Cipaglucosidase alfa (Pombiliti®) in combination with Miglustat for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency)

Disease pattern

- Pompe disease is a **rare, autosomal recessive lysosomal storage disorder caused by the lack or deficiency of an enzyme called alpha-glucosidase**. Patients with Pompe disease have a build-up of the substrate glycogen (complex sugars) in body tissues, including the heart, lung and skeletal muscles, causing enlarged heart, breathing difficulties and muscle weakness [1].
- In the literature, the **clinical spectrum of Pompe disease is categorised in different ways**. It can be described as 'classic infantile', 'childhood' and 'adult' Pompe disease or as 'infantile-onset' (classic and non-classic) and 'late-onset' disease. Earlier onset compared to later onset is usually associated with faster progression and greater disease severity. A definition states that **late-onset Pompe disease (LOPD)** refers to all cases in which hypertrophic cardiomyopathy did not manifest or was not diagnosed at or under the age of 1 year, as well as to all cases with symptom onset above the age of 1 year [2]. Another source states the definition that LOPD patients do not develop cardiomyopathy and may present at any age [1].
- In LOPD, the **primary clinical finding** is skeletal myopathy, with a more protracted course leading to respiratory failure. Affected children usually present with delayed gross-motor development and progressive weakness in a limb-girdle distribution. Early involvement of the diaphragm is a common feature, and sleep-disordered breathing may occur. This usually leads to respiratory failure and death in the second or third decade of life. Affected adults with LOPD also present with progressive, proximal weakness in a limb-girdle distribution, particularly the hip flexors in the earliest stages of the disease. The weakness is accompanied by diaphragmatic involvement, leading to respiratory insufficiency early in the course of the disease [1].

- The following **classifications** apply for LOPD: ICD-10 E74.0 and ORPHA:420429 [3]
- Currently the state funded **new-born screening** in Austria does not cover the screening for Morbus Pompe [4]. However, it might be available in certain hospitals or laboratories [5, 6].
- The literature-reported **birth prevalence** of Pompe disease is a maximum of 11.6 per 100,000 in Austria [7]. There are assumptions that in Europe 58% of infants born with Pompe disease could have the adult onset form of the disease [7]. In 2019, there were approximately 26 LOPD patients/year in Austria, who require treatment. Currently there could possibly be 1 or 2 LOPD patients per year more [8] which is in line with the results of a previous prevalence study [9].

Current treatment

The primary treatment for GAA deficiency is ERT with **Myozyme®** (alglucosidase alfa). Standard dosing is 20 mg/kg given intravenously every two weeks [1, 10]. Dosing may be increased twofold to 20 mg/kg once a week or 40 mg/kg every two weeks in those with a poor response to initial therapy [1].
Criteria when to start and stop ERT have been described elsewhere [11, 12]. At present, there is a lack of verified prognostic factors to help identify which patients would benefit more or less from treatment or when treatment is no longer useful [12].

General information about the drug

Drug description

- The active substance of **Pombiliti®** is **cipaglucosidase alfa (ATB200)**, a recombinant human acid α-glucosidase/GAA (ATC code: A16AB23), which is an enzyme replacement therapy (ERT) that provides an exogenous source of acid α-glucosidase. Pombiliti® helps to break down glycogen and stops it building up abnormally in the cells [13].
- **Pombiliti®** will be available as a 105 mg powder for concentrate for solution for infusion [13]. It is given as an infusion once every two weeks with a dose of 20 mg per kilogram body weight. The infusion should start slowly and then be gradually sped up provided that there are no signs of side effects caused by the infusion. The approximate duration of the infusion is 4 hours [14].
- **Miglustat (AT2221)**, is available as an oral capsule. It is given as a single dose of 4 capsules of 65 mg if the patient weighs at least 50 kg or 3 capsules of 65 mg if the patient weighs between 30 and 50 kg. The capsules should be taken 1 hour before the start of the infusion of cipaglucosidase alfa on an empty stomach (patients have to fast 2 hours before and 2 hours after taking miglustat) [14].
- **Miglustat** which has been absorbed in the blood after oral intake, binds with cipaglucosidase alfa when it is injected and protects it from degradation in the blood.

Indication (EMA)

- **Pombiliti®** is a long-term ERT used in combination with the enzyme stabiliser miglustat for the treatment **of adults with late-onset** Pompe disease (=**LOPD)** (acid α-glucosidase [GAA] deficiency) [13].

- **Nexviadyme®** (avalglucosidase alfa) is indicated for long-term ERT for the treatment of **patients with Pompe disease** (acid α-glucosidase deficiency) [15].

➔ The active substance in **Nexviadyme®, avalglucosidase alfa (GZ 402666, neoGAA),** is a version of the enzyme alpha-glucosidase, which is lacking in people with Pompe disease.
Nexviadyme® is available as a 100 mg powder for concentrate for solution for infusion. The recommended dose is 20 mg/kg of body weight administered once every 2 weeks [15]

Regulatory status

EMA

➔ **Pombiliti® with miglustat** received positive **EMA CHMP opinion** on 15.12.2022. The European public assessment report (EPAR) is expected by the end of February 2023. Pombiliti® was designated as an orphan medicine during its development. EMA is currently reviewing the information available to date to determine if the orphan designation can be maintained. The company name is Amicus Therapeutics Europe Limited [13].

➔ **Pombiliti® with miglustat** received **EAMS (Early Access to Medicinces Scheme)** scientific opinion **in the United Kingdom** on 04.06.2021. Indication is: Long-term treatment of LOPD in adult patients with symptoms and who have received Myozyme® (alglucosidase alfa) for at least 2 years [14].

➔ **Nexviadyme®**: was granted EMA marketing authorisation on 24.06.2022 and is **under additional monitoring** [16]. Nexviadyme® was withdrawn from the Community register of orphan medicinal products in April 2022 at the time of the granting of a EMA marketing authorisation [16]. The Committee for Orphan Medicinal Products (COMP) considered that **the submitted evidence and/or arguments** in the context of the appeal **did not suffice to establish that Nexviadyme® provides a significant benefit over Myozyme®** [7].

Other information:
- The orphan drug status of **Myozyme®** expired in Europe 10 years after EMA marketing authorisation that was received in 2006 [17, 18].
- Marketing authorisation holder of both **Nexviadyme® and Myozyme®** is Genzyme Europe BV. Sanofi-Aventis acquired Genzyme in 2011 [19].

FDA

➔ **Pombiliti® with miglustat**: no FDA approval yet. End of Oct 2022, it was stated that the FDA delayed action on a pending application due to the inability to conduct a required manufacturing site inspection. Previously, the FDA granted breakthrough therapy designation to **Pombiliti® with miglustat for LOPD** based on the results of a Phase 1/2 clinical trial called ATB200-02 (NCT02675465) where it improved walking ability and lung function for up to three years **in adults with the disease** [20, 21].

➔ **Nexviadyme®:** was approved by FDA on 06.08.2021 to treat patients **≥1 year of age with LOPD** [22]. The FDA granted this application a Fast Track, a Priority Review and a Breakthrough Therapy designation. Nexviazyme® also received an orphan drug designation [23].

Costs

Pombiliti®

➔ Approximately 450 000 € per year/per patient

➔ According to the manufacturer, the price is not yet known [24].

Miglustat

➔ Ex-factory price: 84 capsules, 2613.00€ to 3629.16€ [25]

➔ Approximate calculation (in case above mentioned price does not include Miglustat):
Assumption 70kg person, 4 capsules before every infusion: 5226 € to 7258,32€ per year/per patient

Nexviadyme®

➔ Ex-factory price: 100mg/10ml, 5 pieces, 5500€ [25]
Assumption 70kg person, 20mg/kg, given once every two weeks: approx. 401 500€ per year/per patient

Myozyme®

➔ Ex-factory price: 50mg/20ml, 10 pieces, 5500 € [25]

➔ Ex-factory price: 50mg/20ml, 25 pieces, 13750 € [25]
Assumption 70kg person, 20mg/kg, given once every two weeks: approx. 401 500€ per year/per patient

Health care related aspects

➔ A multidisciplinary care team might be useful for coordination of care. It could be led by a clinical biochemical geneticist, with support from physical medicine and rehabilitation; cardiology; pulmonology; orthopedics; nutrition; and physical, occupational, and speech therapy [1].

➔ Treatment should be supervised by a physician experienced in the management of Pompe disease or other inherited metabolic or neuromuscular diseases.

➔ Patients who have no major side effects with the first few infusions (for a few months) may be able to have their infusions given at home. A patient's underlying co-morbidities and ability to adhere to the home infusion requirements need to be taken into account when evaluating the patient for eligibility to receive home infusion [16]. Some recommendations for German-speaking countries were provided for possible home infusion therapy/ERT that, among others, considers adequate execution of treatment and the legal situation for delegating physicians [26].

Warnings and precautions

Pombiliti®

➔ Further information will be available in the EPAR.

Nexviadyme® - detailed information can be found in the EPAR [15].

➔ **Contraindications**: Life-threatening hypersensitivity to the active substance or to any of the excipients (Histidine, Histidine hydrochloride monohydrate, Glycine, Mannitol, Polysorbate 80) when re-challenge was unsuccessful.

➔ **Hypersensitivity reactions, including anaphylaxis,** have been reported in Nexviadyme-treated patients. Appropriate medical support measures, including cardiopulmonary resuscitation equipment especially for patients with cardiac hypertrophy and patients with significantly compromised respiratory function, should be readily available when Nexviadyme is administered.

➔ Patients with an acute underlying illness at the time of Nexviadyme infusion appear to be at greater risk for **infusion-associated reactions (IARs)**. Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from IARs. Antihistamines, antipyretics, and/or corticosteroids can be given to prevent or reduce IARs. However, IARs may still occur in patients after receiving pre-treatment.

➔ Treatment emergent anti-drug antibodies (ADA) testing may be considered if patients do not respond to therapy. Adverse-event-driven immunologic testing, including IgG and IgE ADA, may be considered for patients who have risk for allergic reaction or previous anaphylactic reaction to alglucosidase alfa. IARs and hypersensitivity reactions may occur independent of the development of ADA.

➔ Caution should be exercised when administering Nexviadyme to patients susceptible to fluid volume overload or patients with acute underlying **respiratory illness or compromised cardiac and/or respiratory function** for whom fluid restriction is indicated. These patients may be at risk of serious exacerbation of their cardiac or respiratory status during infusion. Appropriate medical support and monitoring measures should be readily available during Nexviadyme infusion, and some patients may require prolonged observation times that should be based on the individual needs of the patient.

➔ Caution should be used when administering general anaesthesia for the placement of a central venous catheter or for other surgical procedures in patients with infantile-onset Pompe disease (IOPD) with cardiac hypertrophy. Cardiac arrhythmia, including ventricular fibrillation, ventricular tachycardia, and bradycardia, resulting in cardiac arrest or death, or requiring cardiac resuscitation or defibrillation, have been associated with the use of general anaesthesia in IOPD patients with cardiac hypertrophy.

Study characteristics

Trial name	*n*	Intervention (I)	Comparator (C)	Primary endpoint (PE)	Characteristics	Biomarker	Funding	Publication(s)
PROPEL NCT03729362	125 patients enrolled (randomly assigned 2:1)	**Pombiliti®**/Cipaglucosidase alfa (20mg/kg) plus miglustat every 2 weeks for 52 weeks	**Myozyme®**/Alglucosidase alfa (20mg/kg) plus placebo every 2 weeks for 52 weeks	Change from baseline to week 52 in 6-min walk distance (**6MWD**)	International, randomised, double-blind, parallel-group, phase 3 trial	Serum creatine kinase levels, urinary glucose tetrasaccharide levels	Study funded by Amicus Therapeutics (manufacturer of intervention)	Schoser et al 2021 [27]
COMET NCT02782741 Primary analysis period is completed. Open-label extended-treatment phase of the study is ongoing[1].	100 participants randomly assigned (1:1)	**Nexviadyme®**/Avalglucosidase alfa (20mg/kg) every 2 weeks for 49 weeks	**Myozyme®**/Alglucosidase alfa (20mg/kg) every 2 weeks for 49 weeks	Change from baseline to week 49 in upright forced vital capacity[2] percent (**FVC%**) predicted	International, randomised, double-blind, parallel-group, phase 3 trial	Serum creatine kinase levels, urinary glucose tetrasaccharide levels, alanine aminotransferase	Study funded by Sanofi Genzyme (manufacturer of intervention)	Diaz-Manera et al 2021 [28]

[1] An additional extended open-label period of up to 144 weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first) is ongoing. According to clinicaltrials.gov the estimated study completion date is May 2023.

[2] A measure of respiratory function

						, aspartate aminotransferase		

Applicability (population: inclusion/exclusion criteria)

PROPEL:

- 125 **LOPD** patients enrolled (randomly assigned 2:1): **85 patients received cipaglucose alfa plus miglustat, 40 patients received alglucosidase alfa plus placebo.**
- Randomisation was stratified by 6 min walk distance at baseline and previous ERT status (**ERT-naïve or ERT-experienced**). 77.2% of included patients were ERT experienced.
- Eligible **patients were aged ≥ 18** with body weight of at least 40kg and a diagnosis of LOPD, had been **receiving alglucosidase alfa for at least 2 years (20mg/kg once every 2 weeks) or were enzyme replacement therapy-naïve**.
- Patients were required to have a sitting forced vital capacity (FVC) of at least 30% of the predicted value for healthy adults and to have performed two valid 6-min walk tests (both 6-min walk test screening values had to be ≥75 m and ≤90% of the predicted value for healthy adults, and the lower value had to be ≥80% of the higher value).
- Exclusion criteria: receiving any investigational therapy or pharmacological treatment for Pompe disease within 30 days or five half-lives of the therapy before day 1 of the study; receiving gene therapy for Pompe disease; use of ventilation support for more than 6 h per day while awake; taking any prohibited medications (miglitol, miglustat, acarbose, or voglibose) within 30 days before day 1; hypersensitivity to any of the excipients in cipaglucosidase alfa, alglucosidase alfa, or miglustat; or any medical condition or any other extenuating circumstance that might, in the opinion of the investigator or medical monitor, pose an undue safety risk to the patient or might compromise their ability to comply with the study.

COMET:

- **Patients with LOPD aged ≥ 3 years** with LOPD who **had never received Pompe specific treatment**.
- 100 participants were randomly assigned (1:1) to either **avalglucosidase alfa** (n=51) **or alglucosidase alfa** (n=49).
- Randomisation was stratified by baseline FVC% predicted (<55% or ≥ 55%), sex, age (<18 years or ≥ 18 years) and region among participants aged at least 18 years (Japan or outside Japan).
- Participants were able to successfully perform repeated FVC measurements in the upright position of 30–85% predicted and walk at least 40 m without stopping and without using an ambulation-assistance device.
- Exclusion criteria: participants with known Pompe-specific cardiac hypertrophy (reported in their medical history), who required invasive ventilation (non-invasive ventilation was allowed), and who were wheelchair-dependent, clinically significant organic disease (apart from Pompe disease related symptoms), previous or current use of immune tolerance induction therapy, pregnancy or breastfeeding, and being a female of childbearing potential not protected by highly effective contraception or unwilling or unable to test for pregnancy.

Efficacy (I vs. C)

PROPEL: 117 completed the study.

Motor function:

- **Primary endpoint**: At week 52, mean change from baseline in **6MWD** was 20,8m (Standard deviation/SD 42.8; standard error/SE 4.6; n=85) in the Cipaglucosidase alfa plus miglustat group and 7,2m (SD 40.3; SE 6.6; n=37) in the Alglucosidase alfa plus placebo group. The least square mean difference was 13,7m (95% CI -1.2 to 28.5).

Cipaglucosidase alfa plus miglustat did not achieve statistical superiority[3] to alglucosidase alfa plus placebo for improving 6MWD.

Pulmonary function:

- Key secondary endpoint: At week 52, mean change from baseline in **sitting FVC% predicted** was -0.9% (SD 6.2; SE 0.7; n=84) in the Cipaglucosidase alfa plus miglustat group and -4,0% (SD 4.9; SE 0.8; n=37) in the Alglucosidase alfa plus placebo group. The least square mean difference was 2.7% (95% CI

Safety (I vs. C)

PROPEL:

- Treatment-emergent adverse events (TEAEs):

Cipaglucosidase alfa + miglustat group (n=85): 81 (95%)
Alglucosidase alfa + placebo (n=38): 37 (97%)

- TEAEs potentially related to treatment:

Cipaglucosidase alfa + miglustat group (n=85): 26 (31%)
Alglucosidase alfa + placebo (n=38): 14 (37%)

- Serious TEAEs:

Cipaglucosidase alfa + miglustat group (n=85): 8 (9%)
Alglucosidase alfa + placebo (n=38): 1 (3%)

- Serious TEAEs potentially related to treatment:

Cipaglucosidase alfa + miglustat group (n=85): 1 (1%)

[3] In the primary analysis using a mixed-effect model for repeated measures (p=0.097). Because the 6MWD data were not normally distributed, a prespecified non-parametric ANCOVA analysis was employed to compare the two treatment groups (p=0.071)

0.4 to 5.0). The treatment difference is *nominally significant in favour of cipaglucosidase alfa plus miglustat.*

- Other secondary endpoint: At week 52, mean change from baseline in **maximal inspiratory pressure** (**MIP) % predicted** was 2,1% (SD 19.2; SE 2.1; n=84)) in the Cipaglucosidase alfa plus miglustat group and -2.7% (SD 16.9; SE 2.8; n=37) in the Alglucosidase alfa plus placebo group. The least square mean difference was 4.2% (95% CI -3.4 to 11.8) *favouring cipaglucosidase alfa plus miglustat (without statistical significance)*.
- Other secondary endpoint: At week 52, mean change from baseline in **maximal expiratory pressure** (**MEP) % predicted** was 0.6% (SD 21.9; SE 2.4; n=84) in the Cipaglucosidase alfa plus miglustat group and -1.6% (SD 12.8; SE 2.1; n=37)) in the Alglucosidase alfa plus placebo group. The least square mean difference was 1.9% (95% CI -5.5 to 9.2) *favouring cipaglucosidase alfa plus miglustat (without statistical significance)*.

Muscle strength:

- Key secondary endpoint: At week 52, mean change from baseline in **lower manual muscle test (MMT) score** was 1.6 (SD 3.8; SE 0.4; n=80) in the Cipaglucosidase alfa plus miglustat group and 0.9 (SD 2.6; SE 0.4; n=34) in the Alglucosidase alfa plus placebo group. The least square mean difference was 1.0 (95% CI -0.5 to 2.4) *favouring cipaglucosidase alfa plus miglustat (without statistical significance)*.
- Other secondary endpoint: At week 52, mean change from baseline in **upper MMT score** was 1.5 (SD 3.4; SE 0.4; n=83) in the Cipaglucosidase alfa plus miglustat group and 0.7 (SD 3.6; SE 0.6; n=37) in the Alglucosidase alfa plus placebo group. The least square mean difference was 0.9 (95% CI -0.2 to 2.1) *favouring cipaglucosidase alfa plus miglustat (without statistical significance).*

Patient-reported outcomes:

- Other secondary endpoint **EQ-5D-5L** not reported as analyses are ongoing.

Note: Further endpoints can be found in the paper

Efficacy analyses were performed in the **ITT population** (all patients who received at least one dose of study drug).

The study authors performed subgroup analyses: "The treatment effects observed in the primary analyses were supported by the relevant secondary endpoints as nearly all the assessed outcomes numerically favoured Cipaglucosidase alfa plus miglustat over Alglucosidase alfa plus placebo in both the overall and the ERT-experienced populations. Comparisons between treatments groups in ERT-naïve patients were challenging to interpret because of the small sample size, observed heterogeneity, and baseline FVC (% predicted) values that were close to normal (80%)".

COMET (avalglucosidase alfa group n= 51; alglucosidase alfa group n=49)**:**

Pulmonary function:

- **Primary endpoint:** At weeks 49, mean change from baseline in **upright FVC% predicted** was 2.89% (SE 0.88) in the avalglucosidase alfa group and 0.46% (SE 0.93) in the alglucosidase alfa group. The least squares mean difference between the groups was 2.43% (95% CI -0.13 to 4.99) *favouring avalglucosidase alfa*.

Alglucosidase alfa + placebo (n=38): 0

- TEAEs leading to study withdrawal:

Cipaglucosidase alfa + miglustat group (n=85): 3 (4%)
Alglucosidase alfa + placebo (n=38): 1 (3%)

- TEAEs leading to death:

Cipaglucosidase alfa + miglustat group (n=85): 0
Alglucosidase alfa + placebo (n=38): 0

- Infusion-associated reactions:

Cipaglucosidase alfa + miglustat group (n=85): 21 (25%)
Alglucosidase alfa + placebo (n=38): 10 (26%)

- TEAEs by preferred term can be found in the paper [27].

Safety assessments were performed in the safety population, which included all patients who received at least one dose of Cipaglucosidase alfa plus miglustat or Alglucosidase alfa plus placebo.
The safety profiles of both treatments were similar over 52 weeks.

COMET:

- TEAEs:

Avalglucosidase alfa (n=51): 44 (86%)
Alglucosidase alfa (n=49): 45 (92%)

- TEAEs potentially related to treatment:

Avalglucosidase alfa (n=51): 23 (45%)
Alglucosidase alfa (n=49): 24 (49%)

- Serious TEAEs:

Avalglucosidase alfa (n=51): 8 (16%)
Alglucosidase alfa (n=49): 12 (25%)

- Serious TEAEs potentially related to treatment:

Avalglucosidase alfa (n=51): 1 (2%)
Alglucosidase alfa (n=49): 3 (6%)

- Severe TEAEs:

Avalglucosidase alfa (n=51): 6 (12%)
Alglucosidase alfa (n=49): 7 (14%)

- TEAEs leading to study withdrawal:

Avalglucosidase alfa (n=51): 0
Alglucosidase alfa (n=49): 4 (8%)

- TEAEs leading to death:

Avalglucosidase alfa (n=51): 0
Alglucosidase alfa (n=49): 1 (2%)

- Adverse event of special interest (AESIs):

Avalglucosidase alfa (n=51): 13 (26%)

Non-inferiority (of the primary endpoint FVC % predicted) was shown because the lower bound of the 95% CI for the difference far exceeded the predefined non-inferiority margin but did not exclude 0 (p=0.0074), *superiority was not reached* (p=0.063). Motor function: • Key secondary endpoint: At weeks 49, mean change from baseline in **6MWT (6min walk test)** was 32.21 (SE 9.93)) in the avalglucosidase alfa group and 2.19 (SE 10.40) in the alglucosidase alfa group. The least squares mean difference between the groups was 30.01 (95% CI 1.33 to 58.69*) in favour of avalglucosidase alfa, statistically significant at the nominal level of 5%.* Pulmonary function: • Other secondary endpoint: At weeks 49, mean change from baseline in **MIP% predicted** was 8.70 (SE 2.09) in the avalglucosidase alfa group and 4.29 (SE 2.19) in the alglucosidase alfa group. The least squares mean difference between the groups was 4.4 (95% CI -1.63 to 10.44) *favouring avalglucosidase alfa (without statistical significance)*. • Other secondary endpoint: At weeks 49, mean change from baseline in **MEP% predicted** was 10.89 (SE 2.84) in the avalglucosidase alfa group and 8.38 (SE 2.96) in the alglucosidase alfa group. The least squares mean difference between the groups was 2.51 (95% CI -5.7 to 10.73) *favouring avalglucosidase alfa (without statistical significance)*. Muscle strength: • Other secondary endpoint: At weeks 49, mean change from baseline in **hand-held dynamometry (HHD), lower extremity** was 260.69 (SE 46.07) in the avalglucosidase alfa group and 153.72 (SE 48.54) in the alglucosidase alfa group. The least squares mean difference between the groups was 106.97 (95% CI -26.56 to 240.5) *favouring avalglucosidase alfa (without statistical significance)*. • Other secondary endpoint: At weeks 49, mean change from baseline in **HHD, upper extremity** was 173.54 (SE 38.04) in the avalglucosidase alfa group and 109.67 (SE 38.98) in the alglucosidase alfa group. The least squares mean difference between the groups was 63.87 (95% CI -44.76 to 172.51) *favouring avalglucosidase alfa (without statistical significance)*. Patient-reported outcomes: • **Quality of life (QoL)** was measured via health related QoL 12-item short-form health survey. The **physical component summary** was 2.37 (SE 0.99) in the avalglucosidase alfa group and 1.60 (SE 1.07) in the alglucosidase alfa group. The least squares mean difference between the groups was 0.77 (95% CI -2.13 to 3.67) *favouring avalglucosidase alfa (without statistical significance)*. The **mental component summary** was 2.88 (SE 1.22) in the avalglucosidase alfa group and 0.76 (SE 1.32) in the alglucosidase alfa group. The least squares mean difference between the groups was 2.12 (95% CI -1.46 to 5.69) *favouring avalglucosidase alfa (without statistical significance)*. *Note: Further endpoints can be found in the paper* Efficacy analyses were done in the **modified ITT population**, which consisted of participants who received at least one infusion (partial or full) of the assigned treatment.	Alglucosidase alfa (n=49): 18 (37%) • Infusion-associated reactions (protocol defined)[4]: Avalglucosidase alfa (n=51): 13 (26%) Alglucosidase alfa (n=49): 16 (33%) Treatment with avalglucosidase alfa was associated with a more favourable safety profile compared with that of alglucosidase alfa.

[4] Defined as an adverse event that occurred during either the infusion or observation period following the infusion, related or possible related to the investigational treatment

➔ **No core-outcome set** was found for Pompe disease [29]. Studies with LOPD patients used endpoints such as the **6MWT/6MWD and FVC** to assess muscular and respiratory function during disease progression or treatment. However, the **clinical relevance of these markers and the minimal clinically important difference (MCID) for these endpoints in LOPD have not yet been established** [30]. ➔ Open-label studies collecting data of patients treated for 5 or 10 years confirm the first observation that the **initial improvement in the 6MWT and FVC observed during the first months of treatment is followed by a plateau that can last for some years before patients start declining**. There might be a huge variability in how the disease progresses in patients, so long-term trajectories can be different between these cases [31]. A prospective analysis from the French Pompe disease registry concluded that ERT improves walking abilities and likely stabilizes respiratory function in adults with Pompe disease, with a ceiling effect for the 6MWT in the first 3 years of treatment [32].	

Risk of bias (study level)

Trial name	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
PROPEL	yes	yes	yes	unclear[5]	yes[6]	unclear
COMET	yes	yes	unclear[7]	yes	yes[8]	unclear

Other aspects

Ongoing studies (for adults with LOPD)	Registries	Conclusions
NCT04138277: **Pombiliti® + miglustat,** open-label extension study to assess long term safety and efficacy in adult subjects with LOPD who completed **PROPEL study,** single group assignment. Estimated study completion date: December 2023 NCT02675465**:** First-In-Human Study to Evaluate Safety, Tolerability, and pharmacokinetics of intravenous **Pombiliti®** Alone and When Co-Administered With Oral **miglustat,** adults with Pompe disease, open label, single group assignment. Estimated study completion date: December 2023 NCT03865836: expanded access for **Pombiliti® + miglustat** for the treatment of Pompe disease. **Pombiliti® + miglustat**: Studies planned for license extension into paediatric Pompe patients [24]. E.g. NCT03911505; NCT04808505; NCT04327973	NCT00231400: Pompe Disease Registry Protocol. A global, multicenter, international, longitudinal, observational, and voluntary program for patients with Pompe disease. Estimated study completion date: January 2034 There are several disease registries (Pompe disease, rare disease) in Europe [33]. Among others in France, Germany, Netherlands, Switzerland. Furthermore, there is a Sanofi Rare Disease Registry: a global, observational, and voluntary program designed to track natural history and outcomes of patients with pome disease.	➔ Statistical superiority was not reached for Pombiliti® with miglustat versus Myozyme®, nor for Nexviadyme® versus Myozyme® for the primary endpoints. Some results of secondary endpoints are statistically significant, however the clinical relevancy of the differences are still under discussion. ➔ Critical endpoints are 6MWT/6MWD and FVC, however their clinical relevance and the MCID for these endpoints in LOPD have not yet been established. ➔ Both PROPEL and COMET studies have an ongoing open-label extended-treatment phase to assess long term safety and efficacy. Data from current study duration does not allow to make judgements on long-term safety and efficacy; if a plateau could be reached or if a deterioration could occur. ➔ As also indicated by others, the comparison of Pombiliti® with miglustat and Nexviadyme® is difficult due to different inclusion criteria and primary outcomes in the studies [34].

[5] Results not (yet) available for all pre-specified endpoints.

[6] The study was industry funded. The sponsor participated in data collection, study design, supervision of research and writing assistance. Third-party medical writing assistance was provided and funded by the sponsor. Several authors declared conflict of interests.

[7] No information if outcome assessors were blinded.

[8] The study was industry funded. The sponsor provided medical writing and publication support. Several authors declared conflict of interests.

Nexviadyme® NCT05164055: French multicenter phase 4, open label extension study of long term safety and efficacy in patients with Pompe disease who previously participated in **Nexviadyme®** development studies in France. Single group assignment. Estimated study completion date: May 2023		➔ Possibility of home infusions to be discussed: prerequisites, organisation, who is paying for the costs etc. **Conclusions by other institutions:** **Pombiliti® with miglustat** ➔ The National Institute for Health and Care Excellence (NICE) is currently appraising the clinical and cost effectiveness of **Pombiliti® with miglustat** (comparators will be **Myozyme®** and **Nexviadyme®)**. Expected publication date: **12.07.2023** **Nexviadyme®** ➔ NICE: Limited evidence shows Nexviadyme® can enter cells more easily, so reducing glycogen levels more efficiently than Myozyme®. But the clinical benefit is uncertain. In LOPD, the cost-effectiveness estimates are uncertain because of uncertainties in the clinical evidence. But they are below what NICE normally considers an acceptable use of NHS resources, so Nexviadyme® is recommended for LOPD [35]. ➔ Canada´s Drug and Health Technology Agency (CADTH): CADTH recommends that Nexviazyme® be reimbursed by public drug plans for the long-term treatment of patients with LOPD if certain conditions are met. Nexviazyme® should only be reimbursed if prescribed by a clinician experienced in treating lysosomal storage diseases or other types of neuromuscular diseases and the price is less costly than Myozyme® for the treatment of patients with LOPD [36, 37].
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