Switching therapy from alglucosidase alfa to avalglucosidase alfa in patients with late-onset Pompe disease (LOPD): Longitudinal assessment of respiratory function from the COMET trial

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INTRODUCTION

- Avalglucosidase alfa is a recombinant human acid α-glucosidase (GAA) enzyme replacement therapy with increased mannose-6-phosphate content to enhance cellular uptake compared with alglucosidase alfa.[1]
- Avalglucosidase alfa has received marketing authorization in several countries for Pompe disease.[2,3]
  - Avalglucosidase alfa was approved in the United States in August 2021 for patients with late-onset Pompe Disease (LOPD) ≥1 year of age, and in the European Union in June 2022 for the treatment of patients with Pompe disease.[2,3]
- Approval for LOPD was based on the efficacy and safety results of the pivotal Phase 3 COMET trial (NCT02782741).[4]
  - During the 49-week double-blind treatment period, treatment with avalglucosidase alfa resulted in greater improvements in forced vital capacity (FVC), 6-minute walk test (6MWT), and other outcomes, and showed a more favorable safety profile compared with alglucosidase alfa in treatment-naïve participants with LOPD.[4]

OBJECTIVE

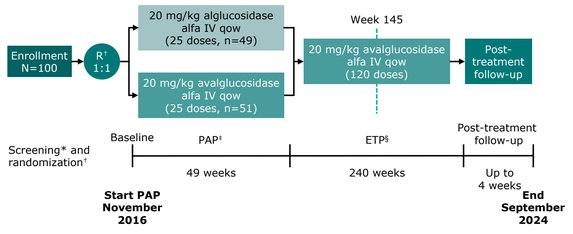
- The objective of this analysis was to examine respiratory function outcomes in patients who switched from alglucosidase alfa to avalglucosidase alfa at Week 49, based on initial treatment response, in COMET.

METHODS

Study design and participants

- COMET is an ongoing Phase 3, multicenter, multinational, randomized, double-blind trial comparing efficacy and safety of avalglucosidase alfa and alglucosidase alfa.
  - The study design is shown in **Figure 1**.
- Patients aged ≥3 years with a diagnosis of LOPD confirmed by GAA enzyme deficiency from any tissue source and/or two confirmed pathogenic *GAA* variants, and were naïve to Pompe disease-specific treatment, were eligible for inclusion.

Figure 1. Study design



Participants were enrolled at 55 study sites across 20 countries.

*Screening phase up to 14 days, may be extended to up to 8 weeks in pre-specified situations. †Randomization 1:1 ratio with stratification factors based on baseline forced vital capacity, sex, age, and country (Japan or ex-Japan). ‡Study drug infusion, safety assessments, and efficacy evaluations. §All patients regardless of prior randomization.

ETP, extended treatment period; IV, intravenous; PAP, primary analysis period; qow, every two weeks; R, randomization

- In the 49-week primary analysis period (PAP), participants were randomized 1:1 to receive 20 mg/kg intravenous avalglucosidase alfa or 20 mg/kg intravenous alglucosidase alfa every 2 weeks.
- Thereafter, in the open-label extended treatment period (ETP), participants who received avalglucosidase alfa in the PAP continued this treatment and participants who received alglucosidase alfa in the PAP switched to avalglucosidase alfa.
- The present study focuses on respiratory outcomes in patients who were treated with alglucosidase alfa in the PAP and then switched to avalglucosidase alfa during the ETP.

Assessment of respiratory function

- FVC percent predicted (FVCpp) in the upright position was calculated as a function of FVC in liters, sex, ethnicity, age, and height at time of measurement using the Global Lung Initiative 2012 reference equations.[5]
- Patients treated with alglucosidase alfa during the PAP were divided into two subgroups based on individual responses of FVC at Week 49, using a threshold for change in FVC of ≥3% predicted to reflect clinically meaningful improvement.
  - Patients with missing FVCpp change from baseline at Week 49 data were considered as having a <3% predicted change from baseline.
  - Derivation of 3% threshold is presented in Poster C0168.
- The trajectory of FVCpp during the study was assessed according to observed change from baseline during the PAP.

Statistical analysis

- Patients who received alglucosidase alfa in the PAP and with at least one avalglucosidase assessment in ETP were included in this *post hoc* analysis.
  - One value at Week 97 was excluded because the change between visits was physiologically implausible.
- Piecewise linear mixed effects modeling was performed in participants randomized to alglucosidase alfa in the PAP who entered the ETP, including FVC response at Week 49 and time (in years) as continuous effects.
- The modeling assumed separate pre- and post-switch slopes for the time variable, and with random intercept and slope at subject level.
- Two time periods were analyzed; the first from baseline to Week 49 (PAP) and the second from Week 49 to Week 145 (ETP).
  - Data cut-off date was 11 March 2022.

RESULTS

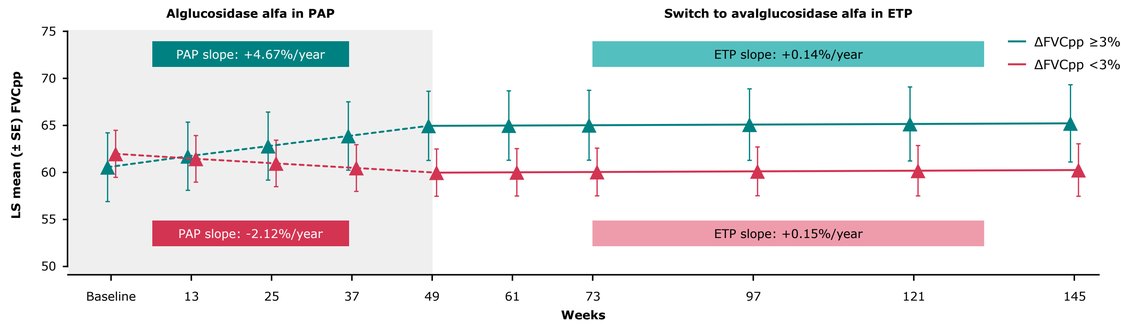
Study participants

- Overall, 49 patients with LOPD were randomized to receive alglucosidase alfa in the PAP, of these 44 were enrolled in the ETP and switched to avalglucosidase alfa and were included in this *post hoc* analysis.
- Of the 44 patients who received alglucosidase alfa, 14 (31.8%) had a change from baseline of ≥3% in their FVC at Week 49 and 30 (68.2%) had a change from baseline of <3% FVC at Week 49.
- Baseline characteristics (at the start of the PAP) were similar between subgroups and are summarized in **Table 1**.

Evolution of FVC based on response at week 49

- Patients with a change from baseline to Week 49 in FVC of ≥3% demonstrated an increase on average in FVCpp during treatment with alglucosidase alfa and maintained this response after the switch to avalglucosidase alfa (**Figure 2**).
  - Baseline to Week 49 estimated slope ± standard error (SE): 4.67 ± 1.28 %/year; p=0.0003.
  - Week 49 to Week 145 estimated slope ± SE: 0.14 ± 0.94 %/year; p=0.8784.
- Patients with a change from baseline to Week 49 in FVC of <3% demonstrated a decline on average in FVCpp while receiving alglucosidase alfa in PAP; however, they stabilized after the switch to avalglucosidase alfa in the ETP (**Figure 2**).
  - Baseline to Week 49 estimated slope ± SE: -2.12 ± 0.87 %/year; p=0.0159.
  - Week 49 to Week 145 estimated slope ± SE: 0.15 ± 0.61 %/year; p=0.8103.

Figure 2. LS mean FVCpp over time in patients treated with alglucosidase alfa in PAP who switched to avalglucosidase alfa in the ETP



Change from baseline to Week 49										
ΔFVCpp ≥3%	14	14	14	14	14	11	12	11	12	9
ΔFVCpp <3%	30	30	29	29	29	26	26	26	24	24

Grey shaded area indicates the PAP when patients were receiving alglucosidase alfa. Dashed line represents treatment with alglucosidase alfa, solid line represents avalglucosidase alfa treatment. Data points are staggered between subgroups to avoid overlapping bars; patients in both subgroups were assessed at the same timepoints.
ΔFVCpp, change in forced vital capacity percent predicted from baseline to Week 49; ETP, extended treatment period; LS, least squares; PAP, primary analysis period; SE, standard error

Table 1. Baseline characteristics of patients treated with alglucosidase alfa in the PAP who switched to avalglucosidase alfa in the ETP

Parameter	Change from baseline to Week 49		
	ΔFVCpp ≥3% (N=14)	ΔFVCpp <3% (N=30)	Overall (N=44)
Age, years			
Mean (SD)	50.9 (13.5)	48.3 (14.3)	49.1 (14.0)
Median (range)	52.0 (26–70)	46.5 (19–77)	47.5 (19–77)
Male, n (%)	7 (50.0)	17 (56.7)	24 (54.5)
Race, n (%)			
White	14 (100)	29 (96.7)	43 (97.7)
Black or African American	0	1 (3.3)	1 (2.3)
Time from disease diagnosis, years, median (range)	1.2 (0–27)	0.7 (0–18)	0.7 (0–27)
Time from first disease symptom, years, median (range)	10.2 (1–29)	9.9 (0–38)	10.0 (0–38)
FVCpp upright, %, mean (SD)	59.6 (12.2)	62.2 (12.8)	61.4 (12.5)

Baseline characteristics are reported at randomization into the PAP.

ΔFVCpp, change in forced vital capacity percent predicted from baseline to Week 49; ETP, extended treatment period; PAP, primary analysis period; SD, standard deviation

DISCUSSION

- Our results show that a switch to avalglucosidase alfa stabilizes respiratory function in patients with LOPD, regardless of their response to alglucosidase alfa.
  - In the subgroup of patients who on average showed improvement during alglucosidase alfa treatment, respiratory function was maintained following the switch.
  - In the subgroup of patients who declined on average during alglucosidase alfa treatment, respiratory function was stabilized following the switch.
- These data suggest there are clinical benefits over 2 years following a switch of therapy to avalglucosidase alfa in patients with LOPD, which can inform patient and healthcare provider decisions regarding treatment options for LOPD.

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DISCLOSURES

KIB has served as a consultant to Sanofi, Amicus Therapeutics, Takeda, Valerion, and has participated in advisory boards for Sanofi, AskBio, Spark Therapeutics and Takeda; he is currently an employee of Sanofi. **JM**, **MP**, **NT**, **KAH**, 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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