Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende avalglucosidase alfa til behandling af sent debuterende Pompes sygdom

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. avalglucosidase alfa
2. Ansøgers endelige ansøgning vedr. avalglucosidase alfa

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01-08-2022

MGK/SNI

Forhandlingsnotat

Dato for behandling i Medicinrådet	31.08.2022
Leverandør	Sanofi-Aventis
Lægemiddel	Nexviadyme (avalglucosidase alfa)
Ansøgt indikation	Sent debuterende Pompes sygdom (LOPD)

Forhandlingsresultat

Amgros har opnået følgende pris på Nexviadyme (avalglucosidase alfa):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Nexviadyme (avalglucosidase alfa)	100 mg	1 stk.	8.908,58	[redacted]	[redacted]

Prisen er **ikke** betinget af Medicinrådets anbefaling og vil altså være gældende uanset hvad Medicinrådets anbefaler.

Amgros har indgået en aftale med leverandøren, som er gældende fra [redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted]

Der er den 13.06.2022 indsendt en anmodning om vurdering til Medicinrådet på cipaglucosidase alfa i kombination med miglustat til Pompes sygdom fra en anden leverandør.

[redacted]

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Styrke/dosis	Pakningsstørrelse	Pakningspris SAIP	Antal pakninger/år*	Årlig lægemiddelpris SAIP pr. år
Nexviadyme (avalglucosidase alfa)	100mg/ 20 mg/kg hver 2. uge, intravenøst	1 stk.	[redacted]	393	[redacted]
Myozyme (alglucosidase alfa)	50 mg**/ 20 mg/kg hver 2. uge, intravenøst	1 stk.	[redacted]	785	[redacted]

*Gns vægt på 75,5 kg,

[redacted]

Status fra andre lande

Norge: Under vurdering. Myozyme (alglucosidase alfa) godtages ikke som eneste komparator i analysen[1].
Sverige: Under vurdering[2]
England: Under vurdering[3]

[1] https://nyemetoder.no/metoder/avalglucosidase-alfa
[2] https://janusinfo.se/nationelltinforandeavlakemedel/beslutomsamverkansniva/lakemedelsomomfattasavnationellsamverkan.4.11b119de1639e38ca5f285c.html
[3] https://www.nice.org.uk/guidance/indevelopment/gid-ta10876

Konklusion

[redacted]

Medicinrådet

Application for the assessment of avalglucosidase alfa for Late-Onset Pompe Disease (LOPD)

Instructions for companies

This is the template for submission of evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new pharmaceutical or new indication for an existing pharmaceutical. The template is not exhaustive; companies must adhere to the current version of the guidelines alongside using this template when preparing their submission.

Headings and subheadings are not to be removed. Additional subheadings can be added when appropriate. All sections in the template must be filled in. If a section is not applicable, state "not applicable" and explain why. Examples of texts and tables are provided in the template. These can be edited or removed. The company can provide different table layouts to accommodate data, as long as the required information is provided.
The submission should be as brief and informative as possible. The main body of submission must not be longer than 100 pages, excluding the appendices. Submissions in Danish and English are accepted.

In addition to this template, the company must submit a health economic model in Excel, with full access to the programming code. All the information requested in this template and described in the guidelines must be presented in the application. The model can be accompanied by a technical document. The information in the technical document will, however, not be considered as part of the application. Hence, all relevant information for the application must also be described in the application (including appendices) itself. This can be done by copying the relevant information from the technical document into the application, and by presenting it as described in this template and in the guidelines. Companies are encouraged to provide the European Public Assessment Report (EPAR) including the scientific discussion as an appendix to the submission (draft versions will be accepted).
When making an evidence submission, companies must ensure that all confidential information is highlighted in yellow and provide the expected date of publication. If confidential appendices are provided, these must be watermarked as "confidential".

Version 1.0

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Table of contents

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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Medicinrådet

1. Basic information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	Nexviadyme
Generic name	Avalglucosidase alfa
Marketing authorization holder in Denmark	Sanofi A/S
ATC code	A16ABxx
Pharmacotherapeutic group	Other alimentary tract and metabolism products, enzymes
Active substance(s)	Avalglucosidase alfa
Pharmaceutical form(s)	Powder for concentrate for solution for infusion
Mechanism of action	ERT for restoring lysosomal GAA activity
Dosage regimen	20 mg/kg every other week
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Late-Onset Pompe Disease (LOPD)
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	No, home infusions will be possible at the patient's own hand or that of a guardian or parent, but under the responsibility of the treating physician

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Overview of the pharmaceutical	
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Vial containing 100 mg
Orphan drug designation	Avalglucosidase alfa was assigned orphan drug designation by EMA in March 2014

2. Abbreviations

Abbreviation	Full name
6MWT	6-minute walk test
ACMG	American College of Medical Genetics and Genomics
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CI	Confidence interval
CK	Creatine kinase
CM	Cost-minimisation
DBS	Dried blood spots
DMC	Danish Medicine's Council
DNA	Deoxyribonucleic acide
eCDF	Empirical cumulative distribution function
EKG	Electrocardiogram
EMG	Electromyogram
ERT	Enzyme replacement therapy
ETP	Extended treatment period

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FDA	Food and Drug Administration
FVC	Forced vital capacity
GAA	Acid-alpha-glucosidase
Glc4	Glucose tetrasaccharide
GSGC	Gait, Stair, Gower's maneuver and Chair
HHD	Hand-held dynamometry
HCP	Health Care Professional
HRQoL	Health related quality of life
IAR	Infusion associated reaction
IOPD	Infantile-onset pompe disease
IPA	International Pompe Association
ITI	Immune tolerance induction
IV	Intravenous
KOL	Key opinion leader
LDH	Lactic acid dehydrogenase
LOPD	Late-onset pompe disease
LS	Least squares
M6P	Mannose 6-phosphate
MCID	Minimal clinically important difference
MEP	Maximum expiratory pressure
MIP	Maximum inspiratory pressure
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
PAP	Primary analysis period

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PD	Pompe disease
PDIS	Pompe disease impact scale
PDSS	Pompe disease symptom scale
PedsQL	Pediatric quality of life inventory
PGIC	Patient global impression of change
PRO	Patient reported outcome
QMFT	Quick motor function test
QoL	Quality of Life
QOW	Every other week
rhGAA	Recombinant human acid α-glucosidase
R-Pact	Rasch-built Pompe-specific activity scale
SAE	Serious adverse event
SE	Standard error
SF-12	Short form-12
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	Standard of care
WK	Week

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3. Tables and Figures

3.1 List of tables

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3.2 List of figures

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4. Summary

4.1 Population, intervention, comparator and outcomes (PICO)

This is a single technology assessment concerning the treatment of patients with late-onset pompe disease (LOPD) via enzyme replacement therapy (ERT). The intervention in question is avalglucosidase alfa, which is an enhanced version of the current standard of care (SOC) alglucosidase alfa. The expected EMA-indication includes both infantile-onset pompe disease (IOPD) and LOPD, but the data for the IOPD population is less mature and further there are only one or two known cases of IOPD in Denmark, thus this application only concerns LOPD patients.

Population: Patients with LOPD, both treatment naïve and switch patients, who have previously been treated with alglucosidase alfa.

Intervention: Avalglucosidase alfa is a recombinant human acid α-glucosidase (rhGAA) indicated for long-term ERT for the treatment of patients with Pompe disease (PD). Avalglucosidase alfa is available as single-dose vials of 100 mg powder for reconstitution as a solution for intravenous (IV) infusion (1). The expected dosing for avalglucosidase alfa is 20 mg/kg every other week in LOPD. Similarly to alglucosidase alfa the infusion should be administered incrementally. It is recommended that the infusion begin at an initial rate of 1 mg/kg/h and be gradually increased by 2 mg/kg/h every 30 minutes if there are no signs of infusion associated reactions (IARs) until a maximum rate of 7 mg/kg/h is reached.

Comparator: The comparator used in the application is alglucosidase alfa (Myozyme), which is currently the only treatment for patients diagnosed with PD. Alglucosidase alfa was granted marketing authorization by EMA in 2006, after receiving orphan designation in 2001. It is an ERT that provides patients with the enzyme they are lacking, which in this case is alpha-glucosidase. Alglucosidase alfa is produced via recombinant DNA technology where a cell receives the gene that makes it able to produce the enzyme. Alglucosidase alfa is available as single-dose vials of 50 mg powder for reconstitution as a solution for IV infusion. It is administered via IV infusions every other week with a dosage of 20 mg/kg of body weight.

Outcomes: The outcome measures considered in this dossier include:

Primary endpoint (analysis method):

- Change from baseline to week 49 in forced vital capacity % predicted in the upright position (Mixed model for repeated measures [MMRM])

Secondary endpoints (analysis method):

- Change from baseline to week 49 in 6-minute walkt test (MMRM)
- Change from baseline to week 49 in maximum inspiratory pressure % predicted and maximum expiratory pressure % predicted (MMRM)
- Change from baseline to week 49 in lower extremity muscle strenght composite score (MMRM)
- Change from baseline to week 49 in quick motor function test total score (MMRM)
- Change from baseline to week 49 in SF-12 physical component summary and mental component summary (MMRM)

Exploratory and tertiary endpoints (analysis method):

- Change from baseline to week 49 in EQ-5D-5L (Descriptive)
- Change from baseline to week 49 in PDSS (Descriptive)
- Change from baseline to week 49 in PDIS (Descriptive)
- Change from baseline to week 49 in PGIC (Descriptive)

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Safety endpoints (analysis method)

- Number of patients with discontinuations (descriptive)
- Number of patients with ≥ 1 treatment emergent adverse events (descriptive)
- Number of patients with ≥ 1 infusion-associated reactions (descriptive)

4.2 Evidence supporting the application

Sanofi has included an extended phase 2/3 study (NEO-EXT), which supports long-term safety and efficacy of avalglucosidase alfa, as the study provides data from up to 6 years of treatment. Further, the evidence includes a randomized head-to-head phase 3 study (COMET), comparing safety and efficacy of avalglucosidase alfa vs alglucosidase alfa.

NEO-EXT: An ongoing open-label, multicenter, multinational extension phase 2/3 study of avalglucosidase alfa in patients with LOPD who had completed the open-label ascending dose phase 1/2 study that assessed the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of avalglucosidase alfa in both treatment-naïve and alglucosidase alfa treated patients (NEO1). The objective of this study is to assess long-term safety and exploratory efficacy of avalglucosidase alfa. Patients enrolled in NEO1 were either treatment-naïve (naïve group) or had received alglucosidase alfa for ≥9 months (switch group); all patients in NEO1 received IV infusions of avalglucosidase alfa every other week at doses of 5 mg/kg, 10 mg/kg, or 20 mg/kg for 24 weeks. Until 2016, when all patients enrolled in the NEO-EXT study were receiving 20 mg/kg of avalglucosidase alfa and until the most recent data cutoff (February 27, 2020), providing data from up to 6 years of treatment.

COMET: A phase 3, multicenter, multinational, randomized, double-blinded trial in treatment naïve patients with LOPD aged ≥3 years. The objective of the trial was to assess the efficacy and safety of avalglucosidase alfa compared with alglucosidase alfa in the enrolled patients with LOPD. In COMET, included patients were randomized 1:1 to receive an IV infusion of 20 mg/kg avalglucosidase alfa (n=51) or alglucosidase alfa (n=49) once every other week during a 49-week blinded treatment period known as the primary analysis period (PAP).

4.3 Presented efficacy

The head-to-head study (COMET) allowed for direct comparison between avalglucosidase alfa and alglucosidase alfa for all relevant outcomes, including primary, secondary and exploratory. In this application primary, secondary and exploratory tertiary efficacy outcomes have been presented in section 7.1.2.2, outcomes not presented here are included in Appendix D. The primary outcome demonstrated clear non-inferiority and that avalglucosidase alfa treatment resulted in a greater increase in the lung capacity test compared to alglucosidase alfa, although not statistically significant at a 5% significance level. Furthermore, among the secondary outcomes, 6-minute walk test (6MWT) and quick motor function test (QMFT) superiority was achieved at the nominal level.
The NEO-EXT study comprising long-term data (up to 6 years) of avalglucosidase alfa treatment in pompe patients that were either naïve to ERT or switched from alglucosidase alfa, reduced the uncertainty surrounding long-term effect and safety, typically rooted in treatments for rare diseases. The data provided evidence that patients remained stable in important clinical parameters, regardless of whether they were in the naïve or switch groups, opposite patients treated with alglucosidase alfa where a decline was seen after 3 to 5 years. Thus, results show that avalglucosidase alfa is at least as effective with an apparent clinically meaningful difference in important outcomes and QoL, when compared to alglucosidase alfa.

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4.4 Presented safety

Safety of avalglucosidase alfa is both presented in the NEO-EXT and the COMET study. The NEO-EXT study demonstrated the safety of avalglucosidase alfa over a 6 year period, where only one treatment discontinuation occurred prior to the extended study period. An acceptable safety profile was demonstrated for both treatment naïve patients and patients who switched from alglucosidase alfa to avalglucosidase alfa.

The COMET study evaluated the safety of avalglucosidase alfa compared to alglucosidase alfa and found that avalglucosidase alfa has a favorable safety profile (due to lower rates of AEs, SAEs, and IARs) in treatment-naïve patients with LOPD. No TEAEs leading to permanent treatment discontinuations or death were reported in patients who received avalglucosidase alfa. These findings were consistent with the long-term safety data from the NEO-EXT study as mentioned above, confirming the favorable safety profile.

4.5 Clinical conclusion

The strength of this application is the direct comparison of the intervention and comparator in the COMET study, further the long-term data contributes to minimize uncertainty concerning long-term safety, as patients were followed for up to 6 years.

The results presented in section 7.1.2 demonstrate that avalglucosidase alfa is statistically non-inferior to alglucosidase alfa, and suggests that it produces clinically relevant improvements for LOPD patients. This is seen in the 6MWT and QMFT outcomes, but also the primary outcome FVC% predicted, where patients in the COMET study showed early improvements that were sustained throughout, which is consistent with the long-term data from the NEO-EXT study demonstrating stable respiratory function up until the data cut-off, comprising 6 years of follow up. Providing stable respiratory- and motor function is crucial in PD, as a decline in these functions leads to immobilization and respiratory failure. The safety results demonstrates both long-term safety for avalglucosidase alfa and numerically lower event rates as compared to alglucosidase alfa.

Finally, although that avalglucosidase alfa is expected to offer greater health benefits than alglucosidase alfa, it will be provided at a similar AIP price, thus a cost-minimization approach is considered the most appropriate.

4.6 Structure and Results of the Health Economic analysis

A cost-minimisation analysis was conducted, as the head-to-head comparison clearly established non-inferiority for avalglucosidase alfa compared to alglucosidase alfa in the primary objective, and because avalglucosidase alfa is estimated to reduce the resources needed for treating LOPD patients. The model was developed in Microsoft Excel for 365® as a simple cost per-patient model with weekly cycles. The model considered only relevant costs as the only difference between treatments is the drug cost. Thus, included costs were associated with drug acquisition, administration and patient time and transportation. A 10-year time-horizon was applied in the base-case analysis. At pharmacy purchase prices (AIP), the total cost was estimated to be [redacted] for avalglucosidase alfa and [redacted] for alglucosidase alfa with a 10-year time-horizon. The incremental cost of avalglucosidase alfa was estimated to be [redacted] with a 10-year time-horizon.

The budget impact analysis at AIP, indicated that a recommendation of avalglucosidase alfa as standard treatment would result in a budget impact of [redacted] in year 5, when compared to a scenario where avalglucosidase alfa is not recommended.

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[redacted]

4.7 Unmet medical need

The efficacy of alglucosidase alfa in the treatment of LOPD, has been demonstrated in numerous studies, as it has been the only treatment option available for over a decade. Results from a 10-year follow-up, showed that more than 90% of patients benefit from ERT, however, improvements were seen to diminish over time, despite of the initial benefits. As result hereof, patients may still require long-term ventilation; as respiratory failure due to weakening of the diaphragm remains the primary cause of death in patients with LOPD, thus an unmet need for better therapeutic options that can sustain improvement and stabilize patients over time still exist.

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5. The patient population, the intervention and choice of comparator

5.1 The medical condition and patient population (LOPD)

PD is an inherited autosomal recessive disorder caused by deficiency of the enzyme acid alpha-glucosidase (GAA), which breaks down glycogen (2). While patients with severe GAA deficiency present symptoms within the first year of life (infantile-onset PD [IOPD]), those with some GAA activity do not experience disease until later in childhood or even adulthood (late-onset PD [LOPD]).

The enzyme deficiency in PD leads to accumulation of lysosomal glycogen in tissues throughout the body, impacting skeletal, cardiac, and smooth muscle. Patients with LOPD typically present with progressive skeletal and respiratory muscle dysfunction, but less severe cardiac involvement than in IOPD (3). The decline in respiratory muscle function, commonly assessed using the percent predicted forced vital capacity (%FVC), manifests as increasing difficulty breathing and may eventually require ventilatory support, either non-invasive (e.g., oxygen for a few hours a day) or even invasive ventilation. At these stages, quality of life (QoL) deteriorates significantly, and respiratory failure is the leading cause of death in LOPD (4). Loss of skeletal muscle function reduces patients' mobility, often measured using the distance walked in a 6-minute walk test (6MWT) (5). This loss may become severe enough that the patient requires a wheelchair. This too has a major impact on QoL. Both the ventilatory and mobility interventions generate significant additional costs and increase the need for care, with impacts on their QoL as well (6). Treatment with ERT (alglucosidase alfa) improves respiratory and mobility function in patients, however these improvements are seen to diminish over time, why improved treatment is necessary (7-16).

Symptoms and manifestations

Early signs of LOPD can include myalgia (muscle pain), fatigue, exercise intolerance, and elevated creatin kinase (CK) levels (17). Initial respiratory signs of the disease can present as dyspnea (shortness of breath), obstructive sleep apnea, morning headache, daytime somnolence (sleepiness), and recurring pneumonia, which may be caused by impaired cough (3). As the disease progresses, patients with LOPD can develop irreversible skeletal (including respiratory) muscle damage (18, 19). Furthermore, smooth muscle damage can also contribute to impairment of respiration, vasculopathy, dysphagia (difficulty swallowing), and incontinence (20). Unlike patients with IOPD, patients with LOPD do not typically present with cardiomyopathy, although this has been observed in a small number of cases (21, 22).

Symptoms of LOPD may present anytime from infancy to adulthood (23). Average symptom onset for patients with LOPD has been reported as 29 years (median: 28 years; range: 2 to 65 years) (2, 24). In a natural history study of 255 patients with LOPD recruited through the International Pompe Association (IPA), responding by postal questionnaire, most reported diagnosis between the ages of 20 and 50 years although age of diagnosis ranged from shortly after birth to 70 years (23). Adult-onset LOPD can present as proximal muscle weakness, respiratory insufficiency, and elevated plasma CK levels, and patients may also show impacts on their speech or swallowing (17). For a more extensive description of symptoms see Table 1. Patients who experience disease onset during childhood or adolescence often have a more rapid rate of disease progression and/or a more severe phenotype compared with adult-onset LOPD (25).

If left untreated, LOPD will lead to progressive disability, including loss of ambulation and dependency on a wheelchair and/or ventilator. Progressive loss of pulmonary function due to weakening of the diaphragm and respiratory access muscles is the hallmark of LOPD (16). Patients also begin to show a reduction/loss of ability to perform activities of daily living (ADL) such as walking, climbing stairs, and rising from a seated or supine position, which are indicators of muscle weakness in the hip girdle, proximal lower extremities, and trunk (16, 26). In the natural history study of 255 untreated patients with LOPD, the odds of requiring wheelchair use and respiratory support increased each year following diagnosis by 13% and 8%, respectively (both $p<0.001$) (23). Approximately 80% of patients with LOPD are affected by proximal muscle weakness including involvement of the abdominal, paraspinal, and hip muscles; proximal weakness in upper extremities is also common (16, 27).

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A review of 225 LOPD case reports from 19 countries found that the median age of death was 25 years for all patients with LOPD and 45 years for those with adult-onset LOPD (15). A separate analysis of data from the Pompe survey conducted by the IPA and Erasmus MC (n=268) demonstrated a 5-year survival rate (without ERT) of 74% for patients who were dependent on a wheelchair and respiratory support compared with 95% for patients independent of such support (28). In a subgroup of Dutch patients from this survey (n=99), the mortality risk over a median of 3.3 years was over 3 times higher in patients with LOPD compared with the general population (p=0.002) (28).

Table 1: Summary of multisystemic symptoms associated with LOPD

Body system	LOPD symptoms and manifestations
Respiratory	▪ Dyspnea (difficulty breathing) ▪ Rapid, shallow breathing ▪ Impaired cough ▪ Macroglossia (enlarged tongue) ▪ Sleep disordered breathing or sleep apnea ▪ Daytime hypercapnia (increased levels of carbon dioxide in the blood) ▪ Morning headache ▪ Diaphragm weakness ▪ Increased risk of aspiration, chest infection, atelectasis, and pneumonia
Musculoskeletal	▪ Muscle weakness in pelvic girdle, trunk, shoulder, neck, face (including tongue), lower extremities, proximal muscles ▪ Dysphagia (difficulty swallowing) ▪ Impaired respiratory muscles ▪ Fatigue, exercise intolerance, decreased endurance ▪ Loss of ambulation ▪ Osteoporosis or compromised bone strength ▪ Vertebral fractures ▪ Scoliosis ▪ Scapular winging (protrusion of the shoulder blades)
Neurological	▪ Small fiber neuropathy ▪ Hearing loss ▪ Orthostasis (sudden decrease in blood pressure upon standing) ▪ Muscle cramps, paresthesia (numbness and tingling) in extremities ▪ Dry eye
Cardiac	▪ Cardiac hypertrophy ▪ Supraventricular tachycardia (increased heart rate due to cardiac electrical abnormalities), Wolff-Parkinson-White syndrome (supraventricular tachycardia with a delta wave on EKG findings)
Vascular	▪ Microhemorrhages, cerebral/intracranial aneurysms ▪ Lacunar encephalopathy (ischemic stroke originating in vessels supplying subcortical areas of the brain) ▪ Aortic abnormalities, dolichoectasia (elongation and dilation) of basilar artery

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Gastrointestinal/genitourinary	▪ Bloating, cramps ▪ Constipation or chronic diarrhea ▪ Early satiety and poor weight gain ▪ Increased BMI ▪ Hepatomegaly ▪ Urinary and bowel incontinence

Abbreviations: EKG = electrocardiogram; LOPD = late-onset Pompe disease, BMI = body mass index. **Source:** (16, 29, 30)

Patient population

PD is classified as an ultra-rare disease, with a worldwide incidence considered to be 1 in 40,000 births, while LOPD is reported to have a lower incidence of 1 in 57,000 (41). Studies from Belgium and Austria have reported a prevalence of less than 1 in 250,000 (42, 43), although the general European prevalence is estimated at 1 in 50,000-100,000. LOPD is more prevalent in certain high-risk populations, as seen in patients presenting with unclassified limb-girdle weakness, unexplained myopathy, and/or persistent, unexplained elevated CK levels, where prevalence is reported as 1 in 100 patients. In Denmark a similar result was found in a study that screened patients with unclassified limb-girdle muscular dystrophies, here the prevalence of LOPD was reported at 1 in 12,5 (44). However, a more recent study screening for LOPD in 654 patients with unspecified myopathy found no cases of LOPD. The prevalence in Denmark is therefore estimated to be lower than the European. In the Danish population, Sanofi is aware of 17 patients diagnosed with LOPD, all of which are considered eligible for treatment with avalglucosidase alfa. Please see Table 2 for estimated number of patients eligible for treatment in Denmark over the coming 5 years.

Table 2: Estimated number of patients eligible for treatment

Year	2021	2022	2023	2024	2025
Number of patients in Denmark who are eligible for treatment with the pharmaceutical in the coming years*	17	18	18	19	19

*KOL estimate

5.1.1 Patient populations relevant for this application

Pompe patients are comprised of two subgroups, Infantile-Onset Pompe Disease (IOPD) and Late-Onset Pompe Disease (LOPD), where the vast majority of the Pompe population treated today consists of LOPD patients. In Denmark all Pompe patients with LOPD, are currently eligible for treatment with the comparator, alglucosidase alfa, which currently total 17 diagnosed patients (45). These 17 LOPD patients, are all considered likely recipients of avalglucosidase alfa, together with all future patients diagnosed with LOPD.

5.2 Current treatment options and choice of comparator

5.2.1 Current treatment options

Alglucosidase alfa is the first and only treatment currently available for PD (31, 34, 46). Although patients are managed by individualized treatment plans in coordination with a multidisciplinary team, most patients receive a disease-modifying ERT (i.e., alglucosidase alfa) in addition to palliative measures and supportive care for individual symptoms (3). ERT targets the underlying cause of PD by replacing absent or deficient GAA enzyme with rhGAA and subsequently reducing glycogen accumulation in various tissues (47); this has become the worldwide standard of care for patients with PD (48). Alglucosidase alfa, received marketing authorization in the US and Europe 2006 and has

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remained the only approved agent in this class for the subsequent 15 years (31, 34, 46, 49). The efficacy of alglucosidase alfa for the treatment of PD has been demonstrated in numerous studies in patients with LOPD (32, 38, 39).

5.2.2 Diagnosis and treatment

Diagnosis

When LOPD is suspected, the clinician will initially confirm whether or not there is a family history of any muscular diseases, and hereafter the diagnostic protocol includes clinical evaluation to assess muscle strength and function, laboratory testing, and genetic testing. Laboratory testing checks for CK levels, as high CK levels is a strong indicator of PD. Confirmatory testing commonly involves enzyme activity assays; screening is often performed on dried blood spots (DBSs), although positive DBS results must be followed up with ≥1 confirmatory test, such as genetic sequencing or tissue-based enzyme activity essays (3).

Table 2 shows the tests that may be used in diagnosing LOPD.

Table 3: Diagnostics for LOPD

Diagnostic test	Assessment
Common initial testing	
Clinical evaluation to assess muscle strength and function	▪ Includes assessment of proximal muscle weakness, back pain, reduction in/loss of ability to perform ADL (e.g., walking, climbing stairs, rising from seated or supine position), rigid spine syndrome ▪ Gait abnormalities, lordosis, or scoliosis ▪ May use modified Gower sign (lack of hip, abdominal, thigh muscle strength)
Laboratory tests	▪ Abnormal CK, transaminases (ALT, AST), and LDH levels are sensitive, but nonspecific to LOPD
Spirometry, particularly FVC	▪ Measures lung capacity ▪ Should be taken in sitting and supine positions ▪ Reduced FVC by ≥10% may indicate diaphragmatic weakness indicative of LOPD
DBS testing	▪ Measures GAA activity in blood spot sample ▪ Preferred screening test for LOPD; however, positive finding is not confirmatory
Other tests	
Urine analysis (e.g., Glc4)	▪ Elevated Glc4 supports LOPD diagnosis; however, also occurs in other glycogen storage diseases
Muscle biopsy	▪ May detect vacuolar myopathy; however, biopsy is not sufficient as may produce false negatives ▪ Invasive; other methods are now preferred (e.g., enzyme testing of lymphocytes or fibroblasts)
Needle EMG, whole body MRI	▪ Myopathy may be observed with needle EMG or with whole body MRI

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	▪ Nonspecific to LOPD
Polysomnography, nocturnal oximetry	▪ Sleep study data may correlate respiratory events with sleep stages ▪ May provide a baseline for monitoring sleep respiratory function
Confirmatory tests	
Enzyme assay	▪ Measures GAA in lymphocytes, skin fibroblasts, or other tissue samples (e.g., muscle biopsy) ▪ GAA activity measures from fibroblasts has been the "gold standard" for diagnosis of PD ▪ May be inconclusive for patients with LOPD with high residual GAA
Genetic analysis	▪ DNA testing (or *GAA* gene sequencing) with a finding of disease-causing pathogenic variants is increasingly recommended as the preferred confirmatory test

Abbreviations: ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; DBS = dried blood spot; DNA = deoxyribonucleic acid; EMG = electromyogram; FVC = forced vital capacity; GAA = acid α-glucosidase; Glc4 = glucose tetrasaccharide; LDH = lactic acid dehydrogenase; LOPD = late-onset Pompe disease; MRI = magnetic resonance imaging. **Sources**: (3, 24)

Treatment

As no Danish treatment guidelines are available for the treatment of PD, general treatment guidelines have been described with departure in the guidelines from the American College of Medical Genetics and Genomics (ACMG) (3) and international articles.

The main goals of treatment for PD are preserving respiratory and musculoskeletal/motor function, slowing disease progression, and preventing complications and death (3). Because PD affects multiple body systems, a variety of outcomes must be measured and monitored regularly to manage the disease (3, 31). Patients are managed by individualized treatment plans in coordination with a multidisciplinary team, however, most patients receive a disease-modifying ERT in addition to palliative measures and supportive care for individual symptoms (3). Because of the rapidly progressive nature of LOPD, early initiation of treatment can help limit further irreversible muscle damage to improve patient outcomes (13, 32, 33).

Alglucosidase alfa, the first and only ERT currently available for the treatment of PD improves respiratory and mobility functions in patients with PD (7, 31, 34, 35). The efficacy of alglucosidase alfa for the treatment of PD has been demonstrated in numerous studies in patients with LOPD and the advent of alglucosidase alfa has also been shown to improve QoL in patients with LOPD (32, 36-39). Improvements, however, may diminish over time and patients may still require long-term ventilation; as respiratory failure due to weakening of the diaphragm remains the primary cause of death in patients with LOPD, an unmet need still exists for a therapy that can sustain improvement and stabilize patients over time (7-16).

The current treatment regiment is 20 mg/kg of body weight, administered through IV infusion every other week, although in practice some patients receive higher dosages. The infusion should be administered incrementally. It is recommended that the infusion begin at an initial rate of 1 mg/kg/h and be gradually increased by 2 mg/kg/h every 30 minutes if there are no signs of infusion associated reactions (IARs) until a maximum rate of 7 mg/kg/h is reached (35).

Prognosis with current treatment

Respiratory failure is the major cause of death in untreated patients with LOPD, and remains the primary cause of LOPD-related patient death in treated patients (15, 28, 40). The risk of death in LOPD is three times higher than the

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general population and untreated patients are five times more likely to die compared with patients who receive treatment (7, 28). Older age at symptom onset and treatment with ERT are associated with lower mortality (7, 15):

- A large, multinational study of 225 published cases of untreated LOPD patients reported that the mean age at death was 25 years across all symptom-onset age groups, but was 45 years in patients whose symptoms presented at an older age (≥18 years) (15). Respiratory failure was the cause in 72% of the 36 deaths reported (15).
- A systematic literature review and meta-analysis of mortality data for 438 patients with LOPD from 22 publications showed that ERT treatment reduced mortality by almost five times compared to no ERT, with a rate ratio for ERT of 0.21 (95% CI: 0.11, 0.41) (7).

5.2.3 Choice of comparator

Since alglucosidase alfa has not previously been assessed by the Danish Medicine's Council (DMC), a placebo comparison is advised. However, a placebo comparison will not be provided in this application, as this does not reflect the real world treatment of Pompe patients, as leaving patients untreated, even in a study design, cannot be ethically defended well knowing that patients benefit from treatment with ERT (QoL and increase in lifespan), hence it would not fulfill the general requirement for the choice of comparator (50). Further, alglucosidase alfa fulfills the described criteria that allows it to be considered as a relevant comparator and therefore placebo can be omitted for comparison as stated in section 2.4.2 of the DMC methods guideline (50). Danish clinicians consider alglucosidase alfa as the standard treatment option for LOPD patients, given its documented effect and lack of treatment alternatives. The effect of alglucosidase alfa has been t20horoughly documented in numerous publications and shows that the ERT improves critical outcomes such as the 6MWT and % predicted FVC (51), while remaining a safe treatment. One study (52), even demonstrates that the disease quickly starts progression, if ERT is withhold, but also that patients benefit from resuming treatment.

Furthermore, the guidelines state that in a case like this, where the comparator has not been evaluated by the DMC, that the reason for a placebo comparison would be to avoid that a new pharmaceutical appears disproportionately cost-effective. However, given that the approach of this application is a cost-minimization analysis, indicating likely savings benefitting from at least an equivalent effect, then such a concern is irrelevant given the current use of the comparator in clinical practice.

In addition, no data is available comparing avalglucosidase alfa with placebo and such a comparison would thus have to rely on old historical natural history studies, since alglucosidase alfa has been used consistently since its approval in 2006. Trying to establish a placebo comparison would therefore only increase uncertainty and likely provide unreliable results.
As a result, the chosen comparator is alglucosidase alfa (Myozyme), as this is the only current available treatment for PD. Alglucosidase alfa, also described in Table 4, is considered an established treatment of PD in the Danish health care sector and has been used since its launch more than a decade ago. Moreover, avalglucosidase alfa is expected to be a PD treatment alternative to alglucosidase alfa.

Table 4: Description of the comparator

Subject	Description
Generic name (ATC-code)	Alglucosidase (A16AB07)
Mode of action	Alglucosidase alfa is an enzyme replacement therapy (ERT), that provides an exogenous source of acid α-glucosidase (GAA). This results in stabilization or

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	restoration of cardiac and skeletal muscle function, including respiratory muscles.
Pharmaceutical form	Powder for concentrate for solution for infusion. White to off-white powder. One vial contains 50 mg
Posology	The recommended dose is 20 mg/kg of body weight administered once every 2 weeks.
Method of administration	Alglucosidase is administered via IV infusion. The infusion should be administered incrementally. It is recommended that the infusion begin at an initial rate of 1 mg/kg/h and be gradually increased by 2 mg/kg/h every 30 minutes if there are no signs of infusion associated reactions (IARs) until a maximum rate of 7 mg/kg/h is reached
Should the pharmaceutical be administered with other medicines	No
Treatment duration / Criteria for end of treatment:	Continuous life-long treatment
Necessary monitoring, both during administration and during the treatment period	A physician with experience in management of patients with PD, should monitor the patient during administration.
Need for diagnostic or other test	No additional testing compared to the current standard will be necessary (see section 5.2.2)

5.3 The intervention

Avalglucosidase alfa is a recombinant human acid α-glucosidase (rhGAA) indicated for long-term ERT for the treatment of patients with PD (1). By replacing deficient endogenous GAA, avalglucosidase alfa allows for the degradation of lysosomal glycogen and prevents its accumulation that results in tissue damage (1). Avalglucosidase alfa is a rhGAA conjugated with multiple copies of a synthetic bis-mannose 6-phosphate (bis-M6P) replacement therapy that has therefore been designed for enhanced receptor targeting and enzyme uptake through greater affinity for mannose 6-phosphate (M6P) receptors on muscle cells to achieve greater glycogen clearance than alglucosidase alfa (47, 53). Avalglucosidase alfa is developed for patients with PD aiming at improving clinical outcomes based on its increased clearance of glycogen (1). The active substance in avalglucosidase alfa is rhGAA conjugated with about 7 synthetic hexamannose structures, each containing 2 terminal M6P moieties (1). Compared to alglucosidase alfa, avalglucosidase alfa contains an approximately 15-fold increase in M6P (1, 54). In vitro, avalglucosidase alfa has demonstrated a more than 10-fold increase in GAA activity and more efficient uptake compared with alglucosidase alfa (55). The increased quantity of M6P on avalglucosidase alfa compared with alglucosidase alfa enhances cellular uptake and improves glycogen clearance, which in Pompe mice, was associated with an approximately 5 times greater clearance of glycogen in all muscle groups, leading to increased muscle strength and motor function (47, 56).

Avalglucosidase alfa is available as single-dose vials of 100 mg powder for reconstitution as a solution for IV infusion (1). The expected dosing for avalglucosidase alfa is 20 mg/kg every other week in LOPD, with no indication that this amount should be exceeded. Similarly to alglucosidase alfa the infusion should be administered incrementally. It is recommended that the infusion begin at an initial rate of 1 mg/kg/h and be gradually increased by 2 mg/kg/h every 30 minutes if there are no signs of infusion associated reactions (IARs) until a maximum rate of 7 mg/kg/h is reached (1). Avalglucosidase alfa has a more favorable safety profile compared with alglucosidase alfa, with a lower incidence of similar adverse events (AEs), serious AEs (SAEs), and infusion-associated reactions (IARs) (57, 58). Avalglucosidase alfa also facilitates increased patient convenience as it allows for home infusions in patients without a history of moderate or severe IARs, although the presence of a health care professional is still necessary. Further, the increased vial size shortens reconstitution time for health care professionals (1) and patients/caregivers.

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Avalglucosidase alfa has been evaluated and may be used in pediatric patients with PD >6 months of age; it can also be used without dose adjustment in patients >65 years. Patients with mild renal impairment can use avalglucosidase alfa without dose adjustments. However, avalglucosidase alfa has not been evaluated for use in patients with hepatic impairment or moderate or severe renal impairment. Avalglucosidase alfa is contraindicated in patients with a life-threatening hypersensitivity to avalglucosidase alfa or any of its excipients when re-challenge is unsuccessful (1).

Multiple regulatory agencies around the world have recognized the added value provided by avalglucosidase alfa over standard of care. Avalglucosidase alfa has been granted Orphan designation for the treatment of PD by the European Commission, Orphan, Breakthrough Therapy, and Fast Track designations by the United States (US) Food and Drug Administration (FDA), and Promising Innovative Medicine designation by the United Kingdom (UK) Medicines and Healthcare Products Regulatory Agency (59-63).

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A systematic literature review (SLR) has been conducted to investigate if any relevant evidence, that could supplement the randomized head-to-head study, was available. Based on this SLR, no new or important information about the safety and efficacy of avalglucosidase alfa compared to the comparator alglucosidase alfa is available. Thus, no further description of the SLR is given.
The relevance of the SLR is further minimized as there is currently only one approved treatment for PD (alglucosidase alfa) and Sanofi have been able to conduct a randomized double-blinded phase 3 head-to-head study (COMET), comparing relevant safety and efficacy endpoints. The COMET trial compared the two treatments over a time-period of 49 weeks and afterwards all participants were given avalglucosidase alfa and followed for 238 weeks in an extended treatment period. The trial evaluated efficacy based on respiratory- and motor function and safety based on AEs and IARs, all of which are considered key parameters within treatment of PD. COMET is a multicenter study and therefore includes patients from all over the world (56 sites across 20 countries). In conclusion, the COMET trial and the below listed phase 2/3 study, should provide sufficient documentation, to proof non-inferiority along with indications of clinically relevant improvements for avalglucosidase alfa compared to alglucosidase alfa.

6.2 List of relevant studies

Avalglucosidase alfa has been studied in a robust clinical program comprising pediatric (≥6 months) and adult patients with LOPD, see Table 5. Three studies are presented below, but in essence this application has its foundation in the NEO-EXT and COMET studies, leaving out the NEO1 study. NEO1 is of less interest as it a dose finding study, whereas the other two studies provide both long-term- and comparative safety and efficacy data. NEO1 is included in the table,

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to ensure transparency as the NEO-EXT is an extension hereof. Further listed is the primary analysis period (PAP) of the pivotal phase 3 COMET study, which has been completed (an extension period for this study is ongoing).

Table 5: Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Study design
Pena LDM, Barohn RJ, Byrne BJ, Desnuelle C, Goker-Alpan O, Ladha S, Laforêt P, Mengel KE, Pestronk A, Pouget J, Schoser B, Straub V, Trivedi J, Van Damme P, Vissing J, Young P, Kacena K, Shafi R, Thurberg BL, Culm-Merdek K, van der Ploeg AT; NEO1 Investigator Group. Safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of the novel enzyme replacement therapy avalglucosidase alfa (neoGAA) in treatment-naïve and alglucosidase alfa-treated patients with late-onset Pompe disease: A phase 1, open-label, multicenter, multinational, ascending dose study. Neuromuscul Disord. 2019 Mar;29(3):167-186.	NEO1	NCT01898364	July 2013 – February 2015	NEO1 is an interventional phase 1/2 clinical trial, multicenter, multinational, open-label, ascending dose study of avalglucosidase alfa in previously-treated and treatment-naïve late-onset Pompe disease (LOPD) patients.
Schoser, B., Barohn, R. J., et al. (2020). NEO1/NEO-EXT studies: Safety and exploratory efficacy of repeat avalglucosidase alfa dosing for up to 6 years in late-onset Pompe disease (LOPD) [poster P.03]. The 25th International Annual Virtual Congress of the World Muscle Society. Sanofi Genzyme Corporation (2020e). An open-label, multicenter, multinational extension study of the long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) in patients with Pompe disease (Data on File). Interim Clinical Study Report.	NEO-EXT	NTC02032524	February 2014 – December 2021 (estimated completion) Data cutoff February 2020	NEO EXT is a phase 2/3 open-label, multicenter, multinational study of the long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa in patients with PD

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Study design
Clemens, P., Attarian, S., et al. (2020). Efficacy and safety of avalglucosidase alfa in patients with late-onset Pompe disease: Results from the phase 3 COMET trial [poster P.07]. The 25th International Annual Virtual Congress of the World Muscle Society. Sanofi Genzyme Corporation (2020f). A Phase 3 randomized, multicenter, multinational, double blinded study comparing the efficacy and safety of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) and alglucosidase alfa in treatment-naïve patients with late onset Pompe disease (Data on File). Clinical Study Report.	COMET	NCT02782741	November 2016 – September 2024 (Estimated completion) Data cutoff March 2020	A Phase 3 Randomized, Multicenter, Multinational, Double-Blinded Study Comparing the Efficacy and Safety of Avalglucosidase Alfa and Alglucosidase Alfa in Treatment-Naïve Patients with Late-onset Pompe Disease (head to head)
Diaz-Manera, J., Kishnani, P., et al. (2021). Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomized, multicentre trial. The Lancet. 2021;20:1012-26	COMET	NCT02782741	November 2016 – September 2024 (Estimated completion)	A Phase 3 Randomized, Multicenter, Multinational, Double-Blinded Study Comparing the Efficacy and Safety of Avalglucosidase Alfa and Alglucosidase Alfa in Treatment-Naïve Patients with Late-onset Pompe Disease (head to head)

For detailed information about included studies, refer to Appendix B.

6.3 List of completeted and ongoing studies not included

- **NEO1 (LOPD) Ph.1 study completed (published)**
  - An open-label, multicenter, multinational, ascending dose study of the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of repeated biweekly infusions of avalglucosidase alfa in naïve and alglucosidase alfa treated late-onset Pompe disease patients
    Clinical trials.gov identifier: NCT01898364
    EudraCT Number: 2012-004167-42
    Publication: Pena LDM, et al. *Neuromuscul Disord.* 2019;29(3):167–86

- **NEO-EXT (LOPD ERT switch+naïve) Ph.2 NEO1 extension study ongoing +7 years**
  - An open-label, multicenter, multinational extension study of the long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa in patients with Pompe disease

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ClinicalTrials.gov identifier: NCT02032524
EudraCT Number: 2013-003321-28

- **COMET (COMparative Enzyme replacement Trial) (LOPD naïve ERT head-Head) Ph.3 study** ongoing – extension phase all patients on Ava (49-week PAP Ava vs Mz published)
    - A phase 3 randomized, multicenter, multinational, double-blinded study comparing the efficacy and safety of repeated biweekly infusions of avalglucosidase alfa and alglucosidase alfa in treatment-naïve patients with late onset Pompe disease
      ClinicalTrials.gov identifier: NCT02782741
      EudraCT Number: 2016-000942-77

- **Mini-COMET (IOPD switch) Ph.2 study ongoing – extension phase alle patients on Ava (25-week PAP done)**
    - An open-label ascending dose cohort study to assess the safety, pharmacokinetics, and preliminary efficacy of avalglucosidase alfa in patients with infantile-onset Pompe disease treated with alglucosidase alfa who demonstrate clinical decline or sub-optimal clinical response
      ClinicalTrials.gov identifier: NCT03019406
      EudraCT Number: 2016-003475-21

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7. Efficacy and safety

The safety of avalglucosidase alfa was first explored in the NEO1 study and subsequently long-term safety and efficacy outcomes were explored in NEO-EXT, which is why the NEO-EXT is considered relevant to include in this application, as it not only represents the results from the NEO1 study, but also for a follow-up time of 6 years in both treatment naïve and switch patients. The COMET study evaluated safety and efficacy of avalglucosidase alfa, compared to the current treatment alglucosidase alfa in treatment naïve patients with LOPD.

Efficacy and safety outcomes presented in this dossier

In the following paragraphs the safety and efficacy outcomes used in the relevant trials are described, including method of analysis and relevant scale or measurement tool.

The efficacy outcomes from the phase 3 head-to-head study (COMET) were all measured as the change from baseline or change from baseline % predicted and analyzed using a mixed model for repeated measures (MMRM). The MMRM model included age, gender, treatment group, visit, treatment-by-visit interaction and baseline value of the corresponding response variable. The most important endpoints are the primary outcome, forced vital capacity (FVC) % predicted and the secondary outcome, 6-minute walk test (6MWT). Supportive secondary outcomes are also listed below, and concerns functional endurance tests and Health related quality of life (HRQoL).

Primary outcome

Forced Vital Capacity (FVC) % predicted

The primary efficacy endpoint in the COMET study is FVC and is measured as a percentage of the predicted normal capacity in the upright position. Forced vital capacity (FVC) is a respiratory outcome variable that is readily obtainable in the clinical setting and commonly reported in studies pertaining to LOPD patients. FVC decline was observed to be associated with an increased incidence of respiratory complications and death. In LOPD, a patient-level data meta-analysis has demonstrated that FVC is associated with numerous outcome measures and the progression in FVC is associated with changes in exercise tolerance, peripheral muscle strength and health-related quality of life. Improvement in FVC is positively associated with a variety of other LOPD measures and outcomes across multiple domains including endurance (6MWT), skeletal muscle strength and patient-reported outcomes (SF-36) (Lachman 2013). Therefore, FVC is the appropriate choice as a primary endpoint to measure the clinical difference between Avalglucosidase Alfa and Alglucosidase Alfa.

The test evaluated respiratory function by making the patient take the deepest breath they possibly can and forcibly exhale, this is measured as the volume of air (in liters) that is blown out. This parameter is considered key by the American Thoracic Society when evaluating respiratory function as it is a reliable and reproducible test(64) and was further used as an endpoint in the initial LOPD LOTS trials for the comparator, alglucosidase alfa. The use of FVC% predicted as the primary outcome is based on the fact, that respiratory insufficiency due to progressive muscle weakness is a major source of morbidity and death in LOPD patients. All pompe patients will eventually experience respiratory dysfunction, thus stabilizing or improving FVC is critical, which is also why it holds clinical relevance and is used in disease management guidelines (3). Furthermore, respiratory function is known to affect other mobility functions. Global Lung Initiative 2012 reference equations were used (65).

Secondary outcomes

6-Minute Walk Test (6MWT)

The main secondary endpoint in the COMET study is the 6MWT. This safe and simple test evaluates the skeletal muscle function, by measuring the distance (in meters) a person can walk within six minutes on a flat and hard surface. In a systematic review evaluating walk tests it was deemed the easy to administer, better tolerated and more reflective of daily living than the comparators and as a result hereof, it is considered the most relevant walk test (66).

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Maximum inspiratory pressure (MIP) and Maximum expiratory pressure (MEP)

The MIP and MEP are measures that are used globally to assess respiratory muscle strength, by measuring the maximum strength of the respiratory muscles during inspiration and expiration. The test is simple and non-invasive, as it simply measures the static maximum pressure in the mouth against an occluded airway. MIP refers to how much air pressure force an individual creates by inhaling through the mouth as hard as possible, while MEP is the greater pressure generated during maximal expiration. These tests are used in combination with FVC% predicted as supportive measurement outcomes, however both MIP and MEP are less reproducible tests that do not consistently reflect the condition of the patient. Both tests are considered relevant outcomes, as MIP is correlated with survival in patients with neuromuscular disease (67), such as pompe disease, and MEP is correlated with FVC (67).

Lower extremity muscle strength by hand-held dynamometry (HHD)

To assess the lower extremity muscle strength a dynamometer is used. The test was performed so that the examiner held the dynamometer still, whilst the patient exerted maximal force against it, and gradually increased the force used until completing a 4-5 second isometric hold. Muscle strength is then collected in Newton. 6 muscle groups (hip: flexion, extension, abduction; knee: flexion, extension and ankle dorsiflexion) were measured twice on each side. The highest value for each muscle group was chosen and a summary score was then produced as the sum of these 12 measurements. The change from baseline indicates whether or not muscle strength has improved or decreased.

Quick motor function test (QMFT)

The QMFT has been validated in PD and consists of 16 items that are considered specifically difficult for PDs. The patient is observed performing all 16 items and is scored based on a 5-point ordinal scale ranging from 0 to 4 points. The scores are aggregated and presented as one result, within a range of 0 to 64 points, where a lower score represents worse motor function and 64 points represent normal muscle function. The test is considered a reliable way of measuring motor function and clinical severity. This test correlates strongly with proximal muscle strength, shows significant differences between patient groups with different disease severities, and measures the ability to perform everyday movements that are particularly difficult for patients with Pompe disease (68).

Short form-12 (SF-12)

The SF-12 is a survey used to elicit HRQoL in patients aged >=18 years at baseline. It provides a physical component summary (PCS) and mental component summary (MCS), based on scores from 8 different health related domains (physical functioning, role-physical, role-emotional, mental health bodily pain, general health, vitality, and social functioning) all with a range from 0 (poor health) to 100 (better health). The higher the score, the better HRQoL.

EQ-5D-5L

EQ-5D-5L is a generic instrument used to assess HRQoL in patients. The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The patient indicates his/her health status by choosing the most appropriate statement of the five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. A combined five-digit number of the five dimensions describes the patient's health state. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled from 'The best health you can imagine' (100) to 'The worst health you can imagine' (0). The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement (69). The EQ-5D-5L dimensions, index score and EQ VAS can be analyzed as mean change from baseline during the primary analysis period (PAP) of the study.

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Pompe Disease Symptom Scale (PDSS)

The PDSS scale is a PRO specific to Pompe disease, and assesses the full spectrum of symptoms in LOPD patients (70). PDSS is a 12-item scale that measures patient-reported breathing difficulties, tiredness, fatigue, muscle weakness, muscle ache, pain, and morning headache. Items are rated from 0 to 10 according to worst symptom severity in the prior 24 hours, with higher scores corresponding to worse outcomes (70-72).

Pompe Disease Impact Scale (PDIS)

The PDIS scale is a PRO specific to Pompe disease, and assesses the full spectrum of key impacts on patient experience in LOPD patients (70). PDIS is a 15-item scale that measures patient-reported anxiety, worry, depression, ability to walk independently, climb stairs, rise from a seated position, bend over and pick up objects, squat, and tolerate exercise.

Some items are rated from 0 to 10 according to worst symptom severity in the prior 24 hours while others require yes/no response or, for walking, without/with/no assistance, with higher scores corresponding to worse outcomes (70-72).

Patient Global Impression of Change (PGIC)

PGIC is a generic single-item instrument used to measure overall health status. The PGIC items consisted of 4 questions pertaining to disease-related symptoms, change in ability of daily activities as well as mobility and breathing issues. The PGIC used 7-point scale to rate improvement from -3 (a great deal worse) to 0 (no change) to 3 (a great deal better) (73).

Other outcomes

Several other outcomes were included in the COMET study, but will not be further elaborated in this application, as they do not affect the conclusions nor add further value.

The outcomes are listed below:

- Gross Motor Function Measure-88
- Gait, Stair, Gower's Maneuver, and Chair (GSGC)
- Upper extremity muscle strength (HDD)
- Pediatric Quality of Life Inventory (PedsQL)
- Rasch-built Pompe-specific activity scale (R-Pact)

Safety outcomes

In accordance with the DMC's methods guidelines' section 4.2 (50), safety outcomes concerning, adverse events (AEs), treatment emergent adverse events (TEAEs) including infusion-associated reactions (IARs) and any treatment discontinuation, will be presented.

TEAEs and IARs

AEs are defined as any untoward medical occurrence in a participant who took a study-drug and it is not necessarily in causal relationship with the treatment. TEAEs are then any AE that developed or worsened during the treatment period, whereas IARs are AEs that occur during infusion or following an infusion, which are deemed related to the study drug.

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7.1 Efficacy and safety of avalglucosidase alfa compared to alglucosidase for LOPD patients

Two studies are considered relevant, as one demonstrates safety and long-term effects of avalglucosidase alfa, while the other offers a comparison of efficacy and safety toward the comparator that is considered standard treatment in Denmark.

1. The NEO EXT phase 2/3 study is an ongoing, multicenter, multinational extension study of avalglucosidase alfa in patients with LOPD who had completed the NEO1 phase 1 study that assessed the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of avalglucosidase alfa in both treatment-naïve and alglucosidase alfa treated patients. The objective of this study is to assess long-term safety and exploratory efficacy of avalglucosidase alfa. Patients enrolled in NEO1 were either treatment-naïve (naïve group) or had received alglucosidase alfa for ≥9 months (switch group); all patients in NEO1 received IV infusions of avalglucosidase alfa every other week at respective doses of 5 mg/kg, 10 mg/kg, or 20 mg/kg for 24 weeks (three cohorts). In 2016, 19 of the 24 patients were enrolled in the NEO-EXT study and received 20 mg/kg of avalglucosidase every other week until the most recent data cutoff (February 27, 2020), providing data from up to 6 years of treatment (full data of 17 patients) (57).
2. The COMET study is a phase 3, multicenter, multinational, randomized, double-blinded trial in patients with LOPD aged ≥3 years. The objective of the trial was to assess the efficacy and safety of avalglucosidase alfa compared with alglucosidase alfa in the enrolled patients with LOPD. In COMET, included patients were randomized 1:1 to receive an IV infusion of 20 mg/kg avalglucosidase alfa (n=51) or alglucosidase alfa (n=49) once every other week during a 49-week blinded treatment period known as the PAP.

7.1.1 Relevant studies

7.1.1.1 NEO EXT

NEO-EXT is an ongoing phase 2/3, multicenter, multinational extension study of avalglucosidase alfa in patients with LOPD who had completed NEO1 (74, 75). NEO1 was a phase 1, multicenter, multinational, open-label study that assessed avalglucosidase alfa treatment in patients with LOPD aged ≥18 years (57). The study was designed to evaluate the safety and tolerability of avalglucosidase alfa in adults with LOPD while also assessing exploratory efficacy and characterizing its pharmacodynamic and pharmacokinetic profiles (57). Patients were either treatment-naïve (naïve group) or had received alglucosidase alfa for ≥9 months (switch group) (57). Treatment was administered via IV infusions every other week at doses of 5 mg/kg, 10 mg/kg, or 20 mg/kg for 24 weeks (57).

The objective of the NEO EXT study is to assess long-term safety and exploratory efficacy of avalglucosidase alfa in the patients who completed NEO1 (74, 75). Patients who were enrolled in NEO-EXT initially continued to receive the same dose of avalglucosidase alfa that they had received in NEO1; in 2016, patients in both groups receiving lower doses of avalglucosidase alfa were switched to 20 mg/kg of avalglucosidase alfa (

Figure 1) (74). Patients can continue receiving treatment in the NEO-EXT trial for up to 8 years (74). Overall, 21 patients completed NEO1 and 19 entered NEO-EXT; 8 were in the naïve group and 11 in the switch group (74). As of the most recent data cut-off (February 27, 2020; includes 6 years of treatment), 17 patients remain in NEO-EXT (7 in the naïve group, 10 in the switch group) (74).

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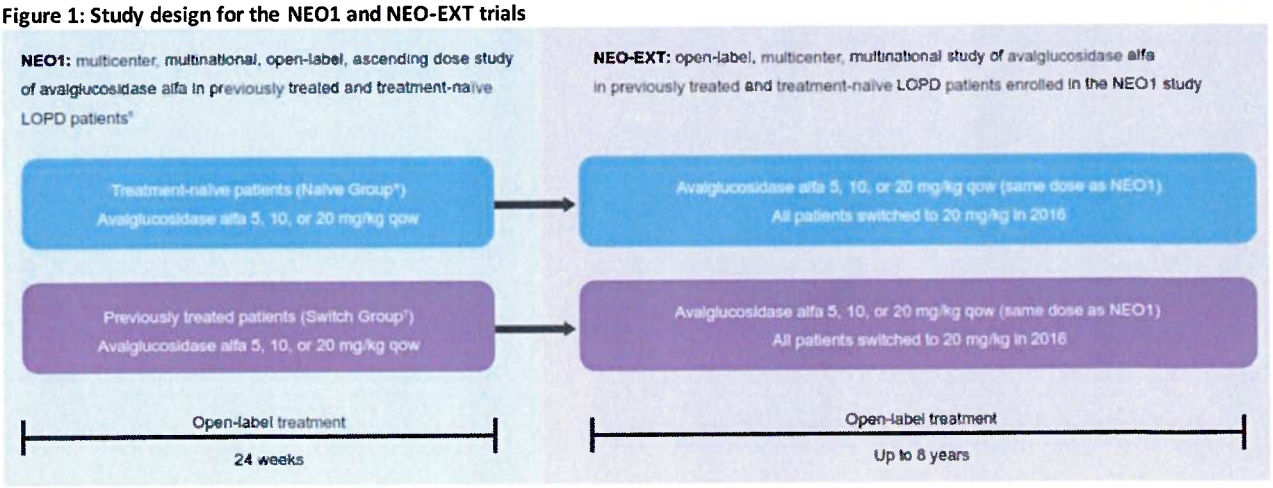
Figure 1: Study design for the NEO1 and NEO-EXT trials



Abbreviations: LOPD = late-onset Pompe disease; qow = every other week

Source: (74)

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for NEO-EXT are the same as those for NEO1. In NEO1 patients were required to have 2 confirmed pathogenic *GAA* gene variants and/or confirmed GAA enzyme deficiency (any tissue source), the ability to walk 50 meters without assistance, and an upright FVC ≥50% (57). Patients with known cardiac hypertrophy or other clinically significant disease were excluded as were patients who were confined to a wheelchair, required invasive ventilation, had magnetic resonance imaging (MRI) contraindications, or had high risk of a severe allergic reaction to avalglucosidase alfa (57). Patients who completed NEO1 were eligible to enroll in NEO-EXT (75).

Endpoints

NEO-EXT phase 2/3 long-term study assessed many of the same endpoints as NEO1; these included measures of safety and tolerability, PD, PK and exploratory efficacy endpoints including respiratory function (FVC, MIP, MEP) and the 6MWT (74). Efficacy outcomes were assessed by plotting individual trajectories for each patient and using a repeated measures mixed model to analyze the summary trend over time (74). Efficacy outcomes were analyzed for all patients who received ≥1 complete infusion of avalglucosidase alfa whereas patients who received any amount of avalglucosidase alfa were included in the safety analysis (75). Analyses are presented for the combined NEO1 and NEO-EXT study periods (75).

7.1.1.2 COMET

COMET is an ongoing, phase 3, multicenter, multinational, randomized, double-blind trial in patients with LOPD aged ≥3 years (58, 76). The objective of the trial is to assess the efficacy and safety of avalglucosidase alfa compared with alglucosidase alfa in the enrolled patients with LOPD (76, 77).

In COMET, included patients were randomized 1:1 to receive an IV infusion of 20 mg/kg avalglucosidase alfa (n=51) or alglucosidase alfa (n=49) once every other week during a 49-week blinded treatment period (PAP) (Figure 2) (58). After 49 weeks, patients continued to the extended treatment period (ETP); and received 20 mg/kg avalglucosidase alfa once every other week for up to an additional 238 weeks (58). Data collection for the PAP (Baseline to Week 49) was completed in March 2020; the ETP is ongoing with an anticipated completion date of September 2024 (78).

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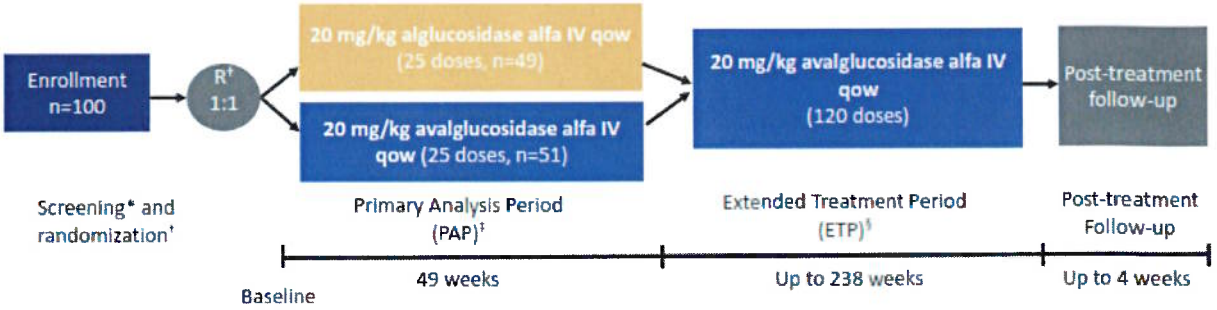
Overall, 100 patients were randomized and 95 completed the PAP (51/51 in the avalglucosidase alfa arm, 44/49 in the alglucosidase alfa arm) and entered the extended period (58). As of the data cut-off (March 19, 2020), 91 patients remained in the ongoing extended treatment phase of the trial (58).

Figure 2: Study design for the phase 3 COMET trial



* Screening phase ≤14 days (extension to ≤8 weeks permitted)

† Randomization was stratified by baseline FVC % predicted (<55% or ≥55%), sex, age (<18 years or ≥18 years), and country (Japan or ex-Japan)

‡ Patients underwent study drug infusion, safety assessments, and efficacy evaluations during the PAP

§ All patients received the same treatment during the ETP regardless of randomized group assignment

Abbreviations: ETP = extended treatment period; FVC = forced vital capacity; IV = intravenous; PAP = primary analysis period; qow = every other week

Source: (58)

7.1.1.2.1 Inclusion and Exclusion Criteria

Key inclusion and exclusion criteria for COMET are presented in Table 6.

Table 6: Inclusion and exclusion criteria for COMET trial

Key inclusion criteria	Key exclusion criteria
▪ Aged ≥3 years	▪ Cardiac hypertrophy (Pompe-specific)
▪ Diagnosis of PD, confirmed by GAA enzyme deficiency from any tissue source and/or ≥2 *GAA* gene variants	▪ Requiring invasive ventilation
▪ Naïve to treatment with alglucosidase alfa (or any other investigational agent for Pompe disease)	▪ Dependent on a wheelchair
▪ Capable of performing repeated upright FVC measurements of ≥30% and ≤85% predicted	▪ Clinically significant organic disease
▪ Capable of walking 40 meters without stopping or use of an ambulation assistance device	▪ Prior/current use of ITI therapy
	▪ Pregnant/breastfeeding
	▪ Female patients of childbearing age unable or unwilling to use highly effective contraception and/or be tested for pregnancy

Abbreviations: FVC = forced vital capacity; GAA = acid alpha-glucosidase; ITI = immune tolerance induction

Source: (58)

7.1.1.2.2 Endpoints

The primary endpoint was the change in respiratory muscle function from Baseline to Week 49, measured by upright FVC percent predicted (58, 76). Secondary endpoints included assessments of mobility, measured by the 6MWT; inspiratory and expiratory muscle strength, measured by MIP and MEP; lower extremity muscle strength, measured by HHD; motor function, measured by the QMFT (validated in PD); and HRQoL, measured by the SF-12; and safety (58, 68, 78).

Efficacy endpoints selected for trials in avalglucosidase alfa, FVC and 6MWT in particular, have been robustly studied and are the gold standard for evaluation in PD; they have been included in the majority of studies of LOPD since 2006, including the phase 3 study of alglucosidase alfa in LOPD (7, 38). FVC, in particular is widely used and one of the key means by which the American Thoracic Society defines evaluation of respiratory function (64). FVC was chosen as the primary endpoint for this trial, due to the unmet need in sustained respiratory function for patients with LOPD, given that respiratory failure is a key cause of patient death (7, 15).

Though respiratory failure is associated with mortality in patients with LOPD and a treatment with sustained, long-term efficacy in FVC is needed, improvement of motor function remains an area that must also be addressed by therapy for LOPD (15, 16). The need to evaluate both motor and respiratory outcomes is further corroborated by the positive correlation between these outcomes (79). Measuring 6MWT as a secondary endpoint allows for evaluation of motor outcomes alongside the primary respiratory endpoint, FVC.

All randomized patients who received 1 infusion (including partial infusions) were included in the modified intent-to-treat (mITT) population, which was used for all evaluations of efficacy (this also comprised the safety population during the randomized period of the trial) (76). The statistical analysis plan for the primary endpoint (FVC) was to initially test for non-inferiority (margin of −1.1) of avalglucosidase alfa compared with alglucosidase alfa; if non-inferiority was demonstrated, it was planned that the primary endpoint (FVC) would be tested for superiority of avalglucosidase alfa compared with alglucosidase alfa (58). The secondary endpoint was tested for superiority; if superiority was demonstrated for the primary endpoint, hierarchical hypothesis testing was performed for the secondary efficacy endpoints (58).

For detailed study characteristics refer to Appendix B. For baseline characteristics of patients included in each study refer to Appendix C.

7.1.2 Efficacy and safety – results per study

This section covers the efficacy and safety results from the NEO-EXT and COMET studies. The NEO-EXT is an extension study that provides up to 6 years of follow-up data, which is rather uncommon in rare diseases and the COMET study is a head-to-head study comparing the efficacy and safety of avalglucosidase alfa and its comparator, alglucosidase alfa, and thus renders section 7.1.3 irrelevant.

7.1.2.1 NEO-EXT

Safety outcomes were evaluated in patients with up to 6 years of follow-up in NEO-EXT, who had received a total of 2,685 infusions (1,043 in the naïve group, 1,642 in the switch group) at the data cut-off (February 27, 2020) (74). No patients died or experienced life-threatening SAEs during either NEO1 or NEO-EXT (57, 74). Most TEAEs were mild and the most frequently reported events, occurring in 3 patients each, included fatigue, headache, nausea, and rash (74). One patient in the naïve group discontinued during NEO1 following treatment-related SAEs (respiratory distress and chest discomfort). There were no treatment-related discontinuations during the NEO-EXT period (74). A summary of TEAEs is shown in Table 7.

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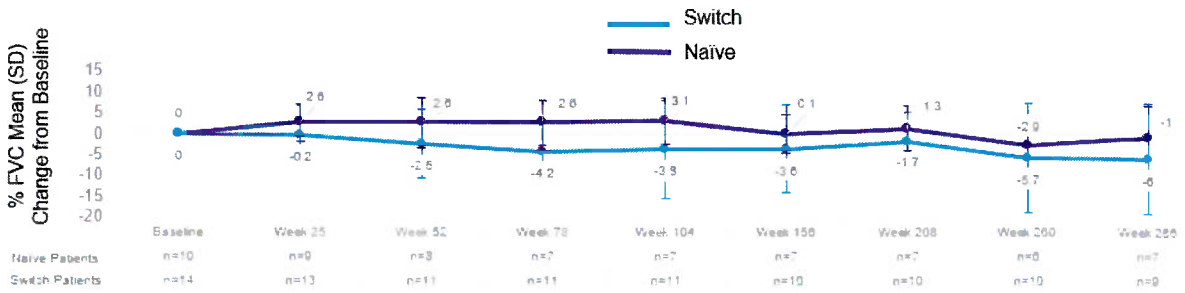
Table 7: NEO-EXT Safety outcomes

Safety outcome	Naïve group (n=10)	Switch group (n=14)
Any TEAE (%)	10 (100)	14 (100)
Treatment-related TEAE (%)	8 (80)	10 (71)
Treatment-emergent SAE (%)	5 (50)	4 (29)
Severe TEAE (%)	2 (20)	0
Any IAR (%)	3 (30)	3 (21)
TEAE leading to permanent discontinuation (%)	1 (10)	0

FVC % predicted

Over the follow-up period of up to 6 years (data cutoff February 27, 2020) upright FVC percent predicted remained stable for most patients, regardless of whether they were in the naïve or switch groups (74). This is also illustrated in Figure 3. Stability in the respiratory function, consequently means avoiding deterioration, which is a problem within PD (7), even patients treated with alglucosidase alfa who initially benefitted from ERT, started to show a decline again after 3-5 years (8).

Figure 3: Respiratory function outcomes over 6 years in the NEO-EXT study



Mean baseline upright FVC, % predicted of Naive group: 69.2 ± 19.27% and Switched group: 77.3 ± 16.45%

6MWT

Most patients in NEO-EXT reported stable percent predicted 6MWT distances over the follow-up period of up to 6 years, with the most notable improvements in distance walked observed in patients aged ≤50 years at the NEO1 study start (Figure 4) (74). The same argument for stability, as presented for FVC% predicted, applies here.

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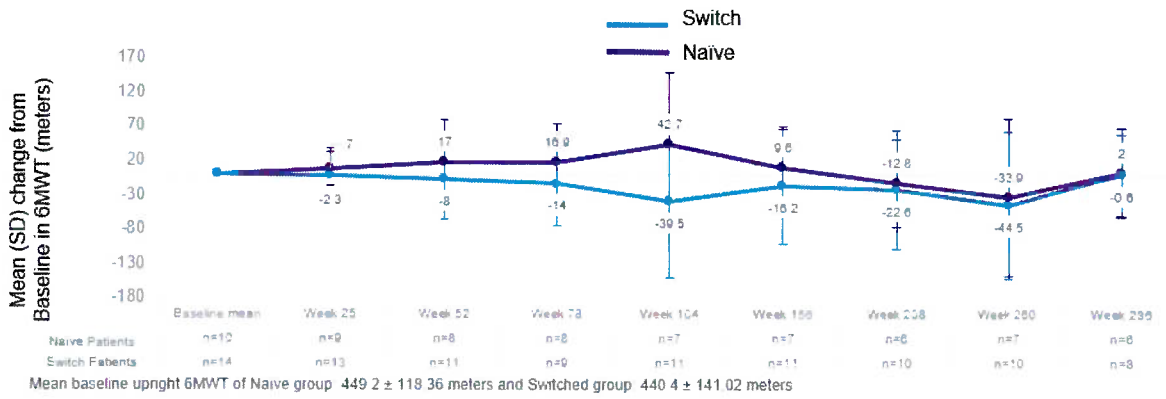
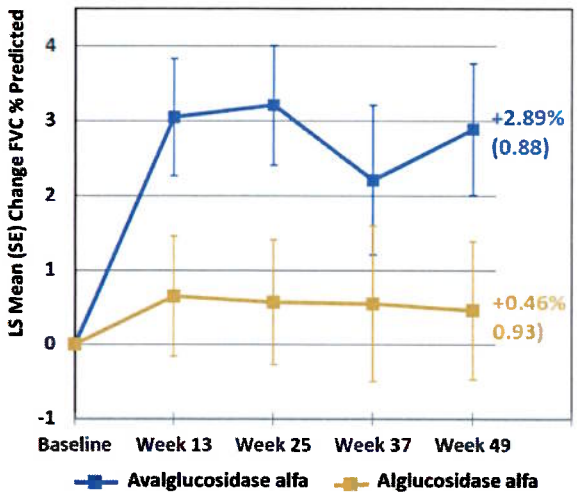
Figure 4: 6MWT over 6 years in the NEO-EXT study



7.1.2.2 COMET

Analysis of the primary endpoint of this study demonstrated a rapid and sustained improvement in respiratory function starting from treatment initiation with avalglucosidase alfa compared with alglucosidase alfa (58). Patients treated with avalglucosidase alfa experienced clinically meaningful improvements in the primary endpoint of Week 49 change from Baseline in upright FVC percent predicted compared with patients who received alglucosidase alfa (LS mean±SE: 2.89±0.88%; 95% CI: 1.13, 4.65 vs. 0.46±0.93%; 95% CI: −1.39, 2.31; Figure 5) (58). This equated to a between-group difference of 2.43% (95% CI: −0.13, 4.99; p=0.0626), which fell within the minimal clinically important difference (MCID) range of 2% to 6%, previously established for idiopathic pulmonary fibrosis, and within the minimal patient relevant change (range 1.7 to 4.1) established in LOPD patients(58, 80) (81). Analysis for non-inferiority was statistically significant (p=0.0074), achieving the study's primary objective (58). The subsequent analysis for superiority, showed a borderline significant (p=0.0626) difference for avalglucosidase alfa compared with alglucosidase alfa (58). Notably, patients treated with avalglucosidase alfa demonstrated greater improvements in FVC compared to alglucosidase alfa as early as Week 13 and these improvements were sustained through Week 49 (Figure 5) (58).

Figure 5 Change in FVC % predicted over time in phase 3 COMET trial



Abbreviations: FVC = forced vital capacity; LS = least squares; SE = standard error

Source: (58)

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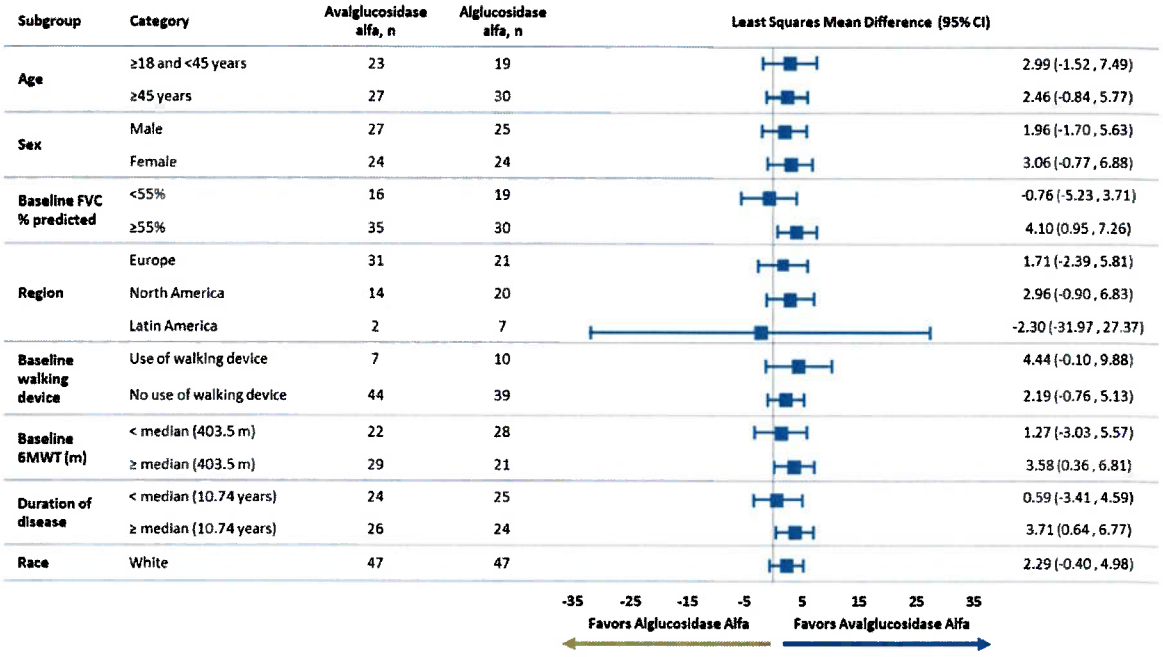
Differences in improvements in upright FVC percent predicted were also reported with avalglucosidase alfa compared with alglucosidase alfa for several subgroups as demonstrated by confidence intervals (CIs) presented in Figure 6 (76). The following subgroup analyses demonstrated greater improvements for avalglucosidase alfa that were statistically significant:

- Patients with a baseline FVC percent predicted ≥55%
- Patients with a baseline 6MWT ≥403.5 meters
- Patients with a duration of disease ≥10.74 years

Figure 6: Subgroup Analyses for change in FVC % predicted over time in phase 3 COMET trial



CIs >0 represent subgroups in which avalglucosidase alfa was favored over alglucosidase alfa

Subgroup analysis for the Asia-Pacific is not included here (4 avalglucosidase alfa patients and 1 alglucosidase alfa)
Subgroup analysis for the Asian/Black or African American is not included here (4 avalglucosidase alfa patients and 2 alglucosidase alfa)
Subgroup analysis for Age, excluded one patient under the age of 18

Abbreviations: 6MWT = 6-minute walk test; ALGLU = alglucosidase alfa; AVAL = avalglucosidase alfa; CI = confidence interval; FVC = forced vital capacity; LS = least squares
Source: (76)

In a pre-specified responder analysis of relative increase from Baseline in FVC percent predicted, at Week 49, more than twice the patients treated with avalglucosidase alfa (19.6%) reported increases from Baseline greater than or equal to the 15% threshold of response compared with patients treated with alglucosidase [redacted]. This is generally accepted as clinically meaningful for patients as these thresholds are above the MCID for IPF as natural progressive decline is generally observed with age and disease progression (82).
A cumulative probability function was plotted, a posteriori, to summarize the distribution of within-patient change in FVC (between baseline and week 49) by treatment group observed in COMET patients (Figure 7) (83). The cumulative probability function displays a continuous plot for avalglucosidase alfa and alglucosidase alfa of the FVC change from baseline on the horizontal axis, and the cumulative proportion of patients experiencing changes from baseline up to that level, on the vertical axis. These curves demonstrate a clear and consistent separation between avalglucosidase alfa and alglucosidase alfa over the full range of possible FVC responder thresholds. The proportion of FVC responders in avalglucosidase alfa compared to alglucosidase alfa, is consistently higher whatever the FVC responder threshold is.

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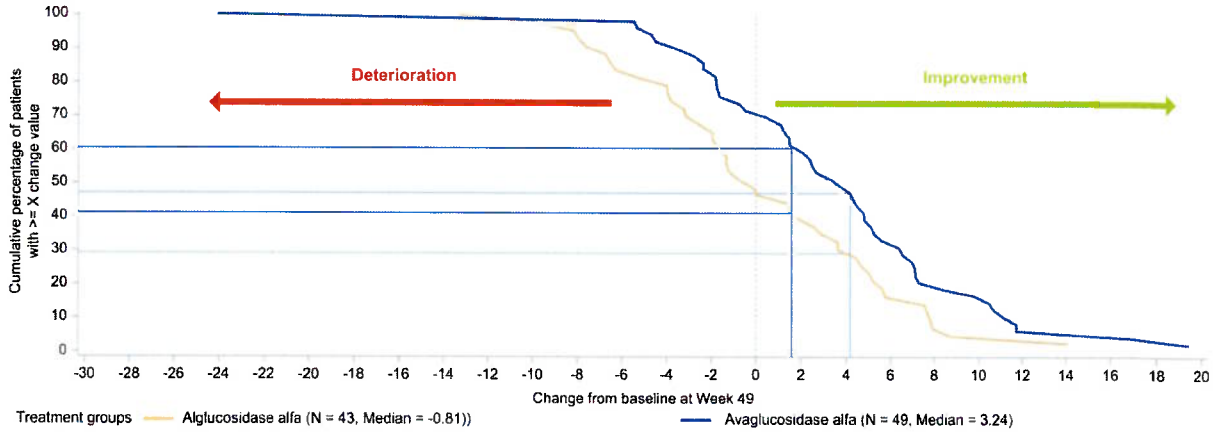
From this figure we can observe that approximately 70% of patients on avalglucosidase alfa improved their FVC over 49 weeks with a positive absolute FVC change from baseline. Since the natural progression of the disease shows gradual decline, any improvement of pulmonary function can be considered a positive response to the therapy (10). In contrast, in the alglucosidase alfa group more than half of the patients had a deterioration of FVC, meaning that they had a negative absolute change from baseline (83).

Figure 7: eCDF of FVC percent predicted change over time in phase 3 COMET trial

Empirical cumulative distribution function of FVC % predicted change scores by treatment groups



The horizontal lines represent the cumulative percentage of patients with an increase in FVC ≥1.7% predicted (dark blue) and FVC ≥ 4.1% predicted (light blue)

Abbreviations: eCDF = empirical cumulative distribution function; FVC = forced vital capacity; neoGAA = avalglucosidase alfa; WK = week. **Source**: (81)

Secondary Efficacy Endpoint Results

6MWT

Avalglucosidase alfa resulted in improvements from Baseline in motor function (as measured by 6MWT) that were both continuous and sustained, beginning in Week 13 and observed through Week 49 (58). Patients treated with avalglucosidase alfa demonstrated a clinically meaningful benefit in mobility as demonstrated by the change from Baseline in 6MWT distance at Week 49 compared with patients treated with alglucosidase alfa (LS mean±SE: 32.21±9.93 meters; 95% CI: 12.47, 51.94 vs. 2.19±10.40 meters; 95% CI: −18.48, 22.86; Figure 8) (58). This equated to a between-group difference of 30.01 meters (95% CI: 1.33, 58.69; nominal p=0.0405), which fell within the MCID range of 24 to 54 meters previously established in several diseases (MCID is not established for PD) (58, 80). It should be noted, however, that analyses of secondary endpoints were not adjusted for multiplicity because superiority was not demonstrated for the primary endpoint, thus statistical significance is assessed at the nominal level (58).

Figure 8: Change in 6MWT over time in phase 3 COMET trial

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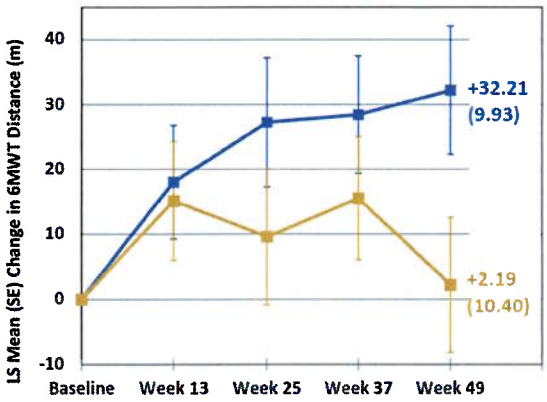


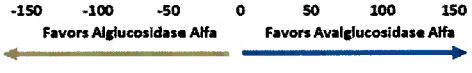
Abbreviations: 6MWT = 6-minute walk test; LS = least squares; SE = standard error. **Source**: (58)

Differences in improvements in 6MWT were also reported with avalglucosidase alfa compared with alglucosidase alfa for several subgroups as demonstrated by CIs presented in Figure 9 (76). The following subgroup analyses demonstrated greater improvements for avalglucosidase alfa: (76)

- Patients aged 18 to <45 years
- Female patients
- Patients with a baseline 6MWT <403.5 meters
- Patients with a duration of disease ≥10.74 years

Figure 9: Forest Plot of 6MWT (distance walked, in meter) - change from baseline at Week 49 for subgroup analyses - mITT population

Subgroup	Category	Avalglucosidase alfa, n	Alglucosidase alfa, n	Least Squares Mean Difference (95% CI)
Age	≥18 and <45 years	23	19	40.95 (7.06, 74.83)
	≥45 years	27	30	27.13 (-20.48, 74.73)
Sex	Male	27	25	7.07 (-25.68, 39.81)
	Female	24	24	50.22 (2.89, 97.54)
Baseline FVC % predicted	<55%	16	19	17.32 (-38.14, 72.78)
	≥55%	35	30	34.40 (-0.88, 69.67)
Region	Europe	31	21	16.84 (-15.65, 49.32)
	North America	14	20	26.153 (-39.282, 91.59)
	Latin America	2	7	-18.90 (-135.01, 97.22)
Baseline walking device	Use of walking device	7	10	39.81 (-65.65, 145.28)
	No use of walking device	44	39	25.88 (-3.02, 54.78)
Baseline 6MWT (m)	< median (403.5 m)	22	28	46.47 (7.16, 85.79)
	≥ median (403.5 m)	29	21	14.26 (-30.26, 58.78)
Duration of disease	< median (10.74 years)	24	25	9.40 (-32.04, 50.84)
	≥ median (10.74 years)	26	24	44.56 (5.80, 83.31)
Race	White	47	47	29.39 (-0.80, 59.58)



CIs >0 represent subgroups in which avalglucosidase alfa was favored over alglucosidase alfa

Abbreviations: 6MWT = 6-minute walk test; ALGLU = alglucosidase alfa; AVAL = avalglucosidase alfa; CI = confidence interval; FVC = forced vital capacity; LS = least squares

Source: (76)

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In a pre-specified responder analysis of relative increase from Baseline in 6MWT, at Week 49, almost twice the percentage of patients treated with avalglucosidase alfa (23.5%) reported increases from Baseline greater than or equal to the responder threshold (54 meters) compared with patients treated with alglucosidase alfa (12.2%; OR: 2.09; 95% CI: 0.70, 6.25) (76).

When the observed changes from baseline to Week 49 in 6MWT are represented as a cumulative probability function, a right shift of the avalglucosidase alfa curve compared to the alglucosidase alfa curve is observed (Figure 10). The figure clearly shows the greater benefit of avalglucosidase alfa whatever the level of change from baseline. More than 80% of patients improved their 6MWT (i.e., had a positive absolute change from baseline) with avalglucosidase alfa, which is clinically meaningful since any improvement in mobility can be considered as positive response to the therapy taking into account the natural progression of the disease with gradual decline (84). In the alglucosidase alfa group more than 40% of the patients had a deterioration of 6MWT (i.e., had a negative absolute change from baseline). These increases exceed the pre-defined clinically meaningful thresholds of 27.5; 30, 37 and 54 meters based on what is perceived as a MCID by patients with LOPD or other chronic diseases affecting ambulation (and not only 54m threshold)(80).

Figure 10 Plot of the cumulative probability function of change from baseline to week 49 in 6MWT total distance walked (meters) - in PAP - mITT population

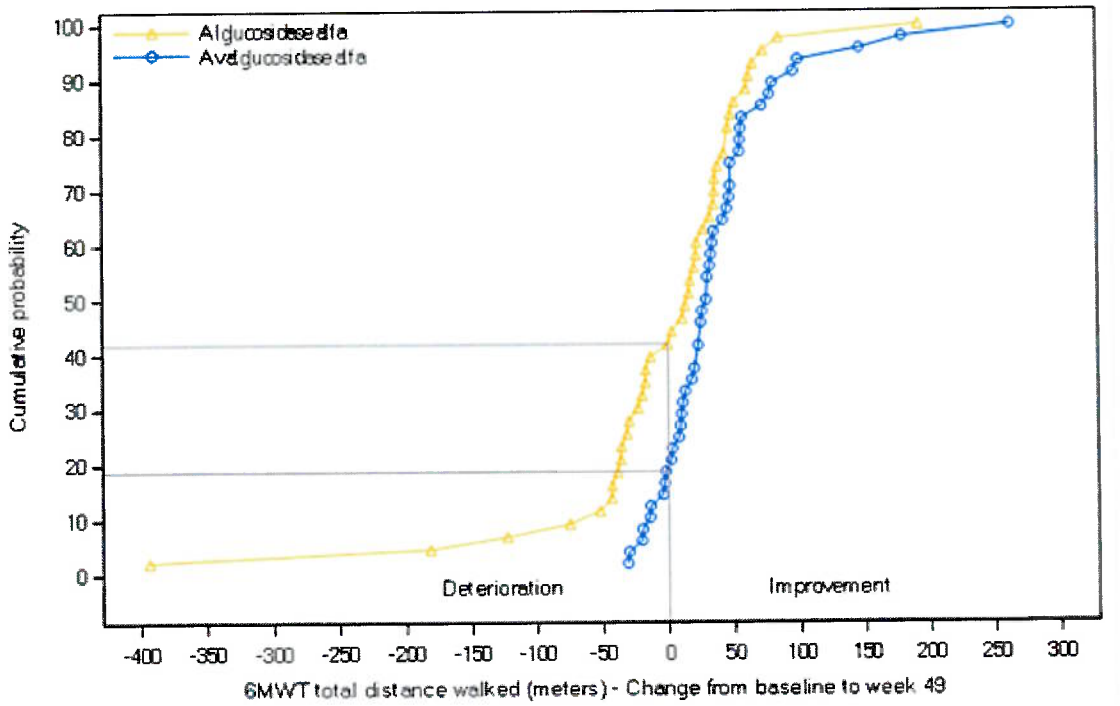

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Figure 11 Responder analysis of 6MWT change from baseline

Parameter	Statistics	Avalglucosidase alfa (N=51)	Alglucosidase Alfa (N=49)
Responder defined as having a change from baseline at week 49 in 6MWT distance of >=27.5 meters			
Yes	n (%)	25 (49.0)	16 (32.7)
Odds ratio from logistic regression	Estimate	1.90	
	95% CI	0.81, 4.45	
	P value	0.141	
Responder defined as having a change from baseline at week 49 in 6MWT distance of >=30 meters			
Yes	n (%)	24 (47.1)	16 (32.7)
Odds ratio from logistic regression	Estimate	1.76	
	95% CI	0.75, 4.15	
	P value	0.195	
Responder defined as having a change from baseline at week 49 in 6MWT distance of >=37 meters			
Yes	n (%)	18 (35.3)	12 (24.5)
Odds ratio from logistic regression	Estimate	1.53	
	95% CI	0.63, 3.74	
	P value	0.352	
Responder defined as having a change from baseline at week 49 in 6MWT distance of >=54 meters			
Yes	n (%)	12 (23.5)	6 (12.2)
Odds ratio from logistic regression	Estimate	2.09	
	95% CI	0.70, 6.25	
	P value	0.188	

Note: Patients without week 49 value will be considered as non-responders;

If a subject had a change from baseline at week 49 in 6MWT distance >=54 meters, s/he will be included in responders of >=27.5, >=30, >=37 and >=54 meter; if a subject has a change >=37 meters, s/he will be included in responders of >=30 and >=37 meters.

Logistic regression models adjust for baseline 6MWT distance, age (in years, at baseline), and gender.

Functional endurance outcomes

Similar to the results seen from the 6MWT, the supportive outcomes evaluating functional endurance, showed improvements from baseline to week 49 in the intervention arm. Avalglucosidase alfa resulted in clinical meaningful improvements for MIP, MEP, HHD and QMFT, with the latter being statistically significant at the 5% significance level, when assessed at the nominal level. These results are presented in further detail in appendix D.

Health related quality of life

SF-12

HRQoL was measured through the use of SF-12, which yields both a physical component summary (PCS) and mental component summary (MCS). Here the results indicated an increase of 0.77 for PCS and 2.12 for MCS from baseline in QoL, although none being statistically significant. The results are presented in Avalglucosidase alfa has demonstrated better improvements compared with alglucosidase alfa in several generic and disease-related measures of HRQoL, including in novel measures of the severity and impact of Pompe disease on the patient experience ([redacted])

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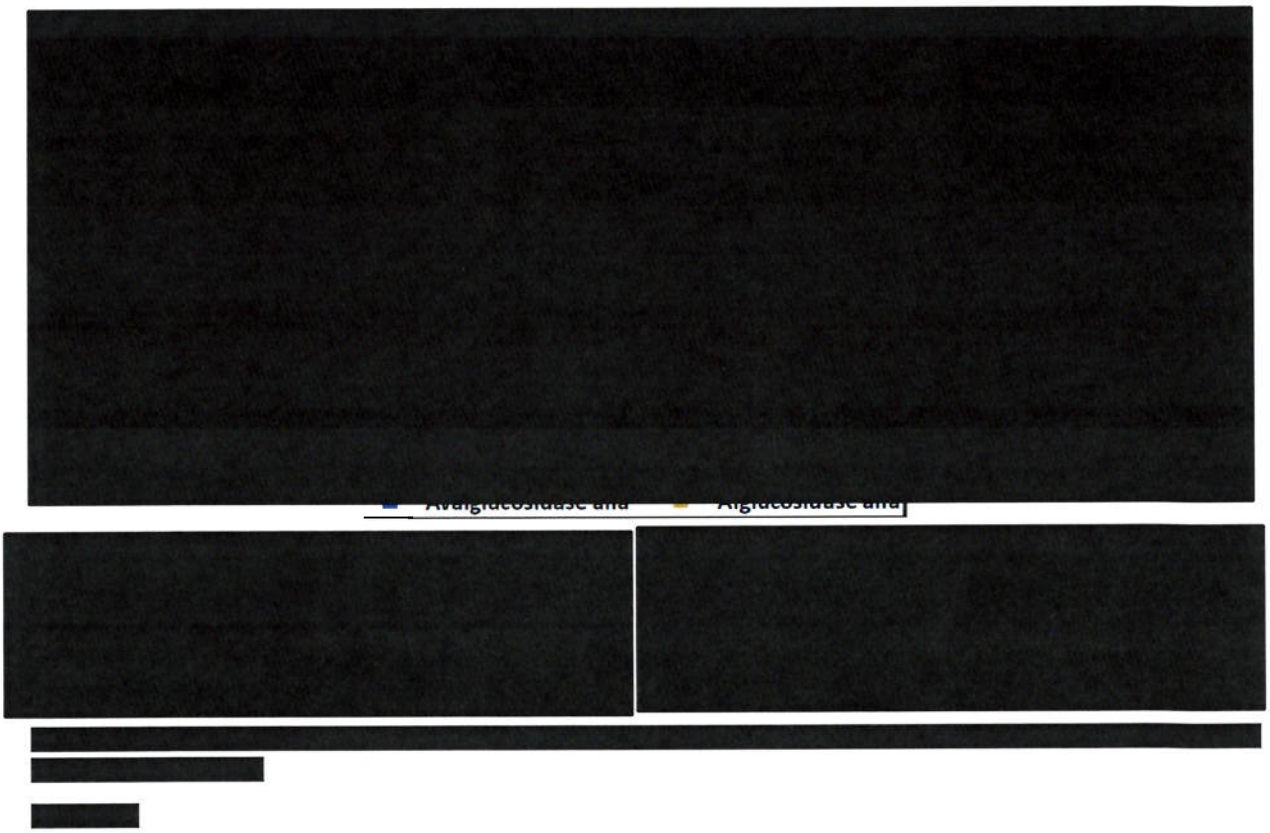

EQ-5D-5L

HRQoL was also measured with EQ-5D-5L, which consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). For the domains of mobility and usual activities in the EQ-5D 5L, as well as for the EQ-5D VAS, patients treated with avalglucosidase alfa experienced greater changes from baseline to week 49 compared with those in the alglucosidase alfa group (Table 8); for all other domains, both groups were similar, demonstrating little change from Baseline to Week 49 (Figure 13) (76). The proportion of patients who had improvements in each EQ-5D-5L domain at week 49 are presented in Figure 14. The odds ratios were >1 in all domains except pain/ discomfort, showing a numerically greater effect with avalglucosidase alfa compared with alglucosidase alfa, this difference was significant (nominal p-value <0.05) in the usual activities domain.

Change from baseline to week 49 was significantly greater (p<0.01) with avalglucosidase alfa for the EQ VAS compared with alglucosidase alfa at nominal level with a mean (SD) increase of 8.80 (15.01) versus a mean (SD) decrease of 0.33 (16.13), respectively (86).

Table 8 Mean changes from Baseline in select EQ-5D 5L domains during the randomized period of phase 3 COMET trial

	Avalglucosidase alfa (n=50*)	Alglucosidase alfa (n=49)
Mobility, mean ±SD	−0.50±0.89	−0.14±0.68
Usual activities, mean±SD	−0.34±0.89	0.00±0.73
VAS, mean±SD	8.80±15.01	−0.33±16.13

Data for self-care, pain/discomfort, and anxiety/depression scores not reported; EQ-5D 5L = 5 Level EuroQoL-5 Dimension Scale; SD = standard deviation.

*1 patient in AVA group was under 18 and therefore was not supposed to complete the PRO questionnaire as per protocol

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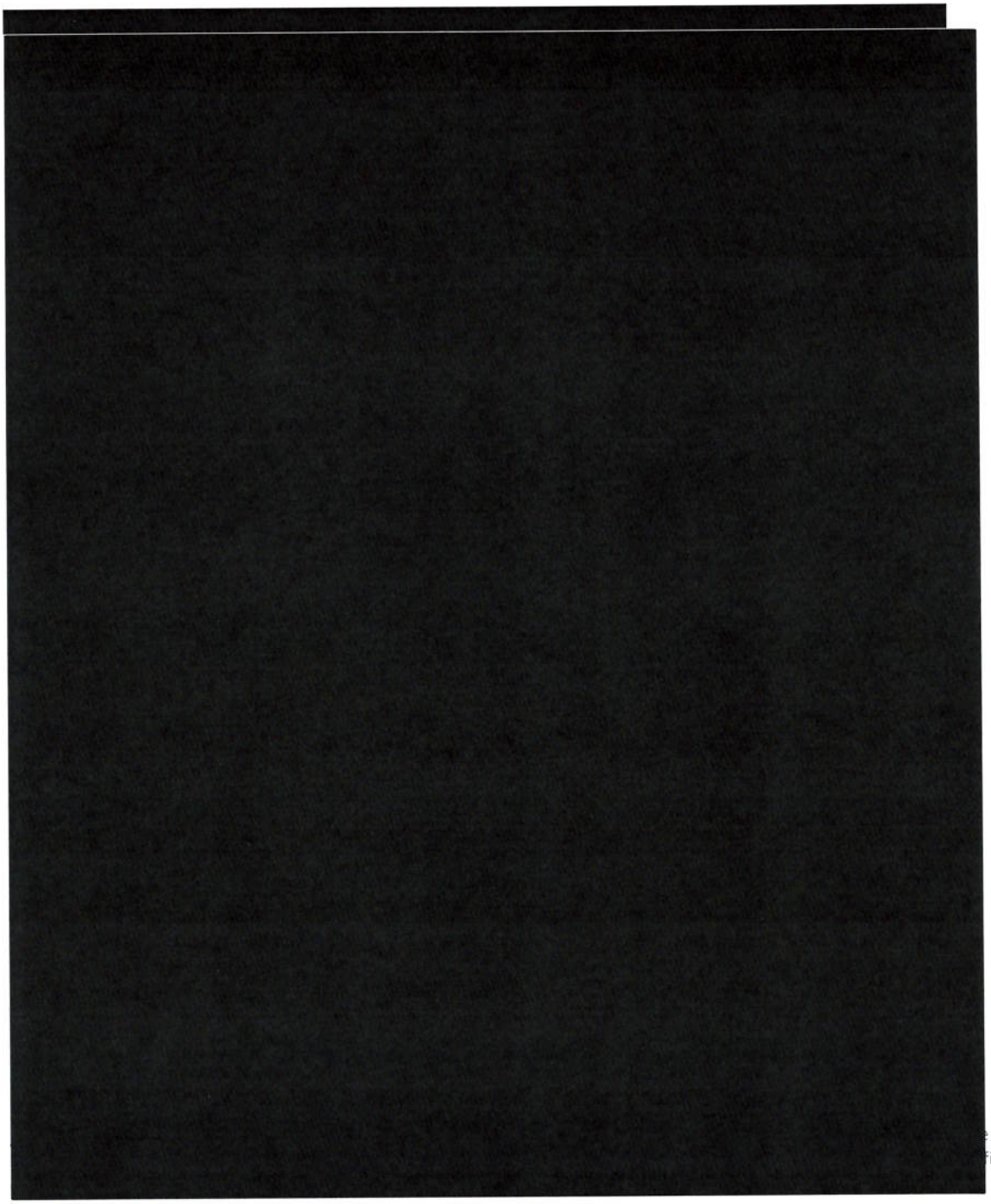
Avalglucosidase alfa has demonstrated better improvements compared with alglucosidase alfa in several generic and disease-related measures of HRQoL, including in novel measures of the severity and impact of Pompe disease on the patient experience (Figure 17).



Disease
fic

Source: (76)

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Safety results

Overall, avalglucosidase alfa demonstrated a more favorable safety profile than alglucosidase alfa as seen in Table 9, and avalglucosidase alfa safety results were comparable to those observed in the NEO-EXT study (58). Among patients treated with avalglucosidase alfa, there were no deaths or TEAEs leading to discontinuation during the randomized PAP; by contrast, four patients treated with alglucosidase alfa withdrew because of TEAEs (including two patients with IARs) and one patient died due to an acute myocardial infarction, unrelated to treatment (58). The most frequently reported TEAEs for the avalglucosidase alfa-treated group were nasopharyngitis (23.5%), back pain (23.5%), and headache (21.6%); only one patient in this group (2.0%) reported a SAE related to study drug (dyspnea) (58). Among patients treated with alglucosidase alfa, the most common TEAEs were headache (32.7%), nasopharyngitis (24.5%), and fall (20.4%) (58). By contrast to avalglucosidase alfa, an approximately three-fold higher occurrence of SAEs related to the study drug (six SAEs in three patients; 6.1%) was observed in patients treated with alglucosidase alfa; these included dizziness, visual impairment, hypotension, dyspnea, cold sweat, and chills (58).

Table 9 Safety data from COMET

	Avalglucosidase alfa (n=51)	Alglucosidase alfa (n=49)
Any TEAE (%)	44 (86.3)	45 (91.8)
Treatment-related TEAE (%)	23 (45.1)	24 (49.0)
Treatment-emergent SAE (%)	8 (15.7)	12 (24.5)
Severe TEAE (%)	6 (11.8)	7 (14.3)
Any IAR[a] (%)	13 (25.5)	16 (32.7)
TEAE leading to permanent discontinuation (%)	0	4 (8.2)
TEAE leading to death (%)	0	1 (2.0)

Data are reported as n (%)

[a] An AE during either the infusion or observation period following the infusion that was related or possibly related to the treatment

Abbreviations: AE = adverse event; IAR = infusion-associated reaction; SAE = serious adverse event; TEAE = treatment-emergent adverse event

7.1.3 Comparative analyses of efficacy and safety

A comparative analysis of efficacy and safety is not relevant as per arguments presented in section 7.1.2.

8. Health economic analysis

Based on the assessment of the clinical data, avalglucosidase alfa proved non-inferiority when compared to alglucosidase alfa. Further, Danish clinicians estimated that the resource use of the two treatments are nearly

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identical, based on the resemblance of the intervention and the comparator. The only perceived difference is the larger vial size of avalglucosidase alfa compared to alglucosidase alfa, which is thought to reduce HCP time spent on reconstitution by 50%. Therefore, in accordance with the DMC guidelines, a cost-minimization (CM) analysis was conducted.

8.1 Model

The CM analysis was conducted as a conservative analysis comparing avalglucosidase alfa to alglucosidase alfa. As no statistically significant differences between the interventions were demonstrated, the model only considered costs associated with drug acquisition and administration, i.e., drug costs, costs of adverse events, and patient administration time and transportation, i.e., patient costs. With the objective of model parsimony, the model is kept as simple as possible to reflect the similarity of the two treatments. This process and the underlying assumptions have been validated by consulting a Danish KOL. Consequently, monitoring costs were not included in the model, as no differences between the interventions are expected in line with the SmPCs and KOL testimony.
The model was developed in Microsoft Excel 365 as a simple cohort model. In order to allow the model to align with the treatment regimens, weekly model cycles have been applied in the model. The model reflects the treatment course based on the posology of each intervention included as per the SmPC for alglucosidase alfa (35) and the expected SmPC for avalglucosidase alfa (1). The model reflects the treatment course of the interventions and estimates the costs associated with each intervention and the associated incremental costs. As there are no significant differences in efficacy between the interventions, no outcomes are modelled, and the patients will remain on treatment throughout the selected time horizon.

8.1.1 Perspective, time horizon and discounting

The model applies a Danish restricted societal perspective, in line with the guidelines presented by the DMC (50).

A 10-year time horizon was applied in the base-case, as this is believed to sufficiently reflect all differences in cost, between the two pharmaceuticals, given that the economic model is a cost-minimization model. The impact on the results of varying the time horizons to 1, 5 and 20 years, respectively, was explored in scenario analyses.
A discount rate of 3,5% was applied to the costs, as defined by the Danish Ministry of Finance and in the DMC guidelines (50, 89).

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

As avalglucosidase alfa demonstrated statistically significant non-inferiority when compared to alglucosidase, a cost-minimization analysis has been conducted and therefore no relative efficacy parameters have been included in the health economic model. Further, based on Danish KOL testimony, the treatment course in Danish clinical practice will be identical for the two interventions. Consequently, many of the following paragraphs in section 8.2 are considered irrelevant for the decision problem.

8.2.1 Presentation of input data used in the model and how they were obtained

Not applicable as no input data regarding clinical efficacy have been included in the model.

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

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All patients with LOPD are considered relevant candidates for avalglucosidase alfa. This includes treatment naïve and patients currently/previously treated with alglucosidase alfa. Currently, there are 17 patients diagnosed with LOPD in Denmark eligible for treatment with avalglucosidase alfa, of which the majority are treated with the comparator and two are already receiving avalglucosidase alfa. The patient characteristics derived from the COMET study have been verified by a Danish KOL in relation to external validity for Danish patients. These were consequently applied in the model, as presented in Table 10. The KOL confirmed that the patients are primarily adults, with no apparent skewness towards one sex.

Table 10: Patient population

Patient population Important baseline characteristics	COMET study	Used in the model (number/value including source)
Age	48.1	48.1
Female (%)	48	48
Weight (kg)	75.5	75.5

8.2.2.2 Intervention

Avalglucosidase alfa is expected to be offered, similarly to alglucosidase alfa, to patients diagnosed with PD. The treatment is administered through IV infusion every other week with a dosing of 20 mg/kg.
The intervention is modelled similar to this description, meaning that patients are set to receive the treatment every other week at a dosage of 20 mg/kg. This is also described in Table 11.

Table 11: Intervention

Intervention – avalglucosidase alfa	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	The recommended dose of avalglucosidase alfa for patients with LOPD is 20 mg/kg administered every other week	Same as clinical documentation	Same as clinical documentation
Method of administration	Intravenous infusion	Intravenous infusion	Intravenous infusion
The pharmaceutical's position in Danish clinical practice	N/A	In line with alglucosidase	In line with alglucosidase

8.2.2.3 Comparators

The selected comparator is alglucosidase alfa as this is the only therapy currently indicated for PD. It is administered through IV infusion every other week at a dosage of 20 mg/kg. The infusions should be administered incrementally such that an initial rate of 1 mg/kg/h is given and hereafter gradually increase by 2 mg/kg/h every 30 minutes until a

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maximum rate of 7 mg/kg/h is reached. Alglucosidase alfa is modelled to represent this method of administration in the cost-minimization analysis. This is also described in Table 12.

Table 12: Comparator

Comparator - alglucosidase alfa	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	The recommended dose of alglucosidase alfa for patients with LOPD is 20 mg/kg administered every other week	Same as clinical documentation	Same as clinical documentation
Method of administration	Intravenous infusion	Intravenous infusion	Intravenous infusion

8.2.2.4 Relative efficacy outcomes

Not applicable as there is no efficacy included in the model.

8.2.2.5 Adverse reaction outcomes

In the model treatment-emergent serious adverse events related to the investigational medicinal product have been added to the first cycle. This is a conservative approach due to the uncertainty about the frequency over time.

8.3 Extrapolation of relative efficacy

Not applicable as there are no efficacy extrapolations made in the model.

8.3.1 Time to event data – summarized:

Not applicable as there are no progression nor events included in the model.

8.4 Documentation of health-related quality of life (HRQoL)

Not applicable as HRQoL has not been included.

8.4.1 Overview of health state utility values (HSUV)

Not applicable as no health states have been included.

8.4.2 Health state utility values used in the health economic model

Not applicable as utilities have not been included.

8.5 Resource use and costs

8.5.1 Pharmaceutical costs

Drug costs have been estimated using AIP. The AIP for alglucosidase alfa has been sourced from Medicinpriser.dk (90) and is listed in Table 13 together with the expected list price of avalglucosidase alfa. In the model, drug costs are applied at every cycle, where an administration occurs based on the posology presented in Table 11 and Table 12.

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Table 13: Pharmaceutical costs used in the model

Drug	Dose (mg)	Cost per pack	Cost per dose	Source
Avalglucosidase alfa	100	DKK 8,909	DKK 134,522	Sanofi
Alglucosidase alfa	50	DKK 3,350	DKK 101,174	Medicinpriser.dk (retrieved 20 Sep 2021)

8.5.2 Cost of adverse events

Since no overall differences in adverse events have been observed between avalglucosidase alfa and alglucosidase alfa, adverse events have only been included in a scenario analyses. The costs and frequencies used for AEs in the scenario analyses are presented below in Table 14 .

Table 14 Treatment-emergent serious adverse events

	Avalglucosidase alfa (n=51)	Alglucosidase alfa (n=49)	Unit costs	Source
Serious TEAEs	**Frequency**	**Frequency**		**Interim clinical study report - Table 27 - Treatment-emergent serious adverse events related to investigational medicinal product (PAP)**
Dizziness	0.00%	2.04%	5,211.00 kr.	DRG 2021, 03MA02: Svimmelhed, Diagnosis: DR429: Vertigo UNS
Visual impairment	0.00%	2.04%	1,013.00 kr.	DRG 2021, 02MA01: Øvrige indlæggelser eller besøg ved øjensygdomme, Diagnosis: DH545: Svær synsnedsættelse på et øje
Hypotension	0.00%	2.04%	1,847.00 kr.	DRG 2021, 05MA08: Andre hjertesygdomme, Diagnosis: DI959: Hypotension UNS
Dyspnoea	1.96%	4.08%	1,799.00 kr.	DRG 2021, 04MA98: MDC04 1 dagsgruppe, pat. Mindst 7 år, Diagnosis: DR060: Dyspnø
Cold sweat	0.00%	2.04%	1,800.00 kr.	DRG 2021, 09MA98: MDC09 1 dagsgruppe, pat. Mindst 7 år, Diagnosis: DR610: Lokaliseret hyperhidrose
Chills	0.00%	2.04%	4,082.00 kr.	DRG 2021, 023MA03: Symptomer og fund, u. kompl. Bidiag., Diagnosis: DR680: Hypotermi, som ikke skyldes kolde omgivelser

8.5.3 Administration cost and resource use in relation to monitoring (Hospital cost)

Avalglucosidase alfa and alglucosidase alfa are both intended for administration by healthcare professionals, and to reflect this in the model a cost has been applied at each administration in the model (see Table 15).

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To avoid unnecessary complexity, no monitoring cost have been included for avalglucosidase alfa, as there are no differences in monitoring between the two treatments. This assumption has been validated with a Danish KOL.

However, it is relevant to acknowledge that the DRG-tariff used for intravenous infusions at the hospital, fails to reflect the reduced reconstitution time of avalglucosidase alfa compared to alglucosidase alfa. Danish KOLs have estimated that given the larger vial size of avalglucosidase alfa, HCP would use 50% less time preparing the ERT. The HCP would on average spent approximately 54 minutes less preparing the ERT, equivalent to DKK 499 per administration. This would accumulate to almost DKK 13.000 per patient per year.

Table 15: Hospital costs used in the model

Type of costs	Unit cost	Cycle frequency	Source
Intravenous infusion at the hospital	DKK 1,518	0.5	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE740H: Glykogenose type II procedure: BWAA62: Medicingivning ved intravenøs infusion

8.5.4 Patient cost and transportation cost

Patient costs (defined as patient costs in DMC guidelines (91))are included in the model in line with the DMC method guidelines. The unit cost per hour is assumed to be DKK 179 in line with the DMC guidelines (91). The time usage for the administration of ERT was assumed to be 3.7 hours per administration, based on the incremental increase in rate of administration, starting with 1 mg/kg/h and increasing with 2 mg/kg/h every 30 minutes until reaching 7 mg/kg/h. Patient costs are reported in Table 16.

Transportation costs are included in the model in line with DMC guidelines. Here an average rate of DKK 3.52 per km is assumed with an average distance of 28 km per hospital visit, in line with DMC's methods guidelines (91). In the model, transportation cost is applied at the occurrence of hospital visits, e.g. administration of ERT. The transportation costs are reported in Table 16.

Table 16: Patient costs associated with administration used in the model

Type of costs	Unit cost	Units per administration	Total cost per administration	Source
Average hourly wage	DKK 179	3.7 hours	DKK 665	Medicinrådet - "Værdisætning af enhedsomkostninger"
Patient transport cost	DKK 99	1	DKK 99	Medicinrådet - "Værdisætning af enhedsomkostninger"

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8.6 Results

8.6.1 Base case overview

Table 17: Base case overview

Comparator	Alglucosidase
Type of model	Cost-minimization model
Time horizon	10 years (120 months)
Treatment line	1st line. Subsequent treatment lines not included.
Included costs	Pharmaceutical costs Hospital costs Patient costs
Dosage of pharmaceutical	20 mg/kg of body weight administered once every 2 weeks
Other important assumptions	Since no difference in efficacy was demonstrated, costs related to disease specific outcomes and resource use have not been included

8.6.2 Base case results

Table 17 presents the total cost for the avalglucosidase alfa and alglucosidase alfa arm, respectively, and the incremental cost of avalglucosidase alfa compared to the alglucosidase alfa. At AIP prices, the total cost is estimated to be DKK 30,616,545 for avalglucosidase alfa and DKK 23,153,358 for alglucosidase alfa. This results in an estimated increase in costs, calculated at AIP, associated with avalglucosidase alfa of DKK 7,463,187. The increase in costs associated with avalglucosidase alfa compared to alglucosidase alfa is solely driven by the higher drug-acquisition costs of avalglucosidase alfa at AIP.

Table 18: Base case results

Per patient	Avalglucosidase alfa	Alglucosidase alfa	Difference
Costs			
Total costs	**DKK 30,616,545**	**DKK 23,153,358**	**DKK 7,463,187**
Drug costs	DKK 30,105,964	DKK 22,642,777	DKK 7,463,187
Administration and monitoring costs	DKK 339,728	DKK 339,728	DKK 0
Patient time and transport costs	DKK 148,795	DKK 148,795	DKK 0

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8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

Scenario analyses were undertaken to assess the impact of varying parametric and methodological assumptions implemented in the model. The rationale and results of the scenario analyses are reported in Table 18.

The scenario analyses indicated that a shorter time horizon would reduce the incremental costs of avalglucosidase alfa; with a time-horizon of 1 year resulting in an incremental cost of DKK 867,037, while a 20-year time horizon resulted in an incremental cost of DKK 12,753,980. These changes in time-horizon illustrates that the incremental costs per year are only affected by the discounting rate, otherwise they remain stable regardless of the time-horizon.

A scenario with an increased dosage of alglucosidase alfa was conducted and was done to reflect that some patients currently receive a higher dosage than actually indicated in the SmPC. [redacted]

Such an increase demonstrates that the result is highly sensitive to changes around dosages and drug acquisition costs, as this is expected to be the only parameters that will impact the results. Further, this showed that avalglucosidase alfa may result in a smaller increase in costs, than presented in the base-case. A similar scenario analysis has not been conducted for avalglucosidase alfa, as there is no indication that the recommended dosage would be exceeded.

One scenario tested the impact of including AEs as the occurrence of these are rather uncertain given the small population and low frequencies. However, such a change had no real impact on the result.

The last scenario tests the impact of changing administration time for patients receiving avalglucosidase alfa, as the increased vial size of avalglucosidase alfa is likely to result in shorter infusion time, because of decreased reconstitution time. This scenario illustrates that the result is not very sensitive to this parameter.

Table 19: One-way sensitivity analyses results

	Change	Reason / Rational	Total cost Ava (DKK)	Total cost Alg (DKK)	Incremental costs	Change from base case (%)
Base case	-	-	DKK 30,616,545	DKK 23,153,357	DKK 7,463,187	**0%**
Time horizon	1 year	To test the impact of various time horizons	[redacted]			
	5 years					
	20 years					
Posology	[redacted]					

	Change	Reason / Rational	Total cost Ava (DKK)	Total cost Alg (DKK)	Incremental costs	Change from base case (%)
Adverse events	With adverse events	Adverse events are based on a small population and are uncertain	[redacted]			
Patient time for avalglucosidase alfa	-20%	The increased vial size of avalglucosidase alfa means that reconstitution time is decreased and with it patient time used for infusions.				
[redacted]						

8.7.2 Probabilistic sensitivity analyses

Non-applicable. Since this is a CM analysis, no incremental cost effectiveness ratios are estimated. Consequently, a probabilistic sensitivity analysis is not meaningful to conduct.

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9. Budget impact analysis

The budget impact model was developed to estimate the expected budget impact of recommending avalglucosidase alfa as a possible standard treatment in Denmark. The budget impact analysis is embedded within the CM model and therefore any changes in the settings of the cost per patient model affects the results of the budget impact model. The costs included in the budget impact model are undiscounted, and patient cost and transportation cost are not included as per the guidelines by the DMC (50).

The analysis compared the costs for the Danish regions per year over five years in the scenario where avalglucosidase alfa is not recommended as possible standard treatment (current scenario) and the second scenario where avalglucosidase alfa is recommended as a possible standard treatment (future scenario). The total budget impact per year is the difference between the two scenarios as presented in section 9.2.

9.1 Number of patients and patient distribution

The number of patients have been based on the patient population described by the Danish KOL (45). The KOL mentioned that 17 patients with LOPD are known in Denmark. Consequently, the budget impact was demonstrated for these 17 patients. All patients are considered eligible for treatment with avalglucosidase alfa in year 1 and one additional patient is expected diagnosed every second year, therefore 1 patient is added to the BIM at year 2 and 4. The numbers in both the not recommended and recommended scenario are based on KOL testimony.

In the scenario (Table 20), where avalglucosidase is not recommended as standard treatment (current scenario), the patients, who are currently on treatment with avalglucosidase alfa continue on this regimen and in addition 2 patients switch to avalglucosidase alfa. The remaining patients already receiving alglucosidase alfa will continue on treatment with alglucosidase alfa.

In the scenario (Table 20), where avalglucosidase alfa is recommended as possible standard treatment, all patients are assumed to switch from alglucosidase alfa in year 1.

Table 20 Number of patients expected to be treated over the next five-year period - if avalglucosidase alfa is not recommended – scenario analysis

All eligible patients	Year 1	Year 2	Year 3	Year 4	Year 5
Avalglucosidase alfa	4	4	4	4	4
Alglucosidase alfa	13	14	14	15	15
Total number of patients	17	18	18	19	19

Table 21: Number of patients expected to be treated over the next five-year period - if avalglucosidase alfa is recommended – scenario analysis

All eligible patients	Year 1	Year 2	Year 3	Year 4	Year 5
Avalglucosidase alfa	17	18	18	19	19

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All eligible patients	Year 1	Year 2	Year 3	Year 4	Year 5
Alglucosidase alfa	0	0	0	0	0
Total number of patients	17	18	18	19	19

9.2 Budget impact result

The estimated budget impact of recommending avalglucosidase alfa as standard treatment in Denmark at AIP is DKK 11,271,115 in year 1 and DKK 13,005,562 in year 5 as shown in Table 22.

Table 22 Expected budget impact of recommending avalglucosidase alfa as standard treatment

Base case	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	DKK 60,129,602	DKK 63,666,637	DKK 63,666,637	DKK 67,203,673	DKK 67,203,673
Without	DKK 48,858,115	DKK 51,528,113	DKK 51,528,113	DKK 54,198,111	DKK 54,198,111
Budget impact	DKK 11,271,487	DKK 12,138,525	DKK 12,138,525	DKK 13,005,562	DKK 13,005,562

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10. Discussion on the submitted documentation

The documentation submitted for this single-technology assessment stems from a comprehensive clinical development program, where avalglucosidase alfa has been evaluated in LOPD patients.

In Denmark the current treatment for these patients is ERT with alglucosidase alfa. However, these patients still experience muscle deterioration over time and need improved treatment. Avalglucosidase alfa has demonstrated that it clinically improves or stabilizes key outcomes in patients with LOPD.

[redacted]

Sanofi has presented a phase 2/3 extended study (NEO-EXT), that demonstrates long-term safety alongside with a randomized phase 3 head-to-head study (COMET), comparing avalglucosidase alfa to alglucosidase alfa. The combination of the two ensures minimum uncertainty related to the clinical outcomes.

The NEO-EXT study showed documentation for avalglucosidase alfa's safety in both naïve and switch patients over a time period of 6 years. The COMET study further corroborated these findings, as avalglucosidase alfa presented a more favorable safety profile. Overall avalglucosidase alfa clearly demonstrated non-inferiority to alglucosidase in the primary analysis of FVC. Further, statistically significant and clinical relevant improvements were observed for 6MWT and QMFT.

Health economic analysis

As avalglucosidase alfa proved non-inferiority demonstrated in the primary outcome and is estimated to save resources for HCPs, a cost-minimization approach has been taken.

In the base-case analysis with AIP prices, avalglucosidase alfa was associated with higher costs when compared to alglucosidase alfa. The cost differences of both arms are solely driven by the difference in AIP price between the two comparators, thus the results of this analysis would be highly sensitive to any change in price.

Scenario analyses were conducted to test the impact of various assumptions. This indicated that a shorter time horizon would result in a lower increase in costs, whereas the opposite occurred with a longer time horizon. [redacted]

11. List of experts

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Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

No extensive description of the conducted literature search was deemed necessary as Sanofi has presented sufficient documentation, by providing a randomized head-to-head study.

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Appendix B - Main characteristics of included studies

Table 23 Main characteristics of NEO-EXT

Trial name: NEO-EXT	NCT number: NCT02032524
Objective	*Assess long-term safety and pharmacokinetics of avalglucosidase alfa*
Publications – title, author, journal, year	▪ ***14th Annual WORLDSymposium™ 2018, February 5–9, 2018, San Diego, CA, USA. Poster:*** *Pena LDM, et al. NEO1 and NEO-EXT: Long-term safety of repeat neoGAA (avalglucosidase alfa) dosing in late-onset Pompe disease patients for 3.5 years. Unpublished late-breaking abstract LB-45. Poster LB-45* ▪ ***Society for the Study of Inborn Errors of Metabolism (SSIEM) 2018 Annual Symposium, September 4–7, 2018, Athens, Greece. Encore Poster:*** *Schoser B, et al. NEO1/NEO-EXT: Long-term safety of repeat avalglucosidase alfa dosing in late-onset Pompe disease patients for 3.5 years. Abstract 1534. Poster: P-370. (WORLDSymposium 2018 encore)* ▪ ***15th Annual WORLDSymposium™ 2019, February 4–8, 2019, Orlando, FL, USA. Platform Presentation and Poster:*** *Pena LDM, et al. NEO1 and NEO-EXT studies: Long-term safety of repeat avalglucosidase alfa dosing for 4.5 years in late-onset Pompe disease patients. Mol Genet and Metab 2019;126(2):S115–6. Poster 278* ▪ ***American Academy of Neurology (AAN) 2019, May 4–10, 2019, Philadelphia, PA, USA. Encore Poster:*** *Dimachkie MM, et al. NEO1 and NEO-EXT Studies: Long-Term Safety of Repeat Avalglucosidase Alfa Dosing for 4.5 Years in Patients With Late-Onset Pompe Disease. Neurology 2019;95(15S):P5.4-003. Poster 4-003 (WORLDSymposium 2019 encore)* ▪ ***5th Congress of the European Academy of Neurology (EAN), June 29–July 2, 2019, Oslo, Norway:*** *ePresentation: Schoser B, et al. NEO1 and NEO-EXT studies: pharmacodynamic and exploratory biomarker assessments following repeat avalglucosidase alfa dosing for up to 4.5 years in patients with late-onset Pompe disease. Eur J Neurol. 2019;26(Suppl.1):326. Abstract EPR3085* ▪ ***24th International Annual Congress of the World Muscle Society (WMS), October 1–5, 2019, Copenhagen, Denmark. Poster:*** *Schoser B, et al. NEO1 and NEO-EXT Studies: Exploratory efficacy of repeat avalglucosidase alfa dosing for up to 5 years in participants with late-onset Pompe disease (LOPD). Neuromuscul Disord. 2019;29(Suppl 1):S60. P.69* ▪ ***2019 American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Annual Meeting, October 16–19, 2019, Austin, TX, USA. Encore Poster:*** *Dimachkie MM et al. NEO1 AND NEO-EXT Studies: Pharmacodynamic/exploratory biomarker and safety assessments following repeat avalglucosidase alfa dosing for up to 4.5 years in patients with late-onset Pompe disease. Poster 98 (EAN 2019 encore)* ▪ ***16th Annual WORLDSymposium™ 2020, February 10–13, 2020, Orlando, FL, USA. Platform presentation and Poster:*** *Dimachkie MM, et al. NEO1 and NEO-EXT Studies: Long-term safety and exploratory efficacy of repeat avalglucosidase alfa dosing for 5.5 years in late-onset Pompe disease patients. Mol Genet Metab. 2020;129(2):S49. Abstract 98* ▪ ***72nd Annual Meeting of the American Academy of Neurology (AAN), April 25, 2020 – May 1, 2020. Virtual Congress. Encore ePresentation:*** *Dimachkie MM, et al. NEO1 and NEO-EXT Studies: Long-term safety and exploratory efficacy of repeat avalglucosidase alfa dosing for 5.5 years in late-onset Pompe disease patients. Neurology 2020;94(15 Supplement):695 (WORLDSymposium 2020 encore)*

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Trial name: NEO-EXT	NCT number: NCT02032524
Publications – title, author, journal, year	▪ ***6th Congress of the European Academy of Neurology (EAN), 23–26 May, 2020. Virtual Congress. ePresentation:*** *Schoser B, et al. NEO1/NEO-EXT studies: Trends over time in exploratory efficacy of repeat avalglucosidase alfa dosing for up to 5.5 years in late-onset Pompe disease (LOPD) patients. Eur J Neurol. 2020;27(Supplement 1):468. Abstract EPR3110* ▪ ***17th Annual WORLDSymposium™ 2021, February 7–12, 2020, Orlando, FL, USA. Platform presentation and Poster:*** *Dimachkie MM, et al. NEO1/NEO-EXT: Safety and Exploratory Efficacy of Repeat Avalglucosidase Alfa Dosing After up to 6 Years in Participants With Late-Onset Pompe Disease. Mol Genet and Metab 132 (2020) S13–S116. Abstract 58* ▪ ***17th Annual WORLDSymposium™ 2021, February 7–12, 2020, Orlando, FL, USA. Platform presentation and Poster:*** *Carlier PG, et al. NEO1/NEO-EXT Studies: Muscle MRI Results in Patients With Pompe Disease After Long-Term Avalglucosidase Alfa Treatment. Mol Genet and Metab 132 (2020) S13–S116. Abstract LB-06*
Study type and design	*Ongoing, open-label, multicenter, multinational extension study of patients who had completed NEO1 (A phase 1 study to assess safety and tolerability).*
Sample size (n)	*17*
Main inclusion and exclusion criteria	*Inclusion criteria:* *Patients with Pompe disease who previously completed a an avalglucosidase study.* *The patient and/or their parent/legal guardian is willing and able to provide signed informed consent, and the patient, if <18 years of age, is willing to provide assent if deemed able to do so.* *The patient (and patient's legal guardian if patient is <18 years of age) must have the ability to comply with the clinical protocol.* *The patient, if female and of childbearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin] at baseline.* *Exclusion criteria:* *The patient is concurrently participating in another clinical study using investigational treatment.* *The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study.* *The patient has clinically significant organic disease (with the exception of symptoms relating to Pompe disease), including clinically significant cardiovascular, hepatic, pulmonary, neurologic, or renal disease, or other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, precludes participation in the study or potentially decreases survival.* *The above information is not intended to contain all considerations relevant to a patient's potential participation in a clinical trial.*
Intervention	*Avalglucosidase alfa administered via IV.* *Until 2016 patients received either 5 mg/kg, 10 mg/kg or 20 mg/kg, afterwards everyone received 20 mg/kg. 17 patients were in the study at data cutoff.*

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Trial name: NEO-EXT	NCT number: NCT02032524
Is the study used in the health economic model?	*No, this study is only included to demonstrate long-term safety*
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** *Primary endpoint was safety i.e. IARs and AEs.* *Exploratory endpoints explored muscle functions based on:* ▪ *FVC* ▪ *6MWT* **Other endpoints:** *Pharmacokinetics and pharmacodynamics* *Functional outcome measures:* ▪ *MIP* ▪ *MEP* ▪ *GSGC* ▪ *GMFM-88-DE* ▪ *QMFT* ▪ *HHD* *And HRQoL based on:* ▪ *PedsQL*
Method of analysis	*Patients included in the analyses were everyone who received 1 or more infusion with avalglucosidase alfa. Efficacy endpoints were analyzed using a repeated measures mixed model, while safety data were descriptive.*
Subgroup analyses	*The method of analysis follows the description above in each subgroup.* *Subgroup analyses were performed on a group of treatment naïve patients (n=10) and a switch group who previously received alglucosidase alfa for more than 9 months (n=14).*
Other relevant information	*No*

Table 24 Main characteristics of COMET

Trial name: COMET	NCT number: NCT02782741
Objective	*Compare safety and efficacy of avalglucosidase alfa vs alglucosidase alfa in treatment naïve LOPD patients.*

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Trial name: COMET	NCT number: NCT02782741
Publications – title, author, journal, year	▪ ***13th International Congress of Inborn Errors of Metabolism (ICIEM), September 5–8, 2017, Rio de Janeiro, Brazil. Poster:*** *Straub V, et al. COMET Methodology: Comparison of the efficacy and safety of the enzyme replacement therapies, neoGAA and alglucosidase alfa, in treatment-naïve patients with late-onset Pompe disease. J Inborn Errors Metab Screen 2017;5:355-356. Abstract 792.* ▪ ***2017 American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Annual Meeting, September 13–16, 2017, Phoenix, AZ, USA. Poster:*** *Ladha S, et al. COMET Methodology: Comparison of the efficacy and safety of the enzyme replacement therapies, neoGAA and alglucosidase alfa, in treatment-naïve patients with late-onset Pompe disease. 2017 Abstract Guide of the 2017 AANEM Annual Meeting. September 13–16, 2017. Phoenix AZ, USA. Muscle Nerve 2017. Abstract 98.* ▪ ***Standalone Sanofi Genzyme Virtual Scientific Session, June 16, 2020. Presentation:*** *Diaz-Manera J, et al. Initial results of the avalglucosidase alfa Phase 3 COMET trial in late-onset Pompe disease patients. Sanofi Genzyme Virtual Scientific Presentation. June 16, 2020.* ▪ ***25th International Annual Congress of the World Muscle Society (WMS25), September 28, 2020–October 2, 2020, Virtual Congress. ePoster:*** *Clemens P, et al. Efficacy and safety of avalglucosidase alfa in patients with late-onset Pompe disease: Results from the phase 3 COMET Trial. Neuromuscul Disord. 2020;30(Suppl 1):S50 P.07.* ▪ ***17th Annual WORLDSymposium™ 2021, February 7–12, 2020, Orlando, FL, USA. Platform presentation and Poster:*** *Kisnani PP, et al. Efficacy and safety results of the avalglucosidase alfa phase 3 COMET trial in late-onset Pompe disease patients. Mol Genet and Metab 132 (2020) S13–S116. Abstract 121* ▪ **WMS2021 Virtual Congress 20–24 September, 2021.** Patient relevant change in forced vital capacity % predicted in late onset Pompe disease (LOPD) in the COMET trial. Berger K. et al., 2021 Poster EP.200. ▪ **WMS2021 Virtual Congress 20–24 September, 2021.** Mobility, usual activities and EQ-5D visual analogue score improvement with avalglucosidase alfa in Late-onset Pompe disease during the COMET trial. Pollissard L. et al., 2021 Poster EP.203 ▪ **Lancet Neurol 2021; 20: 1012–26.** Diaz-Manera, J., Kishnani, P., et al. (2021). Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomized, multicentre trial. www.thelancet.com/neurology Vol 20 December 2021
Study type and design	*Phase 3 randomized, multicenter, multinational, double-blinded study comparing the efficacy and safety of avalglucosidase alfa and alglucosidase alfa in treatment-naïve patients with LOPD age 3 or above.* *Patients were randomized 1:1 to receive an IV infusion of 20 mg/kg avalglucosidase alfa (n=51) or alglucosidase alfa (n=49)*
Sample size (n)	*100*

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Trial name: COMET	NCT number: NCT02782741
Main inclusion and exclusion criteria	*Inclusion criteria:* ▪ ≥ 3 years of age ▪ Diagnosis of PD (Confirmed by GAA enzyme deficiency from any tissue source and/or 2 confirmed GAAgene variants). ▪ Naïve to treatment with alglucosidase alfa or any investigational therapy for PD ▪ Able to successfully perform repeated FVC measurements of ≥30% & ≤85% predicted(upright) ▪ Able to ambulate 40 meters (≈130 feet) without stopping and without an ambulation assistance device ▪ *Exclusion criteria:* ▪ Pompe-specific cardiac hypertrophy ▪ Requires invasive ventilation (non-invasive ventilation is allowed) ▪ Wheelchair dependency ▪ Clinically significant organic disease, apart from PD-related symptoms ▪ Prior or current use of immune tolerance induction therapy ▪ Pregnant or breastfeeding ▪ Female patient of childbearing potential not protected by highly effective contraceptive method of birth control and/or is unwilling or unable to be tested for pregnancy
Intervention	*Avalglucosidase alfa is administered via IV.* *20 mg/kg qow*
Is the study used in the health economic model?	*No, no efficacy has been used in the model*

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Trial name: COMET	NCT number: NCT02782741

Primary, secondary and exploratory endpoints

Primary endpoint:

- Change from baseline in Forced Vital Capacity (FVC) % predicted.

Secondary endpoints:

Secondary endpoints aimed at measuring functional endurance and included:

- Change from baseline in distance walked in 6-minute walk test (6MWT)
- Change from baseline in maximal inspiratory pressure (MIP) % predicted
- Change from baseline in maximal expiratory pressure (MEP) % predicted
- Change from baseline in lower extremity muscle strength assessed by hand-held dynamometry (HHD)
- Change from baseline in Quick Motor Function Test (QMFT)
- Change from baseline in 12-item short-form health survey (SF-12): PCS and MCS

Tertiary endpoints:

- Change from baseline in Gross Motor Function Measure (GMFM-88)
- Change from baseline in Gross Motor Function Classification System (GMFCS)
- Change from baseline in Gait, Stairs, Gower, Chair (GSGC) score
- Change from baseline in Upper extremity muscle strength via HHD
- Change from baseline in EQ-5D-5L
- Change from baseline in PedsQL

Exploratory endpoints

- Change from baseline in patient determined disease steps (PDDS)
- Change from baseline in pompe disease impact scale (PDIS)
- Change from baseline in Rasch-built Pompe-specific activity (R-Pact)
- Change from baseline in patient global impressions scale (PGIC)

Method of analysis

Method of analysis is a modified intention-to-treat (mITT), which includes patients who received at least 1 infusion. This method was used for all efficacy analyses.

Mixed Model for Repeated Measures (MMRM): analysis method used for primary and secondary endpoints (includes the baseline FVC % predicted and age as a continuous variable, and gender, treatment group, visit, and treatment by visit interaction as fixed effects).

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Trial name: COMET	NCT number: NCT02782741

Subgroup analyses

The following subgroup analyses were performed for FVC % predicted and 6MWT, looking at the least-squares mean difference from alglucosidase alfa:

- ***Age (years)***
  - >= 18 and < 45
  - >= 45
- ***Gender***
  - Male
  - Female
- ***Baseline FVC (% predicted group)***
  - Baseline FVC (% predicted) <55%
  - Baseline FVC (% predicted) >=55%
- ***Region***
  - Europe
  - North America
  - Latin America
- ***Baseline walking device group***
  - Baseline use of walking device on the 6MWT
  - Baseline not use of walking device on the 6MWT
- ***Baseline 6MWT (distance walked group)***
  - Baseline 6MWT (distance walked) < median of 403,5 m
  - Baseline 6MWT (distance walked) >= median of 403,5 m
- ***Duration of the disease group***
  - Duration of the disease < median of 10,74 years
  - Duration of the disease >= median of 10,74 years
- ***Race***
  - White

Other relevant information *No*

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Appendix C - Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 25 Baseline characteristics of COMET

	COMET	
	Avalglucosidase alfa (n=51)	*Alglucosidase alfa (n=49)*
Age, mean+SD years	*46.0±14.5*	*50.3±13.7*
Gender, n (%)		
▪ Female	▪ *24 (47.1)*	▪ *24 (49.0)*
▪ Male	▪ *27 (52.9)*	▪ *25 (51.0)*
Race, n (%)		
▪ White	▪ *47 (92.2)*	▪ *47 (95.9)*
▪ Black or African American	▪ *1 (2.0)*	▪ *2 (4.1)*
▪ Asian	▪ *3 (5.9)*	▪ *0*
Ethnicity, n (%)		
▪ Hispanic or Latino	▪ *3 (5.9)*	▪ *12 (24.5)a*
▪ Not Hispanic or Latino	▪ *44 (86.3)*	▪ *32 (65.3)*
▪ Not reported	▪ *4 (7.8)*	▪ *5 (10.2)*
Geographic 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)*
FVC (upright), mean±SD, % predicted	*62.5±14.4*	*61.6±12.4*
6MWT (distance walked), mean±SD, meters	*399.3±110.9*	*378.1±116.2*
MIP (upright), mean±SD, % predicted	*59.9±47.1b*	*60.6±41.0*
MEP (upright), mean±SD, % predicted	*65.77±38.97b*	*74.83±35.22*
HHD (lower extremity) composite, mean±SD	*1330.45±625.44b*	*1466.16±604.91c*
QMFT, mean±SD	*41.29±10.15*	*42.30±10.58c*
SF-12 PCS, mean±SD	*35.95±7.82b*	*36.76±9.40d*
SF-12 MCS, mean±SD	*48.31±10.11b*	*50.58±8.69d*

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GMFCS, n (%)		
▪ **Level I**	▪ *10 (19.6)*	▪ *14 (28.6)*
▪ **Level II**	▪ *36 (70.6)*	▪ *27 (55.1)*
▪ **Level III**	▪ *5 (9.8)*	▪ *8 (16.3)*
▪ **Level IV**	▪ *0*	▪ *0*
▪ **Level V**	▪ *0*	▪ *0*
Walking device on 6MWT, n (%)		
▪ **Straight cane**	▪ *4 (7.8)*	▪ *3 (6.1)*
▪ **Wide-based cane**	▪ *1 (2.0)*	▪ *1 (2.0)*
▪ **One crutch**	▪ *0*	▪ *2 (4.1)*
▪ **Two crutches**	▪ *0*	▪ *0*
▪ **Standard walker**	▪ *0*	▪ *0*
▪ **Rolling Walker**	▪ *0*	▪ *3 (6.1)*
▪ **Orthotics**	▪ *0*	▪ *0*
▪ **Other**	▪ *2 (3.9)*	▪ *1 (2.0)*
None	*44 (86.3)*	*39 (79.6)*

[a] The greater proportion of Hispanic or Latino patients in the alglucosidase alfa group is likely due to the increased number of patients enrolled from North America and Latin America in the alglucosidase alfa group

[b] n=50: 1 patient in the avalglucosidase alfa group was under 18 and per protocol not supposed to answer the questionnaire[c] n=46: 1 patient in the avalglucosidase alfa group was under 18 and per protocol not supposed to answer the questionnaire and missing data

[d] n=48: 1 patient in the avalglucosidase alfa group was under 18 and per protocol not supposed to answer the questionnaire and missing data

6MWT = 6-minute walk test; FVC = forced vital capacity; GMFCS = Gross Motor Function Classification System; HHD = hand-held dynamometry; MCS = mental component summary; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; PCS = physical component summary; QMFT = Quick Motor Function Test; SD = standard deviation; SF-12 = 12-item Short Form Health Survey

Table 26 Baseline characteristics of NEO-EXT

Demographic or disease characteristic	Naïve group (n=10)	Switch group (n=14)
Age at study enrollment, mean±SD, years	44.8±20.26	46.7±14.11
Sex, n (%)		
▪ Female	▪ 7 (70)	▪ 5 (36)
▪ Male	▪ 3 (30)	▪ 9 (64)
Race, n (%)		
▪ White	▪ 8 (80)	▪ 13 (93)
▪ Black or African American	▪ 0	▪ 1 (7)
▪ Multiple	▪ 1 (10)	▪ 0
▪ Other	▪ 1 (10)	▪ 0
Age at diagnosis of LOPD, mean±SD, years	43.3±23.79[a]	36.3±16.39[b]
Family history of Pompe disease, n (%)	4 (40)	6 (43)

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Demographic or disease characteristic	Naïve group (n=10)	Switch group (n=14)
Assistive walking devices/orthoses, n (%)		
▪ None	▪ 8 (80)	▪ 11 (79)
▪ Rolling walker	▪ 1 (10)	▪ 1 (7)
▪ Straight cane	▪ 0	▪ 2 (14)
▪ 2 walking sticks (poles)	▪ 1 (10)	▪ 0

[a] n=8 – full data for pre-study treatment was only available for 8 patients

[b] n=9 - full data for pre-study treatment was only available for 9 patients

LOPD = late-onset Pompe disease; SD = standard deviation

Comparability of the study populations with Danish patients eligible for treatment

There are no known patient-characteristics for the Danish population. However, a KOL confirmed that both the age and gender proportions resembled Danish patients.

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Appendix D - Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

In Table 27 the definition of each included outcome measure is provided. The same definitions were used across the included studies. The table also provides a description of how the validity and clinical relevance of the outcomes has been investigated.

Table 27 Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Change in baseline in Forced Vital Capacity (FVC) % predicted	FVC is measured as a percentage of the predicted normal capacity in the upright position. The test evaluates respiratory function by making the patient take the deepest breath they possibly can and forcibly exhale, this is measured as the volume of air (in liters) that is blown out. Percent of predicted FVC = (actual FVC measurement)/(predicted value of FVC) * 100	This parameter is considered key by the American Thoracic Society when evaluating respiratory function (64) and was further used as an endpoint in the initial trials for the comparator, alglucosidase alfa.	The use of FVC% predicted as the primary outcome is based on the fact, that respiratory insufficiency due to progressive muscle weakness is a major source of morbidity and death in LOPD patients.
Change from baseline in total distance walked during 6-Minute Walk Test (6MWT)	This safe and simple test evaluates the skeletal muscle function, by measuring the distance (in meters) a person can walk within six minutes on a flat and hard surface.	It is developed for the assessment of aerobic activity in patients with respiratory disease and is validated in numerous patient populations within musculoskeletal diseases. Further, Ten clinical studies of late-onset Pompe patients reported the 6MWT as a functional outcome measure (80).	It assesses the integrated response of the pulmonary, cardiovascular and musculoskeletal systems and reflects the functional exercise level required to perform daily life activities.
Change from baseline in Maximal Inspiratory Pressure (MIP) % predicted in upright position	It is a test to measure strength of inspiratory muscles, primarily diaphragm and allows for assessment of ventilatory failure, restrictive lung disease and respiratory muscle strength. MIP refers to how much air pressure force an individual creates by inhaling through the mouth as hard as possible.	It has been used as an endpoint in several RCTs considering chronic diseases with respiratory failure. It is used as a part of the recommended routine evaluation of Pompe-patients (3).	It is a direct measure of respiratory muscle strength that may be more sensitive in detecting early respiratory muscle dysfunction compared with spirometry. It has a close relationship with diaphragmatic muscle strength and given that respiratory muscle dysfunction (especially that of the diaphragm) is common in PD, it provides a relevant outcome measurement (67).
Change from baseline in Maximal Expiratory Pressure (MEP) %	MEP is a test to measure strength of expiratory muscles, primarily diaphragm, and allows for assessment of ventilatory failure, restrictive lung disease and respiratory muscle strength. MEP is the	It is used as a part of the recommended routine evaluation of Pompe-patients (3).	It is a direct measure of respiratory muscle strength that may be more sensitive in detecting early respiratory muscle dysfunction compared with spirometry.

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Outcome measure	Definition	Validity	Clinical relevance
predicted in upright position	greater pressure generated during maximal expiration.		
Change from baseline in Lower Extremity Muscle Strength Assessed by Hand-Held Dynamometry (HHD)	HHD: a portable method for strength quantitation. To complete a make test, participant exerted maximal force against dynamometer with gradual increase in force and completed isometric hold for 4-5 seconds. Muscle strengths were collected in Newton. Every muscle group (hip: flexion, extension, abduction; knee: flexion, extension and ankle dorsiflexion) were measured 2 times and highest value was reported. Summary score was sum of 12 measurements (2 measurements per muscle group) from 6 muscle groups on each side (left and right). An increase from Baseline was reflective of increased muscle strength, whereas a decrease from Baseline was reflective of decreased muscle strength.	HHD is frequently used for measuring lower limb strength.	Pompe patients experience a decrease in skeletal muscle strength which leads to a loss of the ability to walk without a walking aid. The muscle strength in the lower extremities is easily measured by the use of a HHD.
Change from baseline in Quick Motor Function Test (QMFT)	The QMFT was an observer administered test to evaluate changes in motor function. QMFT comprised of 16 items specifically difficult for participants with PD. Each item was scored separately on a 5-point ordinal scale (ranged from 0 to 4, higher score indicated better outcome). Total QMFT score was obtained by adding the scores of all items and ranged from 0 (unable to perform motor function tests) to 64 (normal muscle function), higher score represented better outcome.	The QMFT was constructed on the basis of the clinical expertise of several physicians in the care of Pompe patients. The test can reliably rate clinical severity and motor function in Pompe patients.	The argument for its validity also argues its clinical relevance.
Change from baseline in 12-item Short-form Health Survey (SF-12): Physical Component Summary (PCS) and Mental Component Summary (MSC)	SF-12, a 12 item-questionnaire, used to assess HRQoL in participants aged >=18 years at screening/baseline. SF-12 consisted of 12 items, which were categorized into eight domains (subscales) of functioning and well-being: physical functioning, role-physical, role emotional, mental health, bodily pain, general health, vitality and social functioning, with each domain score ranged from 0 (poor health) to 100 (better health), higher scores indicated good health condition. These eight domains were further summarized into 2 summary scores, PCS and MCS. The score range for each of these 2 summary scores was from 0 (poor health) to 100 (better health), higher scores indicated a better HRQoL.	The SF-12 is one of the most widely used instruments for assessing self-reported HRQoL. It covers the same 8 health domains as SF-36, but with fewer questions making it more practical.	The argument for its validity also argues its clinical relevance. Further, LOPD affects HRQoL for patients, making it a relevant outcome measure.

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Results per study

Table 28 Safety data collected in the NEO-EXT study.

Safety outcome	Naïve group (n=10)	Switch group (n=14)
Any TEAE (%)	10 (100)	14 (100)
Treatment-related TEAE (%)	8 (80)	10 (71)
Treatment-emergent SAE (%)	5 (50)	4 (29)
Severe TEAE (%)	2 (20)	0
Any IAR (%)	3 (30)	3 (21)
TEAE leading to permanent discontinuation (%)	1 (10)	0

Table 29 Efficacy data from NEO-EXT

Outcome	At week 286			
Changes from baseline	Group	N	Result (SD)	Median
6MWT (m)	Naïve	6	2.0±64.89	-6.0
	Switch	8	-0.6±58.83	3.0
Upright FVC % predicted	Naïve	7	-1.0±13.16	1.4
	Switch	9	-6.0±7.67	-7.3
MIP (upright), % predicted	Naïve	6	0.5±22.48	-7.7
	Switch	6	1.5±8.77	1.8
MEP (upright), % predicted	Naïve	6	12.6±24.76	8.4
	Switch	6	9.8±5.54	10.6

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Table 30 Changes from baseline to week 49 in predefined primary and secondary objectives for efficacy in COMET study

Outcome	Avalglucosidase alfa (n=51)	Alglucosidase alfa (n=49)	Least-squares mean difference between treatments (95% CI)
Upright FVC% predicted	2·89 (0·88)	0·46 (0·93)	2·43 (–0·13 to 4·99)
6MWT, m	32·21 (9·93)	2·19 (10·40)	30·01 (1·33 to 58·69)
6MWT% predicted	5·02 (1·54)	0·31 (1·62)	4·71 (0·25 to 9·17)
MIP% predicted*	8·70 (2·09)	4·29 (2·19)	4·4 (–1·63 to 10·44)
MEP% predicted*	10·89 (2·84)	8·38 (2·96)	2·51 (–5·7 to 10·73)
HHD, lower extremity	260·69 (46·07)	153·72 (48·54)	106·97 (–26·56 to 240·5)
HHD, upper extremity	173·54 (38·04)	109·67 (38·98)	63·87 (–44·76 to 172·51)
QMFT total score	3·98 (0·63)	1·89 (0·69)	2·08 (0·22 to 3·95)
SF-12 PCS score	2·37 (0·99)	1·60 (1·07)	0·77 (–2·13 to 3·67)
SF-12 MCS score	2·88 (1·22)	0·76 (1·32)	2·12 (–1·46 to 5·69)

Data are least-squares mean (SE), unless otherwise indicated. All efficacy analyses were done in the modified intention-to-treat population using a MMRM (includes the baseline FVC % predicted and age as a continuous variable, and gender, treatment group, visit, and treatment by visit interaction as fixed effects). 6MWT=6-minute walk test. FVC=forced vital capacity. HHD=hand-held dynamometry; MCS=mental component summary. MEP=maximum expiratory pressure. MIP=maximum inspiratory pressure. PCS=physical component summary. QMFT=quick motor function test. SF-12=health-related quality of life 12-item short-form health survey. *Four participants (two in each group) with implausibly high MIP% predicted and MEP% predicted values at baseline were excluded from all MIP and MIP analyses.

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Table 33 Safety data from COMET

	Avalglucosidase alfa (n=51)	Alglucosidase alfa (n=49)
Any TEAE (%)	44 (86.3)	45 (91.8)
Treatment-related TEAE (%)	23 (45.1)	24 (49.0)
Treatment-emergent SAE (%)	8 (15.7)	12 (24.5)
Severe TEAE (%)	6 (11.8)	7 (14.3)
Any IAR[a] (%)	13 (25.5)	16 (32.7)
TEAE leading to permanent discontinuation (%)	0	4 (8.2)
TEAE leading to death (%)	0	1 (2.0)

Data are reported as n (%)

[a] An AE during either the infusion or observation period following the infusion that was related or possibly related to the treatment

Abbreviations: AE = adverse event; IAR = infusion-associated reaction; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Table 34 Safety data from COMET - Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb) Responses

	Avalglucosidase alfa (n=51)	Alglucosidase alfa (n=49)
ADA Status, n (%)		
▪ **Always negative**	2 (3.9)	2 (4.2)
▪ **Ever positive but negative at baseline**	47 (92.2)	44 (91.7)
▪ **Positive at baseline**	2 (3.9)	2 (4.2)
Treatment-emergent ADA, n (%a)	49 (96.1)	46 (95.8)
▪ **Treatment-induced ADA, n (%b)**	47 (95.9)	44 (95.7)
▪ **Transient ADA**	1 (2.0)	1 (2.2)
▪ **Persistent ADA**	43 (87.8)	39 (84.4)
▪ **Tolerized ADA**	3 (6.1)	4 (7.7)
▪ **Treatment-boosted ADA, n (%c)**	2 (100)	2 (100)
ADA peak titer, n (%)		
▪ **100-800**	17 (33.3)	8 (16.7)
▪ **1600-6400**	20 (39.2)	20 (41.7)
▪ **≥12,800**	10 (19.6)	16 (33.3)

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Nab response type based on enzyme activity inhibition, n (%)		
▪ **Always negative**	49 (96.1)	44 (91.7)
▪ **Positive at baseline**	0	0
▪ **Positive post baseline**	2 (3.9)	4 (8.3)
Nab response type based on enzyme uptake inhibition, n (%)		
▪ **Always negative**	38 (74.5)	28 (58.3)
▪ **Positive at baseline**	1 (2.0)	1 (2.1)
▪ **Positive post baseline**	12 (23.5)	19 (39.6)

Note: All ADAs are either anti-avalglucosidase alfa antibodies or anti-alglucosidase alfa antibodies; ADAs were assessed monthly during the study

a100 x (treatment boosted + treatment induced ADA positive patients)/(number of evaluable patients); b100 x (treatment induced ADA positive patients)/(number of evaluable patients with ADA negative at baseline); c100 x (treatment boosted ADA positive patients)/(number of evaluable patients with ADA positive at baseline)

Appendix E - Safety data for intervention and comparator(s)

All safety data is presented in Appendix D.

Appendix F - Comparative analysis of efficacy and safety

Not relevant as head-to-head data is presented Appendix D.

Appendix G – Extrapolation

Not applicable as no extrapolations have been made.

Appendix H – Literature search for HRQoL data

Not relevant as the presented model is a cost-minimization model without HRQoL data.

Appendix I - Mapping of HRQoL data

Not relevant as the presented model is a cost-minimization model without HRQoL data.

Appendix J - Probabilistic sensitivity analyses

Non-applicable. Since this is a CM analysis, no ICERs are estimated. Consequently, a PSA is not meaningful to conduct.

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Appendices K, L ... etc. Company-specific appendices

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