Avalglucosidase Alfa Improves Symptoms and Functioning in Late-Onset Pompe Disease Patients vs Alglucosidase Alfa: Post-Hoc Analyses of Patient-Reported Outcomes from COMET Trial

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BACKGROUND

- Late-onset Pompe disease (LOPD) is a rare, hereditary muscle disorder caused by pathogenic variants in the *GAA* gene resulting in progressive muscle damage, weakness and respiratory insufficiency with limited cardiac manifestations.[1, 2]
- The first available treatment since 2006 was alglucosidase alfa (ALG), an enzyme replacement therapy (ERT).[1, 3]
- Avalglucosidase alfa (AVA) has received marketing authorisation in several countries for infantile-onset Pompe disease and/or LOPD. It was approved in August 2021 for patients with LOPD ≥1 year of age in the United States and in June 2022 for patients with Pompe disease in the European Union.
- The pivotal Phase 3 trial (COMET, NCT02782741) provides evidence of clinically meaningful improvement of AVA (*n* = 51) vs ALG (*n* = 49) in respiratory function, ambulation and functional endurance, with no new safety signals.[4]
- The COMET trial also assessed multiple Patient Reported Outcome Measures (PROMs) that help understand the quality of life or the functional status associated with AVA and ALG from a patient's perspective in patients with LOPD.[4]

OBJECTIVES

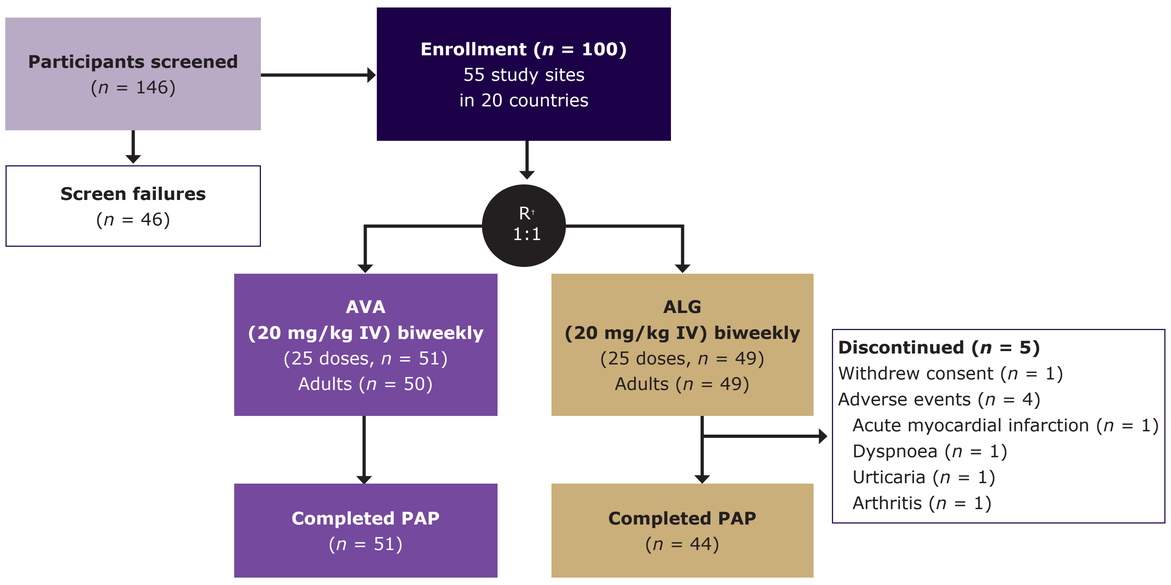
- To evaluate the clinical benefits of AVA vs ALG on symptoms and functioning based on the three LOPD-specific PROMs during the 49-week primary analysis period of the COMET study in adult patients with LOPD using post-hoc analysis.

METHODS

Study design and participants

- The details of study design and treatment groups are presented in **Figure 1**.
- In this study, participants were analysed by modified intention to treat (mITT), which refers to the primary analysis population that included participants who received at least one infusion (partial or full) of the assigned treatment.
- PROMs were assessed in patients aged ≥18 years (AVA [*n* = 50] and ALG [*n* = 49]).

Figure 1: Study design and patient disposition



†Randomisation (R): 1:1 ratio with stratification factors: baseline FVC% predicted (<55%, ≥55%), gender, age (<18 years, ≥18 years) and country (Japan or ex-Japan).
ALG, alglucosidase alfa; AVA, avalglucosidase alfa; FVC, forced vital capacity; IV, intravenous; PAP, primary analysis period

PROM assessment

- Three LOPD-specific PROMs, including the Pompe Disease Symptom Scale (PDSS), Pompe Disease Impact Scale (PDIS) and Rasch-Built Pompe-Specific Activity (R-PAct) Scale were used in these analyses.
- The PDSS and PDIS were assessed using 24-h recall diary entries throughout the entire screening period and then for 2 weeks between visits.
- The PDSS contains 12 items, with a response scale ranging from 0 (none) to 10 (as bad as I can imagine) and yields scores for the following five domains: shortness of breath, overall fatigue, pain, upper extremity weakness and morning headache.
  - All of the domain scales were scored as an average of the items (0–10 range).[5, 6]
- The PDIS contains 15 items. The response scales vary according to the item type with some items on a 0 (none) to 10 (as bad as I can imagine) scale, others on a 3-point scale (no, not physically able; no, but physically able; yes) and others on a 5-point scale (0 = not at all difficult, 1 = a little difficult, 2 = somewhat difficult, 3 = very difficult and 4 = extremely difficult).
  - The PDIS yields scores for two domains: mood and difficulty performing activities. Both scores are calculated as the average of the component items. The mood score ranges from 0–10, whereas the difficulty performing activities score ranges from 0–4.[5, 6]
- Patients with Pompe disease experienced symptoms across multiple PDSS and both PDIS domains.[4] Therefore, apart from assessing the domain scores in isolation, the percentage of responders to multiple PDSS domains and both PDIS domains were evaluated for AVA and ALG.
- The R-PAct is an 18 item-scale that measures the effects of Pompe disease on a patient's ability to carry out daily living activities.[6] These items included three response options, ranging from unable to perform (0), able to perform but with difficulty (1) and able to perform without difficulty (2). A person score was derived using the Rasch Item Response Theory model, and a standardized scale of 0–100 was provided.
  - The R-PAct was developed in Dutch and translated into English; hence, it could only be completed in select countries, including the United Kingdom, the United States, Canada, Belgium and the Netherlands (AVA [*n* = 21]; ALG [*n* = 25]).
  - In R-PAct, the percentage of patients (≥18 years of age) who switched from 'unable to do' at baseline to 'able to do' a daily activity at week 49 on key R-PAct scale items was assessed. The percentage of patients was determined as = (Number of patients who changed from 'unable' to 'able' at week 49)/(Number of "unable" patients at baseline).

Statistical analyses

- Post-hoc analyses were performed to assess the percentage of patients in each treatment group who were responders in multi-PDSS domains (on ≥ 1, ≥ 2, ≥ 3, and ≥ 4 domains) and PDIS domains (on both domains – mood and difficulty performing activities) at week 49.
- Odds ratios for AVA vs ALG along with their 95% confidence intervals (CIs) and *p*-values were derived using a logistic regression models adjusted for age (in years) at baseline and gender; superiority of AVA over ALG was tested with a two-sided 5% significance level.
- In the R-PAct analysis, no statistical test was performed due to the small sample size of patients unable to perform activities at baseline.

RESULTS

Demographic details

- The baseline characteristics of patients is provided in **Table 1**. The characteristics are comparable between the two treatment groups.

Treatment effects on PROMs

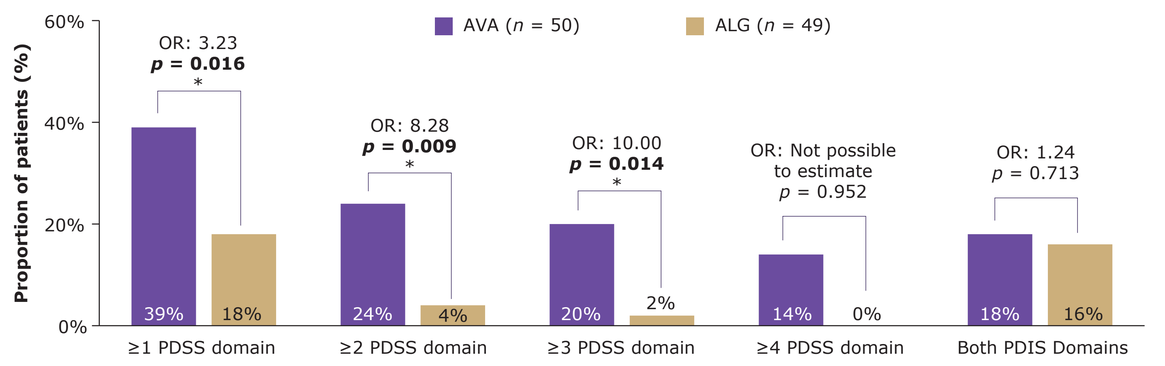
- In the multi-PDSS domain responder analysis, AVA (*n* = 50) was numerically superior and statistically significant, at nominal *p*-value (across all domains except ≥ 4 PDSS domain) over ALG (*n* = 49) at Week 49 (**Figure 2**).
- A similar proportion of responders to PDIS domains was observed in each AVA (*n* = 50) vs ALG (*n* = 49) treatment group (**Figure 2**).

Table 1: Baseline characteristics of patients (mITT population ≥18 years)

Parameter[1]	AVA (*n* = 50)	ALG (*n* = 49)
Age (years), mean (SD)	46.1 (14.0)	49.8 (13.7)
Gender, male (*n* [%])	26 (52.0)	25 (51.0)
Race, *n* (%)		
White	47 (94.0)	47 (95.9)
Asian	2 (4.0)	0
Black/African American	1 (2.0)	2 (4.1)
Ethnicity, *n* (%)		
Not Hispanic or Latino	43 (86.0)	32 (65.3)
Hispanic or Latino	3 (6.0)	12 (24.5)
Not reported	4 (8.0)	5 (10.2)
Region, *n* (%)		
Europe	31 (60.8)	21 (42.9)
North America	14 (27.5)	20 (40.8)
Latin America	2 (3.9)	7 (14.3)
Asia-Pacific	4 (7.8)	1 (2.0)
BMI (kg/m^2)		
Mean (SD)	26.48 (6.84)	26.69 (5.42)
Min; max	14.0; 42.7	16.9; 44.6
Age at diagnosis (years), mean (SD)	44.7 (14.7)	48.2 (14.6)
Time from diagnosis to first infusion of study drug (years), mean (SD)	1.30 (2.67)	2.21 (4.99)
PDSS, mean (SD)		
Shortness of breath	2.79 (2.03)	2.27 (2.20)
Overall fatigue	4.22 (1.79)	4.20 (2.06)
Pain	3.69 (2.14)	3.72 (2.50)
Upper extremity weakness	1.97 (1.66)	2.33 (2.23)
Morning headache	1.25 (1.53)	0.90 (1.38)
PDIS, mean (SD)		
Negative mood	2.08 (1.75)	1.98 (1.76)
Difficulty performing activities	2.35 (0.81)	1.96 (1.03)
RPAct scale*		
RPAct summary score	57.05 (16.03)	57.48 (17.44)

[1]Result is reported for AVA (*n* = 50) and ALG (*n* = 49) patients, unless otherwise indicated.
*R-PAct scale was completed in AVA (*n* = 21) and ALG (*n* = 25).
ALG, alglucosidase alfa; AVA, avalglucosidase alfa; BMI, body mass index; max, maximum; min, minimum; mITT, modified intent-to-treat; PDIS, Pompe Disease Impact Scale; PDSS, Pompe Disease Symptoms Scale; R-PAct, Rasch Built Pompe Specific Activity; SD, standard deviation

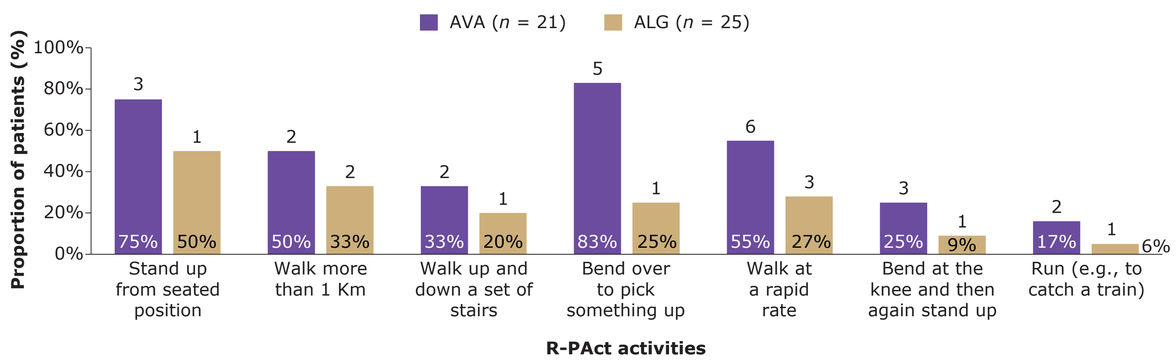
Figure 2: Percentage of responder patients across multiple PDSS domains and both PDIS domains



*statistically significant.
Responder threshold for PDSS considered meaningful to patients: a reduction of 1.5 points between baseline and week 49 for pain, shortness of breath, overall fatigue and upper extremity weakness; a reduction of 1.0 point between baseline and week 49 for morning headache.[7]
Responder threshold for PDIS considered meaningful to patients: a reduction of 1.5 points between baseline and week 49 for mood; 1.0 point between baseline and week 49 for difficulty performing daily activities.[7]
ALG, alglucosidase alfa; AVA, avalglucosidase alfa; PDIS, Pompe Disease Impact Scale; PDSS, Pompe Disease Symptoms Scale; OR, odds ratio

- A numerically greater percentage of patients receiving AVA (*n* = 21) vs ALG (*n* = 25) was able to complete selected R-PAct activities at week 49 that they could not perform at baseline (**Figure 3**).

Figure 3: Percentage of patients who switched from 'unable to do' at baseline to 'able to do' at week 49



Numbers above bars are the number of patients who switched from 'unable to do' at baseline to 'able to do' at week 49.
ALG, alglucosidase alfa; AVA, avalglucosidase alfa; R-PAct, Rasch Built Pompe Specific Activity

Limitations

- Statistical test could not be performed because of the small sample size of patients unable to perform activity at baseline with the R-PAct scale.
- Generalisability of results outside of the sample tested is unknown.

CONCLUSIONS

- The PDSS, PDIS and R-PAct measure symptoms and functional limitations outlining the major critical manifestations of the underlying pathophysiology in patients with LOPD.
- Across all analyses, patients treated with AVA were more likely to experience a meaningful improvement in their symptoms and activities and, in some cases, this improvement was in multiple areas of daily functioning.
- Current post-hoc analyses extend the findings from exploratory endpoint analyses of the COMET trial based on the LOPD-specific PRO measures.
- The results illustrate the positive and consistent trends throughout these PROMs in favour of AVA over ALG in treatment-naïve patients with LOPD, highlighting the favourable impact of AVA over ALG on aspects of Pompe disease relevant in patients' daily lives.

Conflicts of Interest

AT- Honoraria: Sanofi
ATvdP - Consulting, advisory board, grants: Amicus, Biomarin, Sanofi via agreements between Erasmus MC and industry
KB - Advisory boards: Sanofi, Amicus Therapeutics, AskBio, Spark Therapeutics, Takeda; Consultant fees: Sanofi, Amicus Therapeutics, AskBio, Spark Therapeutics, Takeda, Valerion
MMD - Consultant: Amazentis, ArgenX, Catalyst, Cello, Covance/Labcorp, CSL-Behring, EcoR1, Janssen, Kezar, Medlink, Momenta, NuFactor, Octapharma, RaPharma/UCB, Roivant Sciences Inc, Sanofi, Shire Takeda, Scholar Rock, Spark Therapeutics, Abata/Third Rock, UCB Biopharma, UpToDate; Research or educational grants or contracts: Alexion, Alnylam Pharmaceuticals, Amicus, Biomarin, Bristol-Myers Squibb, Catalyst, Corbus, CSL-Behring, FDA/OOPD, GlaxoSmithKline, Genentech, Grifols, Kezar, Mitsubishi Tanabe Pharma, MDA, NIH, Novartis, Octapharma, Orphazyme, Ra Pharma/UCB, Sanofi, Sarepta Therapeutics, Shire Takeda, Spark Therapeutics, The Myositis Association, UCB Biopharma/RaPharma, Viromed/Healixmith & TMA
BS - Advisory boards: Argenx, Amicus, Astellas, Lupin, Sanofi, Spark; Contracted research: Amicus, Merck; Honoraria: Kedrion; Travel Grant: Kedrion
CG - Consulting fees: Sanofi
JM, AH, NT, LP - Employees, shareholders: Sanofi
PSK - Advisory boards: Amicus, Baebies, Sanofi; Consulting fees: Amicus, AskBio, Sanofi, Vertex; Contracted research: Amicus, Sanofi, Valerion; Honoraria: Amicus, AskBio, Sanofi, Vertex; Travel Grant: Amicus, Sanofi; Ownership interests: AskBio, Baebies

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^Kenneth I. Berger was a full-time employee of Bellevue Hospital at the time of the study conduct and is now an employee of Sanofi.

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