp numerically favour AVA vs Cipa+mig. 6MWT, 6-minute walk test; AVA, avalglucosidase alfa; CFB, changes from baseline; CI, confidence interval; Cipa+mig, cipaglucosidase alfa plus miglustat; ERT, enzyme replacement therapy; FVCpp, forced vital capacity percent predicted; m, metre; MMRM, mixed-model repeated measures; *n*, number of patients; STC, simulated treatment comparison.

Figure 4: STC estimates for the difference in CFB in (A) FVCpp and (B) 6MWT for AVA vs Cipa+mig at Weeks 48–52 for the ERT-experienced population



The number of patients for FVCpp (AVA [*n* = 50]; Cipa+mig [*n* = 79]) and 6MWT (AVA [*n* = 51]; Cipa+mig [*n* = 81]). Both MMRM/MMRM and MMRM/Mean CFB in FVCpp and 6MWT numerically favour AVA vs Cipa+mig. 6MWT, 6-minute walk test; AVA, avalglucosidase alfa; CFB, changes from baseline; CI, confidence interval; Cipa+mig, cipaglucosidase alfa plus miglustat; ERT, enzyme replacement therapy; FVCpp, forced vital capacity percent predicted; MMRM, mixed-model repeated measures; *n*, number of patients; NE, not estimated; STC, simulated treatment comparison.

Limitations

- The small sample size and heterogeneity in the baseline characteristics might have contributed to uncertainty in the estimates.
- The CIs could not be estimated for MMRM/MMRM treatment-experienced patients due to the lack of standard error values for patients with Cipa+mig.
- An unanchored STC was performed due to the absence of a common comparator in the ERT-experienced population, requiring additional assumptions.
- Some demographic characteristics of patients (age, sex, race and region) were reported for the overall population in PROPEL, not specific to Cipa+mig. Information on disease duration, the use of ventilation at baseline and baseline weight and height, was not reported in PROPEL or ATB200-02 and, thus, could not be adjusted in present analyses.

Conclusions

- The analysis demonstrated favourable respiratory function and mobility outcomes with AVA compared to Cipa+mig in patients with LOPD, regardless of prior ERT experience and across analyses using different statistical methods for the component trials.
- The results using the same analytical method (MMRM) for both AVA and Cipa+mig represent the most consistent comparison between the two treatments and are more favourable for AVA than those in which different statistical methods are used across data sources and were statistically significant for 6MWT.
- This ITC may provide information to healthcare professionals and policymakers about the comparative efficacy of different treatments for LOPD to aid in decision-making.

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CONFLICTS OF INTEREST

MER is a member of the advisory boards for Amicus Therapeutics, BioMarin, Sanofi, and Spark Therapeutics.
IP and **PS** are employees of Evidera and may hold stocks in the company.
PG, **LO**, **NSR** and **LP** are employees of Sanofi and may hold stocks and/or stock options in the company. **RP-J** was an employee of Sanofi during the study conduct and holds stocks in the company.

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