CO122

Late-Onset Pompe Disease Patients Treated with Avalglucosidase alfa Show Favorable Results Compared with Cipaglucosidase alfa Plus Miglustat: Indirect Treatment Comparison

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BACKGROUND

- Late-Onset Pompe disease (LOPD) is a rare progressive hereditary disorder caused by the deficiency of acid α-glucosidase (GAA) enzyme[1] that results in proximal muscle weakness and progressive respiratory muscle degeneration.[2]
- Enzyme replacement therapy (ERT) is the standard of care for Pompe disease.[3]
- There has been no head-to-head study comparing avalglucosidase alfa (AVA), which is approved in multiple countries worldwide[4,5] and cipaglucosidase alfa plus miglustat (Cipa+mig), which is currently under review by health authorities.[6]

OBJECTIVE

- To estimate the relative efficacy of AVA (20 mg/kg, intravenous) vs. Cipa (20 mg/kg, intravenous) + mig in patients with LOPD using indirect treatment comparison (ITC).

METHODS

- Two independent ITCs, one for naïve and one for experienced patients, were conducted.
- For the ERT-naïve population, the common comparator (alglucosidase alfa [ALG]) between the Phase 3 studies[1,7] allowed us to conduct an anchored ITC, which is the recommended approach (**Figure 1**).
- For the ERT-experienced population, due to the lack of a common comparator, we used an unanchored ITC, using all data available from Phase 3[7] and Phase 1[8] studies (**Figure 1**).
- Data of the ERT-naïve patients were obtained from COMET[1] (NCT02782741; Phase 3; AVA [*n* = 51] and ALG [*n* = 49]) and PROPEL[7] (NCT03729362; Phase 3; Cipa+mig [*n* = 20] and ALG [*n* = 7]) trials.
- Data of ERT-experienced patients were obtained from COMET-OLE[9] (open-label-extension, [*n* = 44]), NEO-1[8] (NCT01898364; Phase 1)/ NEO-EXT[10] (NCT02032524; Phase 2) (NEO-1/EXT; *n* = 15) (AVA; *n* = 59), and PROPEL (*n* = 65) + ATB200-02[11] (NCT02675465, *n* = 16) (Phase 1/2 cohorts 1 and 4) (Cipa+mig; *n* = 81) trials.
- Individual patient data from index studies (COMET[1] + NEO-1[8]/NEO-EXT[10]) were used in conjunction with aggregate data from comparator studies (PROPEL + ATB200-02[11]), adjusting for prognostic and treatment effects modifier variables.
- Outcomes were assessed at 1 year (Week 49 or 52 depending on the study considered).
- The outcomes of interest were 1-year change from baseline (49 or 52 weeks, depending on study) in forced vital capacity percent predicted (FVCpp), maximal inspiratory pressure percent predicted (MIPpp), maximal expiratory pressure percent predicted (MEPpp), and 6-minute walk test (6MWT).
- In the ERT-experienced patients, in the first step, unanchored simulated treatment comparison (STC) analyses, including baseline age, sex, baseline values of each outcome, ERT duration, visit, and region, were conducted for COMET[1] + NEO-1[8]/ NEO-EXT[10] (in a PROPEL-like population using Cipa+mig characteristics) vs. PROPEL[7] and COMET[1] + NEO-1[8]/NEO-EXT[10] (in a ATB200-02-like population using Cipa+mig characteristics) vs. ATB200-02. In the second step, the results were meta-analyzed to get the treatment effect of AVA vs Cipa+mig. As ATB200-02 did not report MIP and MEP, only STC for COMET[1] + NEO-1[8]/NEO-EXT[10] vs. PROPEL[7] was conducted.
- In the ERT-naïve population, anchored STC analyses, including the same variables as above and additionally treatment group, and interaction terms between treatment groups and each of the variables (visit, age, sex, and baseline value of each outcome) were conducted to estimate the treatment effect of AVA vs. ALG in a PROPEL-like population (using PROPEL[7] pooled characteristics). As we have a common comparator, a Bucher ITC was conducted to estimate AVA vs Cipa+mig using the STC estimates.

Figure 1. Indirect treatment comparison in the ERT-naïve and ERT-experienced patients

Anchored (using ALG as a common comparator) and unanchored STCs were conducted adjusting for variables including prognostic factors and treatment effect modifiers. Solid line, data available; Dashed line, data based on estimates.
ALG, alglucosidase alfa; AVA, avalglucosidase alfa; Cipa+mig, cipaglucosidase alfa+miglustat; ERT, enzyme replacement therapy

RESULTS

Baseline characteristics

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

Table 1. Baseline characteristics of the ERT-naïve population

Characteristic	COMET[1]			PROPEL[7]		
	AVA (*n* = 51)	ALG (*n* = 49)	Pooled (*n* = 100)	Cipa+mig (*n* = 20)	ALG (*n* = 7)	Pooled (*n* = 27)
6MWT (m)	399.30 (110.93)	378.09 (116.22)	388.91 (113.48)	393.60 (112.40)	420.90 (135.70)	398.90 (117.27)
FVCpp (%)	62.55 (14.39)	61.56 (12.40)	62.06 (13.39)	80.20 (18.70)	79.10 (22.60)	79.99 (19.51)
MIPpp (%)	59.88 (47.10)[i]	60.65 (41.05)	60.26 (43.98)[ii]	63.50 (20.20)	80.70 (25.20)	68.00 (21.50)
MEPpp (%)	65.77 (38.97)[i]	74.83 (35.22)	70.25 (37.25)[ii]	70.90 (19.80)	77.50 (18.90)	72.60 (19.60)
Age at enrolment (years)	45.98 (14.46)	50.33 (13.69)	48.11 (14.18)	47.60 (13.30)	45.10 (13.30)	46.80 (13.30)
Male, *n* (%)	27 (52.9)	25 (51.0)	52 (52.0)	36 (42.4)	20 (52.6)	56 (45.5)
Region, *n* (%)						
APAC+EU	35 (68.6)	22 (44.9)	57 (57.0)	59 (69.4)	23 (60.5)	82 (66.7)
North/South America	16 (31.4)	27 (55.1)	43 (43.0)	26 (30.6)	15 (39.5)	41 (33.3)

Green color: these baseline patient characteristics were not available in the ERT-naïve population; therefore, an assumption was made that average baseline characteristics of the ERT-naïve population were similar to the overall population. Data presented as mean (SD) unless specified otherwise.
[i]As patient baseline values for MIP and MEP were missing for one patient in each, data were reported for 50 patients owing to missing baseline values; [ii]Data were reported for 99 patients owing to missing baseline values.
6MWT, 6-minute walk test; ALG, alglucosidase alfa; APAC, Asia Pacific; AVA, avalglucosidase alfa; Cipa+mig, cipaglucosidase alfa+miglustat; ERT, enzyme replacement therapy; EU, European Union; FVCpp, forced vital capacity percent predicted; MEPpp, maximal expiratory pressure percent predicted; MIPpp, maximal inspiratory pressure percent predicted; *n*, number of patients; SD, standard deviation

Table 2. Characteristics at the time of switch of the ERT-experienced population

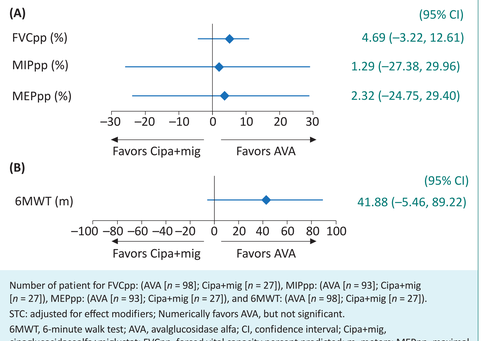
Characteristic	AVA			Cipa+mig	
	COMET (*n* = 44)	NEO-1/NEO-EXT (*n* = 15)	Pooled (*n* = 59)	PROPEL[i] (*n* = 65)	ATB200-02 (*n* = 16)
6MWT (m)	384.66 (139.63)	419.27 (151.71)	393.46 (142.27)	346.90 (110.20)	390.34 (120.37)
FVCpp (%)	61.49 (13.51)[ii]	73.26 (21.88)	64.48 (16.66)	67.90 (19.10)	56.89 (16.27)
MIPpp (%)	56.91 (22.40)[ii,iii]	69.87 (27.57)	60.20 (24.25)	61.30 (27.90)	NA
MEPpp (%)	77.41 (28.04)[ii,iii]	82.43 (25.96)[iv]	78.68 (27.39)[v]	70.70 (23.50)[vi]	NA
Age (years)	50.58 (13.91)	46.94 (16.54)	49.65 (14.56)	47.60 (13.30)	46.37 (NR)
Male, *n* (%)	24 (54.6)	7 (46.7)	31 (52.5)	36 (42.4)	11 (64.7)
Region, *n* (%)					
APAC+EU	35 (68.6)	22 (44.9)	57 (57)	59 (69.4)	23 (60.5)
North/South America	16 (31.4)	27 (55.1)	43 (43)	26 (30.6)	15 (39.5)
Use of walking aid, *n* (%)	9 (20.5)	2 (13.3)	11 (18.6)	17 (20.0)	NA
Previous ERT duration, *n* (%)					
<3 years	44 (100.0)	6 (40.0)	50 (84.7)	4 (6.2)	NA
3 to 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 (0.04)	4.67 (2.65)	1.87 (2.10)	7.50 (3.40)	6.64 (1.47)
Age at first ERT dose (years)	49.70 (13.90)	41.30 (16.96)	47.56 (15.06)	40.80 (12.70)	NA

Green color: These baseline patient characteristics were not available in the ERT-experienced population; therefore, an assumption was made that average baseline characteristics of the ERT-experienced population were similar to the overall population. Data presented as mean (SD) unless specified otherwise.
[i]Age and sex are reported only for the overall population. For the analyses, an assumption was made that average baseline characteristics of the ERT-experienced population is similar to overall population; [ii]One patient each had re-baseline defined at Week 37 for 6MWT, FVCpp, MIPpp, and MEPpp instead of Week 49. To be aligned with other patients and how the baseline is defined for other outcomes, the baseline was assumed to be week 49 for this patient as well; [iii]Data reported for 44 patients; [iv]Data reported for 15 patients; [v]Data reported for 59 patients. [vi]Data reported for 65 patients.
6MWT, 6-minute walk test; AVA, avalglucosidase alfa; APAC, Asia Pacific; Cipa+mig, cipaglucosidase alfa+miglustat; ERT, enzyme replacement therapy; EU, European Union; FVCpp, forced vital capacity percent predicted; MEPpp, maximal expiratory pressure percent predicted; MIPpp, maximal inspiratory pressure percent predicted; *n*, number of patients; NA, not available; NR, not reported; SD, standard deviation

Efficacy outcomes

- In the ERT-naive patients, AVA was found to be numerically favorable vs. Cipa+mig for FVCpp (4.69; 95% confidence interval [CI]: [−3.22, 12.61]), MIPpp (1.29; [−27.38, 29.96]), MEPpp (2.32; [−24.75, 29.4]), and 6MWT (41.88; [−5.46, 89.22]) (**Figure 2**).

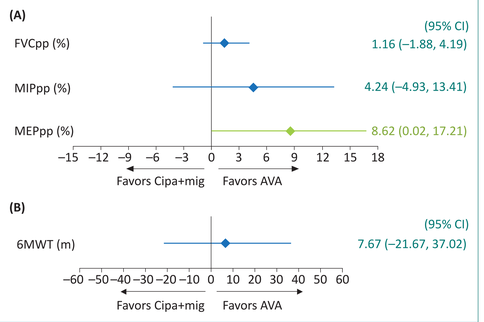
Figure 2. STC difference in change from baseline in AVA vs. Cipa+mig at Week 49–52 for the ERT-naïve patients: (A) respiratory parameters and (B) mobility parameter



Number of patient for FVCpp: (AVA [*n* = 98]; Cipa+mig [*n* = 27]), MIPpp: (AVA [*n* = 93]; Cipa+mig [*n* = 27]), MEPpp: (AVA [*n* = 93]; Cipa+mig [*n* = 27]), and 6MWT: (AVA [*n* = 98]; Cipa+mig [*n* = 27]).
STC: adjusted for effect modifiers; Numerically favors AVA, but not significant.
6MWT, 6-minute walk test; AVA, avalglucosidase alfa; CI, confidence interval; Cipa+mig, cipaglucosidasealfa+miglustat; FVCpp, forced vital capacity percent predicted; m, meters; MEPpp, maximal expiratory pressure percent predicted; MIPpp, maximal inspiratory pressure percent predicted; *n*, number of patients; STC, simulated treatment comparisons

- In the ERT-experienced patients, AVA was found to be numerically favorable vs. Cipa+mig for FVCpp (1.16; [−1.88, 4.19]), MIPpp (4.24; [−4.93, 13.41]), and 6MWT (7.67; [−21.67, 37.02]). For MEPpp, results were statistically significant (8.62; [0.02, 17.21]) (**Figure 3**).

Figure 3. STC difference in change from baseline in AVA vs. Cipa+mig at Weeks 49–52 for the ERT-experienced patients: (A) respiratory parameters and (B) mobility parameter



Number of patients for FVCpp: (AVA [*n* = 50]; Cipa+mig [*n* = 79]), MIPpp: (AVA [*n* = 50]; Cipa+mig [*n* = 64]), MEPpp: (AVA [*n* = 50]; Cipa+mig [*n* = 64]), and 6MWT: (AVA [*n* = 51]; Cipa+mig [*n* = 81]).
STC: adjusted for prognostic factors and effect modifiers; Numerically favors AVA, but non-significant (Blue color) and statistically significant (Green color).
6MWT, 6-minute walk test; AVA, avalglucosidase alfa; CI, confidence interval; Cipa+mig, cipaglucosidase alfa+miglustat; FVCpp, forced vital capacity percent predicted; MEPpp, maximal expiratory pressure percent predicted; MIPpp, maximal inspiratory pressure percent predicted; *n*, number of patients; STC, simulated treatment comparisons

STRENGTHS

- The STC is a recommended method to adjust for baseline differences in treatment effect modifiers (for anchored comparisons such as the one conducted in ERT-naïve patients) and prognostic factors (for unanchored comparisons as conducted in ERT-experienced patients).
- Separate comparisons for ERT-naïve and ERT-experienced patients provide greater flexibility for using all available data, including single arm studies (for ERT-experienced patients) with a methodologically valid approach.

LIMITATIONS

- The limited sample size results in some uncertainty in the estimates.
- Some patient characteristics (age, sex, race, and region) were only reported for overall population in the PROPEL study. ERT-naïve patients might be younger than ERT-experienced patients.
- In the ERT-experienced population, we adjusted for mean ERT duration; however, the distribution of prior ERT duration was different across the treatments and individual patient data were limited to AVA data.
- Due to the absence of a common comparator for the ERT-experienced subgroup, unanchored STC was performed, which requires additional assumptions as we need to adjust for not only treatment effect modifiers, but also prognostic factors, and is therefore more susceptible to bias.

DISCUSSION

- Multiple methods are available to indirectly compare treatments that have not been studied in a head-to-head trial.
  - These methods cannot replace direct, head-to-head evidence, but can provide insight into potential differences between treatments.
  - It is critical to select a method that will produce results that are congruent with the available direct evidence for each treatment and minimizes bias.
- A recent ITC by Fu *et al.*[12] included single-arm studies in a network of randomized controlled trials (RCTs) and reported incoherent results that contradict direct evidence from both COMET[1] and PROPEL Phase 3[7] studies.
- In addition, the sensitivity analyses from Fu *et al.*[12] favor AVA vs Cipa+mig in contradiction with their base case results and highlighting the lack of robustness of the latter.
- Based on the level of detail available for the analyses by Fu *et al.*[12], it is difficult to determine the causes of contradictory results to their base case and of the differences with the present ITC. It can be speculated that inclusion of the two single arm studies may have caused bias (e.g., owing to imbalance of ERT duration), and/or that overfitting and misspecification may have occurred.
- Our analysis followed the recommended method (i.e., STC) to estimate treatment differences between AVA and Cipa+Mig and provides an accurate reflection of the uncertainty of each comparison based on available data.
  - Analysis of ERT-naive patients maintained an anchored network through the common comparator, ALG.
  - Single-arm study data were only included in the unanchored comparison of ERT-experienced patients.

CONCLUSIONS

- The present ITC suggests that AVA may be more favorable than Cipa+mig for all outcomes considered, regardless of prior ERT experience.
- Ongoing real-world experience with AVA among ERT-experienced patients will provide additional evidence.

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CONFLICTS OF INTEREST
MR is part of the Advisory Boards for Amicus Therapeutics, BioMarin, Sanofi, Spark Therapeutics; **IP** and **PS** are employees of Evidera and may hold shares of Evidera; **PG, MP, NT, AH, NT,** and **LP** are employees and may hold stock and/or stock options in Sanofi; **LRF** was an employee of Sanofi at the time of study conduct and holds stock in Sanofi; he is currently an employee of Aixial, a CRO working with Sanofi.

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