Defining Clinically Meaningful Thresholds (CMT) for Forced Vital Capacity (FVC) and six-Minute-Walk Test (6MWT) in Patients with Late-Onset Pompe Disease (LOPD)

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BACKGROUND

- Patients with LOPD usually present with progressive muscle weakness, leading to motor disability and respiratory insufficiency.[1,2]
- FVC and 6MWT are common outcome measures of respiratory and motor function/endurance in patients with LOPD.[3–5]
- Interpretation of FVC and 6MWT changes is challenging as a defined CMT for improvement in within-patient change or between-group differences' improvement in LOPD has not been published.

OBJECTIVE

- This study leverages data from the randomized, double-blind, phase 3 COMET (NCT02782741) clinical trial to define the within-patient and between-group CMTs for upright FVC% predicted (FVC_{up}%) and 6MWT in adult patients with LOPD.

METHODS

- The COMET trial data evaluating the safety and efficacy of avalglucosidase alfa (AVA) versus alglucosidase alfa (ALG) in LOPD were analyzed.[5] All analyses were performed on the modified intent-to-treat (mITT) population using data from all patients, irrespective of their subsequent treatment arm.[5]
- Distribution and anchor-based methods were used to estimate within-patient CMTs for absolute change in FVC_{up}% and 6MWT.
- Distribution-based methods used standard error of measurement (SEM) computed using the baseline standard deviation (SD) of FVC and 6MWT.
- Multiple patient-reported outcomes, assessed in adult patients, were tested as anchors (Patient Global Impression of Change, Pompe Disease Impact Scale, 12-item Short-Form health survey, and EuroQol-5 dimension-5 level), using two different timepoints (Week 49 [W49] and Week 97 [W97]).[6]
- Anchor appropriateness was assessed using Spearman correlations between the change in FVC_{up}% and 6MWT scores and the anchors, with correlations >0.30 considered preferable.[7]
- Since Pompe disease is a rare disorder, anchors with a correlation (r) ≥0.25 were included in the weighted average calculation, allowing for a small margin of variance.[7]
- Data from the different anchors were triangulated into a single value at each timepoint Week 49 (W49) and Week 97 (W97) using a weighted average and 95% confidence interval (CI).[6]
- Derived within-patient CMTs were applied post-hoc to COMET data to compare the proportion of responders in AVA versus ALG using logistic regression. Odds ratios (ORs) and 95% CI were provided, along with the nominal p-value.

RESULTS

Study population

- The study population for the current analysis included 99 patients aged ≥18 years, out of the 100 patients (AVA [n = 51]; ALG [n = 49]) enrolled in COMET trial, and detailed demographics and baseline characteristics were presented previously.[5]
- For the overall population, mean (SD) age: 48.1 (14.2) years, male: 52%, mean (SD) age at the first symptom onset: 35.3 (16.3) years, mean (SD) FVC_{up}%: 62.1 (13.4), and mean (SD) 6MWT: 388.9 m (113.5 m).

Distribution-based estimates

- The SEM for FVC_{up}% and 6MWT were 3.5% and 16 m, respectively.

Anchor-based estimates for within-patient and between-group clinically meaningful improvement threshold

- Correlations between anchors and absolute change from baseline in FVC_{up}% and 6MWT were <0.30 at W49, with some anchors exceeding 0.30 at W97.
- A narrow range of estimates for within-patient and between-group CMTs were derived for both FVC_{up}% and 6MWT (**Table 1**).

Table 1. Summary of within-patient and between-group clinically meaningful improvement threshold estimates at W49 and W97

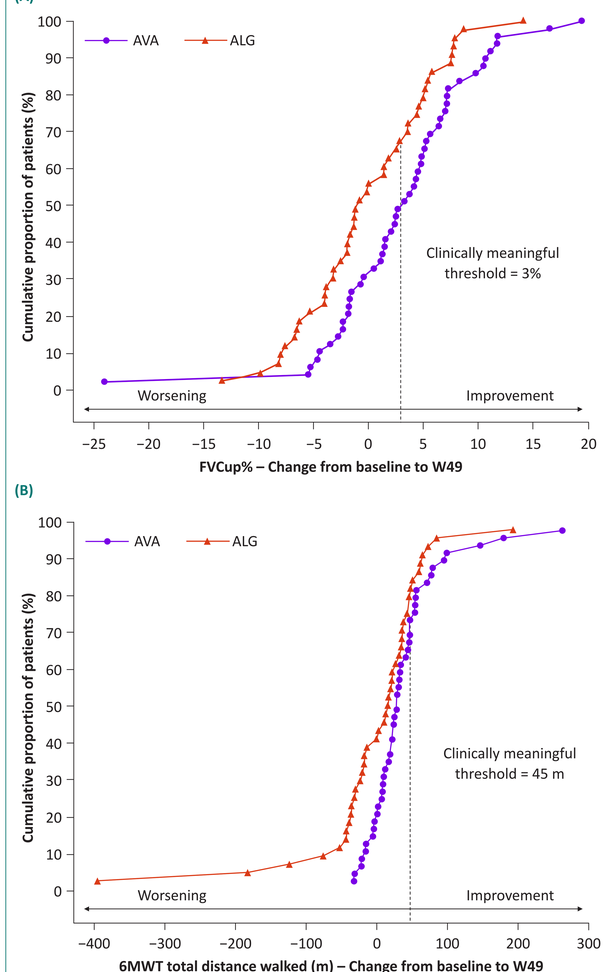
	Absolute change in FVC_{up}% from baseline (in %)	Absolute change in 6MWT score from baseline (in meters)
Correlation-weighted average estimate [95% CI]		
Estimates at W49		
Within-patient	3.0 [2.3; 3.8]	45.0 [28.4; 61.6]
Between-group	2.1 [1.1; 3.1]	33.1 [16.6; 49.6]
Estimates at W97		
Within-patient	2.9 [2.6; 3.1]	46.1 [24.6; 67.6]
Between-group	1.2 [0.5; 1.8]	52.1 [39.5; 64.8]
Recommended threshold estimate [range]*		
Within-patient	**3 [2–4]**	**45 [28–62]**
Between-group	**2 [1–3]**	**33 [17–50]**

*The suggested estimated CMTs are based on the weighted average at week 49 rounded to the nearest integer.
6MWT, six-Minute-Walk Test; CI, confidence interval; CMT, clinically meaningful threshold; FVC_{up}%, upright forced vital capacity percent predicted; W49, Week 49; W97, Week 97.

Responder analysis

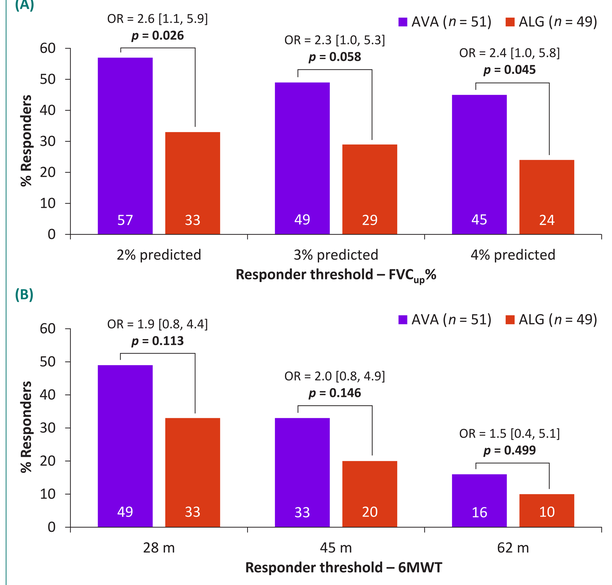
- The empirical cumulative distribution function (eCDF) curves of absolute change in FVC_{up}% and 6MWT showed the expected shift to the right and indicated a clear separation between treatment groups at each level of change from baseline to W49 (**Figure 1**).
- **Figure 2** illustrates the ORs for a clinically meaningful improvement in FVC_{up}% and 6MWT in patients treated with AVA versus ALG, using various thresholds spanning the range of within-patient CMTs.
- Irrespective of the CMTs used, a greater number of patients receiving AVA reported an absolute increase in the FVC_{up}% and 6MWT scores from baseline to W49 compared with patients receiving ALG (**Figure 2**).

Figure 1. The eCDF for absolute change in FVC_{up}% (A) and 6MWT (B) scores by treatment groups



Orange and purple lines: Cumulative proportion of patients that reached threshold of improvement for FVC_{up}% (3%) and 6MWT (45 m) for ALG and AVA.
6MWT, six-Minute-Walk Test; ALG, alglucosidase alfa; AVA, avalglucosidase alfa; eCDF, empirical cumulative distribution function; FVC_{up}%, upright forced vital capacity percent predicted.

Figure 2. Responder analysis for absolute change in FVC_{up}% (A) and 6MWT (B) from baseline to W49



OR values greater than 1.0 represent better odds for AVA compared with ALG. Patients with missing values are considered as non-responders.
6MWT, six-Minute-Walk Test; ALG, alglucosidase alfa; AVA, avalglucosidase alfa; FVC_{up}%, upright forced vital capacity percent predicted; OR, odds ratio.

LIMITATIONS

- The COMET trial has a defined eligibility criterion; thus, inferences drawn from this study should be applied with caution when applying to the wider LOPD population.
- Some of the correlations observed in the present study between patient reported outcomes and absolute changes in FVC_{up}% and 6MWT score were in the expected direction but weak (coefficients in absolute values <0.30).

CONCLUSIONS

- This study derived within-person and between-group CMTs for FVC_{up}% and 6MWT in LOPD, which can aid the interpretation of longitudinal changes in these measures in both clinical trials and routine care in LOPD and potentially other neuromuscular disorders.
- Responder analyses performed using the derived CMTs confirm that patients treated with AVA were more likely to demonstrate clinically meaningful improvements in respiratory function and exercise capacity than ALG.

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CONFLICTS OF INTEREST

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