Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende cipaglucosidase alfa i kombination med miglustat til behandling af Pompes sygdom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. cipaglucosidase alfa
2. Forhandlingsnotat fra Amgros vedr. cipaglucosidase alfa
3. Ansøgers endelige ansøgning vedr. cipaglucosidase alfa
4. Tillæg til ansøgningen: Response to the DMC additional questions

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29th January 2024 Amicus comments to assessment report

Section 1.4

The alglucosidase alfa reference used in the DMC report includes only previously untreated patients: In a placebo-controlled study, alglucosidase alfa has shown a stabilizing effect on gait and lung function for up to 78 weeks. The PROPEL study includes previously treated patients with a mean of > 7 years on previous treatment and is the only randomized phase 3 trial to include previously treated LOPD patients.

Section 1.5.2 the assessment report states that (cipaglucosidase alfa in combination with miglustat had a better effect than alglucosidase alfa in the first 4 weeks of treatment, after which the difference evened out.

The EPAR states Cipaglucosidase alfa dose-dependently reduced glycogen levels in muscle, which was significantly greater (up to 1.8x in skeletal muscle) compared to alglucosidase alfa and did so at comparatively lower exposures. However, GAA activity was overall not significantly improved compared to alglucosidase alfa at any dose or combination. These differences more or less plateaued after 4-weeks, after which the efficacy of alglucosidase alfa approached but did not meet that of cipaglucosidase alfa.

Section 2.2.1

PROPEL is the only randomized, phase 3 study with a superiority design in naive and previously treated LOPD patients (mean time on previous treatment > 7 years.)

Section 2.3.1 and 2.6

DMC suggests that the PROPEL pts were less effected than Danish population and infer that the trial is not representative. In the Phase I and II data included in Appendix Q and in additional questions there was a small defined cohort of non ambulatory patients who participated. Whilst the numbers were small the data is presented in the full publication supplementary tables. Moreover, about 1/3 of the eligible LOPD population in Denmark were included in PROPEL so the study is representative.

Section 2.3.2 and Section 3.3.1

Report states: Home infusion is frequently used in Danish clinical practice, but there are differences in how this is organized for comparator and intervention, see further in section 3.3.

Home infusion differences are due to the fact that cipaglucosidase alfa patients are still following a clinical study protocol, requiring nurse visit. Clinician's viewpoint was that once the trial has finished the requirement of a nurse for a home infusions will be similar, and cost difference on nurse time will be 0 DKK. The SMPC for alglucosidase alfa was developed when no patients were considered suitable for treatment at home.

Section 2.3.4 and 2.4.4 6

Report states: Several studies, primarily of Duchenne muscular dystrophy, have shown that a change in walking distance of more than 30 meters is correlated to a long-term effect [17}.

The value of 30m is referring to other diseases, compared against placebo and only in patients who are naïve to any treatment. For a patient switching between therapies it is not expected that they would be able to have the same magnitude of improvement compared to baseline or against another active therapy. The size of improvement is also related to the patients initial baseline values. No data is available that has established minimal clinically important change in previously treated patients.

Section 3.3.1

The mean PROPEL weight is 74.7 Kg, rounded to 75 by DMC, scenarios at 70 and 80 Kg are reported. the scenarios chosen use exact vials of the competitor product, which inflates the cost differential cipaglucosidase alfa. Every patient will be treated on an exact weight based dose. Data from Sweden (2023) shows the mean

weight of adult LOPD pts at treatment initiation was around [redacted] To assess the budget impact, scenarios should be run at 68, 75 & 82Kg to allow for different wastage scenarios.

Section 3.3.2

The assumption that patients require more prep time to take miglustat is erroneous When patients arrive in hospital, they must wait for their ERT to be raised from refrigerated to room temperature and then reconstitute multiple vials before an infusion can begin. When patients are on home infusion the time to take miglustat also becomes irrelevant.

There are roughly 2x as many vials to reconstitute for alglucosidase alfa compared to cipaglucosidase alfa, which would indicate a cost saving for cipaglucosidase alfa due to less time for reconstitution.

Section 4.1

The assessment does not fully reflect either the patient experience or data demonstrating the declining efficacy of alglucosidase alfa in both walking and pulmonary function e.g. in section 1.4. This leads to a simplified conclusion in the budget impact discussion where only price is expected to impact treatment choice. The availability of newer medicines to offer patients alternative options to support their battle with a serious rare disease is very important.

In the assessment report it is concluded in section 2.4.4-5 that cipaglucosidase alfa plus miglustat is at least as effective as alglucosidase alfa in 6MW-test. The assessment report states that cipaglucosidase alfa in combination with miglustat reduces the deterioration of lung function significantly more than alglucosidase alfa.

In the budget impact discussion, it is concluded that the treatment related to the lowest cost is expected to be used. As there it is highly unlikely that a cost effectiveness analysis of alglucosidase alfa ever will be done and yet currently most patients are treated with this treatment Amicus argues that rejection or approval of the cipaglucosidase alfa and miglustat should be based on comparison with current net price of alglucosidase alfa and not best supportive care or a hypothesis that the cost of alglucosidase alfa is too high. Amicus do not consider it to be a valued argument that the general cost for ERT treatment in Pompe disease is too high as alglucosidase alfa has been standard of care since 2007.

Amicus believe that it is an ethical matter to allow alternative treatments to alglucosidase alfa. Amicus made a choice to invest in Danish life science and we pleased to give the patients the opportunity to participate in the PROPEL trial

Section 9.3

It is important to highlight that alglucosidase alfa historically only has data in naïve patients compared to placebo. The only study to represent the Danish cohort is the PROPEL trial.

The scenario of vs BSC does not bear any reality to the state of care in Denmark. All eligible patients are treated with alglucosidase alfa, so it is the only appropriate comparator for economic analysis. There is no actual data of cipaglucosidase alfa vs BSC, as this would be unethical to do in a study, so the comparison vs BSC is estimated through an ITC (indirect comparison). DMC highlight this approach has great uncertainties and therefore it is not appropriate to use BSC as a comparator.

9.3.3

Utilities were collected using UK interview but were converted to Danish values. The utility cited for the Danish norm of 0.9 is not for patients who have a rare disease such as Pompe. The utility baseline of 0.72 from Kantars 2011 is from Dutch Pompe patients who are NOT currently receiving treatment and is the most appropriate starting value in the model.

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23.01.2024
BMC/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.02.2024
Leverandør	Amicus Therapeutics
Lægemiddel	Pombiliti (cipaglucosidase alfa)
Ansøgt indikation	Cipaglucosidase alfa anvendes i kombination med enzymstabilisatoren miglustat til behandling af voksne med sent debuterende Pompes sygdom.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Pombiliti (cipaglucosidase alfa):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Pombiliti	105 mg	1 htgl.	8.917,22	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

Aftaleforhold

Amgros har ved forhandling fået ovenstående pris fra leverandøren. Da der findes flere lægemidler til samme indikation, har Amgros publiceret et udbud, der kører parallelt med konkurrenterne Myozyme (alglucosidase alfa) og Nexviadyme (avalglucosidase alfa). Aftalen kan starte den 01.10.2024 med mulighed for prælevering fra den 03.04.2024.

Konkurrencesituationen

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler inkluderet i Medicinrådets vurderingsrapport.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Pombiliti	105 mg	1 htgl.	20 mg/kg IV hver 2. uge	[redacted]	[redacted]
Miglustat	65 mg	4 stk.	260 mg PO hver 2. uge	[redacted]	[redacted]
Pris for kombination af Pombiliti og Miglustat					[redacted]
Myozyme	50 mg	1 htgl.	20 mg/kg hver 2. uge	[redacted]	[redacted]
Nexviadyme	100 mg	1 htgl.	20 mg/kg hver 2. uge	[redacted]	[redacted]

*vægt = 75 kg jf. Medicinrådets vurderingsrapport

[redacted].

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke ansøgt	
Sverige	Under vurdering	Link til vurdering
England	Anbefalet	Link til anbefaling

Konklusion

[redacted]

Application for the assessment of cipaglucosidase alfa/miglustat for long-term treatment of adults aged 18 years and older with a confirmed diagnosis of Late onset Pompe disease

Table of contents

Basic information

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Overview of the pharmaceutical	
Proprietary name	Pombiliti®/Opfolda®
Generic name	cipaglucosidase alfa/miglustat
Marketing authorization holder in Denmark	Amicus Therapeutics
ATC code	Cipaglucosidase alfa: A16AB23 Miglustat: A16AX06
Pharmacotherapeutic group	Enzyme replacement therapy
Active substance(s)	cipaglucosidase alfa and miglustat
Pharmaceutical form(s)	cipaglucosidase alfa: intravenous infusion miglustat: oral hard capsule
Mechanism of action	Cipaglucosidase alfa/miglustat is a next-generation two-component therapy comprising the rhGAA and enzyme stabiliser miglustat (N-butyl-deoxynojirimycin) (Xu 2019), designed to overcome three well-characterised challenges in delivering rhGAA to the skeletal muscle (Do 2019, Selvan 2021). Owing to enhanced levels of CHO-derived bis-phosphorylated N-glycans, including M6P, cipaglucosidase alfa has high affinity cation-independent mannose 6-phosphate receptor-mediated cellular uptake and processing into the mature and most active form of GAA compared with the precursor protein (Do 2019, Selvan 2021). rhGAAs are significantly less stable in blood (pH 7.4) than in the lysosome (pH 5.2) owing to the difference in pH between the two environments. Co-administration with miglustat, a small molecule that binds selectively to cipaglucosidase alfa in the physiological pH of blood during infusion, stabilises cipaglucosidase alfa in the circulation following perfusion minimising the loss of enzyme activity while in circulation (Xu 2019). Stabilisation of cipaglucosidase alfa is the sole function of miglustat; it is dosed to optimise 1:1 binding and stabilisation of the recombinant enzyme while in the circulatory system, then rapidly eliminated and excreted

Overview of the pharmaceutical	
Dosage regimen	**Cipaglucosidase alfa** IV infusion every 2 weeks at 20 mg/kg, with an average of 4 hours infusion time **Miglustat** Orally administered 1 hour prior to IV infusion of cipaglucosidase alfa (fasting required prior to administration) to maximise occupancy and ensure enzyme stabilisation while in circulation • For patients weighing ≥ 50 kg, four capsules of 65 mg (260 mg total) • For patients weighing ≥ 40 kg–< 50 kg, three capsules of 65 mg (195 mg total) In the event of cipaglucosidase alfa infusion delay, the start of infusion should not exceed 3 hours from the oral administration of miglustat
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	For long-term treatment of adults aged 18 years and older with a confirmed diagnosis of Late onset Pompe disease (LOPD)
Other approved therapeutic indications	**Miglustat (Janssen-Cilag International NV)** The oral treatment of adult patients with mild to moderate type 1 Gaucher disease (for whom enzyme replacement therapy is unsuitable) • Dosing: 100 mg miglustat (1 × 100-mg oral capsules) 3 times per day – 300 mg daily The treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease • Dosing: 200 mg miglustat (2 × 100-mg oral capsules) 3 times per day – 600 mg daily **Cipaglucosidase alfa (Amicus Therapeutics)** *No other approved therapeutic indications*
Will dispensing be restricted to hospitals?	No
Combination therapy and/or co-medication	Cipaglucosidase alfa is administered in combination with miglustat
Packaging – types, sizes/number of units, and concentrations	**Cipaglucosidase alfa** Vial containing 105 mg of cipaglucosidase alfa (lyophilized powder for solution for intravenous infusion) **Miglustat** Capsules containing 65mg as an SKU bottle of 4 or 24 capsules
Orphan drug designation	No

Abbreviations

Acronym	Definition
ACMG	American College of Medical Geneticists
AD	Aggregate data
ADL	Activity of daily living
AE	Adverse event
AGSD	Association for Glycogen Storage Disease UK
ATC	Anatomical therapeutic chemical
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CEM	Cost-effectiveness model
CFB	Change from baseline
CFBL	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
CI-MPR	Cation-independent mannose 6-phosphate receptor
CK	Creatine kinase
COMP	Committee for Orphan Medicinal Products
CRD	Centre for Reviews and Dissemination
CRIM	Cross-reactive immunological material
CSR	Clinical study report
DBS	Dried blood spot
DKK	Danish krona
DMC	Danish Medicines Council
DMD	Duchenne muscular dystrophy
DRG	Diagnosis related group
EED	NHS Economic Evaluation Database
EMA	European Medicines Agency
EMG	Electromyography
ENMC	European Neuromuscular Centre
EOS	End of study
EPAR	European Public Assessment Report
EPOC	European Pompe Consortium
ERS	European Respiratory Society
ERT	Enzyme replacement therapy
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale
FVC	Forced Vital Capacity
GAA	Acid α-1,4-glucosidase
GMFM 88/66	Gross Motor Function Measure 88/66
GSCG/GSGC	Gait, Stairs, Gowers', Chair

HCP	Healthcare professional
HCRU	Healthcare resource use
HFMSE	Hammersmith Functional Motor Scale Expanded
HHD	Hand-held dynamometry
HR	Hazard ratio
HSUV	Health state utility values
HTA	Health technology assessment
IAR	Infusion-associated reaction
ICER	Incremental cost-effectiveness ratio
IOPD	Infantile-onset Pompe disease
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
LOCF	Last observation carried forward
LOPD	Late-onset Pompe disease
LOTS	Late-Onset Treatment Study
LS	Least-squares
MAIC	Matched adjusted indirect treatment comparison
MCID	Minimal clinically important difference
MDA	Muscular Dystrophy Association
MENA	Middle East and Northern Africa
MEP	Maximal expiratory pressure
MHRA	UK Medicines and Healthcare products Regulatory Agency
MIP	Maximal inspiratory pressure
ML-NMR	Multi-level network meta regression
MMRM	Mixed-effect model for repeated measures
MMT	Manual muscle test
MOS	Medical Outcomes Study
MPS	Morquio syndrome
MVV	Maximum voluntary velocity
6MWT	6-minute walk test
NBS	New born screening
NCPE	National Centre for Pharmacoeconomics
NHS	National Health Service
NHSEED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	Network meta analysis
NMB	Net monetary benefit
NORD	US National Institute for Rare Disorders
NR	Not reported
OLE	Open label extension
PD	Pharmacodynamics
PF	Progression-free
PFT	Pulmonary function test

PGIC	Physician's global impression of change
PI	Principal investigator
PICO	Population, Intervention, Comparator, Outcome
PK	Pharmacokinetics
PPP	Pharmacy purchasing price
PRIMA	Preliminary Independent Model Advice
PRO	Patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QMT	Quantitative muscle testing
QOW	Every other week
RCT	Randomised controlled trial
RHS	Rotterdam Handicap Scale
RULM	Revised Upper Limb Module
SAE	Serious adverse events
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SE	Standard error
SF-36 PCS	36-item Short-Form Health Survey Physical Component Summary
SGIC	Subject Global Impression of Change
SKU	Stock keeping unit
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SNIP	Sniff nasal-inspiratory pressure
SSIEM	Society for the study of inborn errors of metabolism
STC	Simulated treatment comparison
SVC	Slow vital capacity
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TTO	Time trade-off
TUG	Timed Up & Go
UK	United Kingdom
US/USA	United States of America
VAS	Visual analogue scale
VAT	Value-added tax
VC	Vital capacity
WGM	Walton and Gardner-Medwin
WHO	World Health Organization
WHOQOL	World Health Organization Quality of Life: Brief Version-BRE
YHEC	York Health Economics Consortium

Tables and Figures

Summary

Population

Pompe disease is a rare and multisystem disease (Scott 2013). It can be classified into two main types: infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD), with the former presenting in paediatric patients younger than 1 year of age with significant cardiac manifestations and rapid disease progression, and the latter with disease onset after 1 year of age and slower progression (Taverna 2020). LOPD is the focus of this submission.

LOPD encompasses the broad spectrum of phenotypes that present after 1 year of age and those that present within 1 year of age without cardiac manifestations (Park 2021). Most patients with LOPD initially experience slow, progressive loss of muscle function, typically starting with the trunk and lower limbs. Consequently, patients may experience instability in their gait, problems with walking and difficulty climbing stairs (Winkel 2005, van der Ploeg 2017), as well as gastrointestinal issues including abdominal discomfort, chronic diarrhoea or constipation, and poor weight gain (Chan 2017).

Intervention and clinical trial

Cipaglucosidase alfa/miglustat is a two-component therapy for LOPD that received Breakthrough Therapy Designation from the FDA in 2019 (Amicus Therapeutics 2019), highlighting it as a promising therapy for patients living with Pompe disease who currently have a significant unmet need. The indication for cipaglucosidase alfa/miglustat is for the treatment of adults 18 years of age and older living with LOPD disease. Cipaglucosidase alfa was granted EMA approval in March 2023. Miglustat was granted EMA approval in June 2023. The two-component therapy consists of cipaglucosidase alfa, a novel rhGAA enzyme, co-administered with miglustat, an oral pharmacological enzyme stabiliser.

The clinical efficacy and safety of cipaglucosidase alfa/miglustat was investigated in the phase 1/2, open-label, single-arm study ATB200-02 in 29 adult patients with Pompe disease, vs best supportive care (BSC) and in the head-to-head, phase 3 RCT PROPEL in adult patients with LOPD, who either have previously received at least 24 months of alglucosidase alfa treatment (ERT-experienced) or who have not received previous treatment with alglucosidase alfa (ERT-naïve), compared with alglucosidase alfa/placebo.

Amicus has incorporated input from clinical experts and adults with Pompe disease to ensure that the PROPEL study investigated patient-centric and clinically meaningful endpoints, while remaining scientifically robust and highly relevant for cost-effectiveness decision making. For example, in patient advisory boards, people with Pompe disease noted that improvements in muscle strength, respiratory function, and QoL were most important to them, with motor and muscle function endpoints being transferrable to the ability to carry out daily tasks (Amicus Data on file 2015, Amicus Data on file 2018). Motor, respiratory and muscle function, were therefore measured in the trials (Amicus data on file 2019).

The clinical expert consulted in Denmark confirmed that 6MWD and % predicted FVC are important outcome measures in Pompe disease, which should also be used when assessing long-term efficacy of therapy (List of experts, section 11). The clinical expert consulted in Sweden also pointed out that small changes in the short-term can extrapolate to an important change long-term: even a 1% annual improvement or stabilisation of symptoms long-term (over a decade) can impact delaying the need for ventilation and or motor support (Amicus data on file).

The improved efficacy of cipaglucosidase alfa in combination with miglustat compared to alglucosidase alfa has been demonstrated in the PROPEL trial, across a range of endpoints relevant to people with LOPD—both ERT experienced and naive patients—covering motor function, respiratory function, muscle strength and patient-reported outcomes (PROs). In the total population of the PROPEL trial, 6MWD (the primary efficacy endpoint) showed greater improvement with cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa but did not demonstrate statistical superiority.

Health economic evaluation

The health economic base case results shows that the incremental cost between cipaglucosidase alfa in combination with miglustat and alglucosidase alfa was around [redacted], the incremental QALY gain was [redacted] in favour of cipaglucosidase alfa in combination with miglustat. The associated ICER was estimated to [redacted]. The theoretical scenario comparing vs best supportive care estimated [redacted] in incremental costs and a QALY gain of [redacted]. The associated ICER vs best supportive care was [redacted]. The results vs BSC highlights the severity of the disease if left untreated; despite higher incremental costs vs active treatment, the gain in QALYs due to a significant lower rate of progression is very high.

The patient population, the intervention and choice of comparator

5.1. The medical condition and patient population

5.1.1. Disease background

Pompe disease is a rare and multisystem disease (Scott 2013). It can be classified into two main types: infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD), with the former presenting in paediatric patients younger than 1 year of age with significant cardiac manifestations and rapid disease progression, and the latter with disease onset after 1 year of age and slower progression (Taverna 2020). Patients experience slow and progressive loss of muscle function, culminating in the need for ambulatory and ventilatory support (Kishnani 2004, Kishnani 2006). In addition, the debilitating clinical features of Pompe disease lead to a reduced health-related quality of life (HRQoL) and a shortened lifespan, and as well places a major burden on carers and family members of patients.

Pompe disease is an autosomal recessive condition caused by pathogenic mutations in the gene for acid α-1,4-glucosidase (*GAA*) that result in a deficiency of GAA (Meena 2020), an enzyme responsible for the degradation of glycogen within the lysosome (Harlaar 2019). Deficiency of GAA leads to the accumulation of lysosomal glycogen in nearly all tissues, with clinical symptoms typically presenting as a result of glycogen accumulation in skeletal, cardiac and smooth muscles (Lim 2014, van der Ploeg). Glycogen accumulation causes enlargement and rupture of the lysosomes (Thurberg 2006, Lim 2014, van der Ploeg 2017), which displaces the contractile elements of muscle fibres, leading to fibrosis, loss of function and irreversible muscle damage (Lim 2014, Al Jasmi 2015).

5.1.1.1. Disease presentation

The presentation of Pompe disease – including age of onset, organ involvement, severity and rate of progression – can differ among patients, leading to a clinical spectrum of disease severity. This is caused by genetic variation, as more than 580 different inherited mutations in the *GAA* gene have been detected (van der Ploeg 2017). Pompe disease is broadly categorised into two main types (Table 1) (Taverna 2020):

- IOPD, with disease onset at younger than one year of age and presenting more urgently with cardiomegaly and associated cardiac issues; this is the most severe and rapidly progressing form (van den Hout 2003, Kishnani 2006). IOPD has been further characterised as classical or non-classical; although in classic IOPD, symptoms become apparent within the first few months (typically about 4 months) followed by rapid disease progression, non-classical IOPD presents less severely within the first year of life (Winkel 2005).
- LOPD, with disease onset after 1 year of age and slower progression, most significantly affecting skeletal muscles and leading to worsening pulmonary function and eventual respiratory failure (Kishnani 2006, Taverna 2020). LOPD is the focus of this submission.

LOPD encompasses the broad spectrum of phenotypes that present after 1 year of age and those that present within 1 year of age without cardiac manifestations (Park 2021). Most patients with LOPD initially experience slow, progressive loss of muscle function, typically starting with the trunk and lower limbs. Consequently, patients may experience instability in their gait, problems with walking and difficulty climbing stairs (Winkel 2005, van der Ploeg 2017), as well as gastrointestinal issues including abdominal discomfort, chronic diarrhoea or constipation, and poor weight gain (Chan 2017). As a patient's disease progresses, they may experience deterioration of the diaphragm and other muscles involved in respiration, leading to difficulties in feeding, swallowing and breathing (Kishnani 2004, Kishnani 2006). Over time, progressive loss of muscle function in patients may lead to organ failure and the need for ventilatory and ambulatory support (Kishnani 2004, Kishnani 2006). Some patients may experience dysfunction of the respiratory muscles before deterioration of motor function (e.g. limp-girdle weakness) (Boentert 2016a), with approximately one-third of patients requiring ventilatory support prior to wheelchair dependence (Boentert 2016b). Cerebrovascular abnormalities, including

dolichoectasia of the basilar artery, white matter lesions, microbleeds and aneurysms, may also present in patients with Pompe disease (Hensel 2018).

Table 1: Types of Pompe disease

Clinical spectrum				
Subtype	**IOPD**		**LOPD**	
	Classic (CRIM-positive and CRIM-negative)	**Non-classic (CRIM-positive)**	**Juvenile-onset**	**Adult**
Age at onset	0 to ≤ 1 year	Usually 0 to ≤ 1 year	1 to < 18 years	≥ 18 years
GAA deficiency	Complete or near complete; < 1% residual GAA activity	Partial	Partial; 2–40% residual GAA activity	Partial; 2–40% residual GAA activity
Cardiomyopathy	Significant	None/not persisting and progressive	None/not persisting and progressive	None
Evolving views	Pompe disease is considered a continuous spectrum of phenotypes rather than two discrete subtypes. Clinically severe and rapidly progressive phenotypes in infants younger than 1 year of age with hypertrophic cardiomyopathy are now considered classic IOPD, and the less severe, slowly progressive phenotypes as LOPD (Güngör 2013). Atypical infantile, juvenile-onset and non-classic IOPD are a few of the terms used to describe paediatric patients with Pompe disease who do not have significant and progressive hypertrophic cardiomyopathy characteristic of IOPD; hence, their phenotype is more closely comparable to LOPD (Park 2021). Therefore, it may be more prudent to characterise all individuals with disease onset before 1 year of age without cardiomyopathy and all those with onset after age 1 year as LOPD (Park 2021).			

Abbreviations: CRIM, cross-reactive immunological material; GAA, acid α-1,4-glucosidase; ; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease.
Source: (Güngör 2013, Taverna 2020, Park 2021)

Without treatment, patients with LOPD typically experience a shortened lifespan, with a median age of death of 56 years as reported in an international observational study conducted in Australia, Canada, Germany, the Netherlands, the UK and the USA from 2002 to 2009 (Güngör 2011). This is lower than the recorded life expectancy for the general population in Europe (females, 83 years; males, 76 years) (Eurostat 2021) and the USA (females, 81 years; males, 76 years) (Arias 2014) in 2009. Patients with untreated LOPD reported a significantly lower HRQoL than the general population with regard to physical and general health, vitality and social functioning (all $p < 0.001$), as measured by the 36-item Short-Form Health Survey (SF-36) (Hagemans 2004, van der Ploeg 2017). The difference was most profound for the physical functioning scale, with an adjusted mean score among patients of 29.3, compared with 83.1 (standard deviation [SD] not reported) in the general population.

Treatment with the current standard of care ERT, alglucosidase alfa (Myozyme®/Lumizyme®, Sanofi Genzyme), has had a substantial impact on reducing mortality in patients with LOPD, resulting in an approximately fivefold lower mortality compared with untreated patients (rate ratio, 0.21; 95% confidence interval [CI], 0.11, 0.41 [country not reported]) (van der Ploeg 2017). However, substantial morbidity persists in most patients across the disease spectrum (van der Ploeg 2017). Patients can experience a secondary decline in pulmonary function, muscle function and muscle strength after 2–3 years of alglucosidase alfa treatment (Semplicini 2020), and up to 24% and 30% of patients with LOPD do not demonstrate any initial benefit or stabilisation in 6MWD or FVC, respectively (van der Ploeg 2017). Consequently, the variable effectiveness of alglucosidase alfa represents a major issue for patients with LOPD, most of whom will have received the same treatment for several years with declining effectiveness. These patients represent a population with a substantial unmet need for effective treatments.

5.1.1.2. Mortality

For patients with untreated LOPD, mortality varies depending on the rate of disease progression and the extent of respiratory involvement and presence of other comorbidities, and can extend from early childhood to late adulthood (Kishnani 2004, Kishnani 2006). Respiratory failure is the main cause of morbidity and mortality in patients with untreated LOPD (Kishnani 2004, Winkel 2005, Kishnani 2006), accounting for more than 70% of deaths (Johnson 2016).

A targeted literature review (York Health Economics Consortium 2020b) commissioned by Amicus identified seven studies that reported mortality data; three among people with IOPD, three among people with LOPD and one in a mixed IOPD and LOPD population. Table 2 summarises the mortality data from the four studies investigating patients with LOPD.

Güngör *et al.* (2011) analysed data from 268 patients in a prospective international observational study conducted from 2002 to 2009. The median age at diagnosis and at study entry was 38 years and 48 years, respectively.

In a further study conducted by Güngör *et al.* (2013) that included 283 adult patients with untreated LOPD, 46 patients (61% [n = 28] of whom had never received ERT with alglucosidase alfa) had died at follow-up (median, 6 years; range, 0.04–9 years), with 21 deaths (46%) attributed, or possibly attributed, to LOPD. The association between disability level and risk of death was statistically significant for both wheelchair use and respiratory support (hazard ratio [HR], 5.32; 95% CI, 2.25, 12.56; $p < 0.001$) (Güngör 2013).

Table 2: Summary of mortality data

Study name/ Countries	n	Study design	Intervention	Dose	Time point of assessment, weeks	Experiencing mortality event at follow-up, n/N (%)
LOPD						
(Koeberl 2018) *The USA*	13	RCT	ERT + clenbuterol	ERT: 20 mg/kg Clenbuterol: 80 µg	52	0/8 (0)
			ERT + placebo	ERT: 20 mg/kg	52	0/5 (0)
(van der Ploeg 2010) *France, the Netherlands, the USA*	90	RCT	Alglucosidase alfa	20 mg/kg	78	1/60 (1.67)
			Placebo	NA	78	0/30
(Güngör 2013) *International (Australia, Canada, Germany, the Netherlands, the UK, the US)*	283	Cohort study	ERT	NR	NR	36/204 (17.6)
			No ERT	NR	NR	28/79 (35)
IOPD and LOPD						
(Wyatt 2012) *The UK*	IOPD; Early onset: 12 Late onset: 3 LOPD: 62	Case series	Alglucosidase alfa	NR	NR	1/77 (1.3)

Abbreviations: ERT, enzyme replacement therapy; IOPD, infant-onset Pompe disease; LOPD, late-onset Pompe disease; LOTS, Late-Onset Treatment Study; NA, not applicable; NR, not reported; RCT, randomised controlled trial.

5.1.1.3. Risk factors and biomarkers

Pompe disease is inherited in an autosomal recessive pattern; the most common scenario is a child born to two parents who are both carriers (one variant copy, or allele) of the *GAA* gene (Leslie and Bailey 2007, Taglia 2011, 2020). Their children have an equal 25% chance of being unaffected or of inheriting Pompe disease, and a 50% chance of being a carrier. Most carriers do not have signs or symptoms of Pompe disease but can pass it to their children (Leslie and Bailey 2007, Taglia 2011, 2020).

Biomarkers such as urine hexose tetrasaccharide (Hex4), Creatine Kinase (CK) or urinary glucose tetrasaccharide (Glc_4) are important non-invasive monitoring tools in the multidisciplinary management of Pompe disease; however, they are unable to determine the location and extent of accumulated glycogen (Kishnani 2012). Hex4, CK and urinary Glc_4 and their use in monitoring LOPD progression, are further explained in 5.1.1.4 below. Neuromuscular experts confirmed at several global advisory boards conducted by Amicus that very little data are available in neuromuscular diseases to support biomarkers predictive of future disease progression.

5.1.1.4. Measurable clinical parameters in Pompe disease

Pompe disease is a multisystemic, heterogenous and progressive disease affecting muscle strength and motor and pulmonary functions. The management of Pompe disease requires continual monitoring of clinical parameters to assess disease progression in patients irrespective of ERT use. Monitoring involves frequent laboratory and functional outcome assessments, including those outlined in Table 87 in Appendix S – Pompe disease-related parameters routinely measured in clinical practice. These parameters also form the endpoints of the pivotal, phase 3 PROPEL randomised controlled trial (RCT) (Schoser 2021a) that assessed the efficacy of the two-component ERT cipaglucosidase alfa/miglustat in patients with LOPD against the standard of care, alglucosidase alfa/placebo (Section 7). The use of different clinical parameters is required to determine the efficacy of ERT because not all late-onset patients respond in the same way (Angelini 2009).

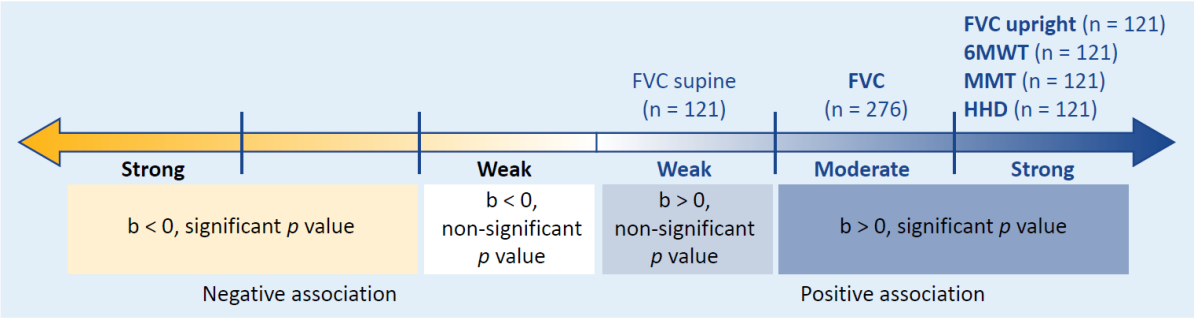
5.1.1.4.1. Correlation between clinical parameters

Correlations have been shown between functional measures in Pompe:

- **6MWD** was shown to have a statistically significant correlation with the following functional measures: GSGC, 4-stair climb test, time to walk 10 minutes, Walton and Gardner-Medwin (WGM) score, Fatigue Severity Scale (FSS) and FVC (Amicus Therapeutics 2021a)
- **FVC** was shown to have a statistically significant correlation with the following functional measures: maximum inspiratory pressure (MIP), Modified Medical Research Council dyspnea scale, WGM score, 6MWD, peak cough flow and forced expiratory volume in one second (Amicus Therapeutics 2021a)
- **SF-36** physical component summary was shown to be statistically significantly correlated with 6MWD, upright FVC, manual muscle test (MMT) and hand-held dynamometry, which highlights that improvements in functional measures such as 6MWT and FVC translate into improvements in HRQoL of the patients (Amicus Therapeutics 2021a)
- Findings from a literature review conducted by Amicus Therapeutics in 2021 showed that, across the various rare muscular, skeletal, and neurodegenerative diseases analysed, strong and statistically significant associations were found between physician-measured functional outcomes, such as 6MWD and % predicted FVC, and patient-reported HRQoL (Figure 1 and Figure 2) (Shohet 2021).

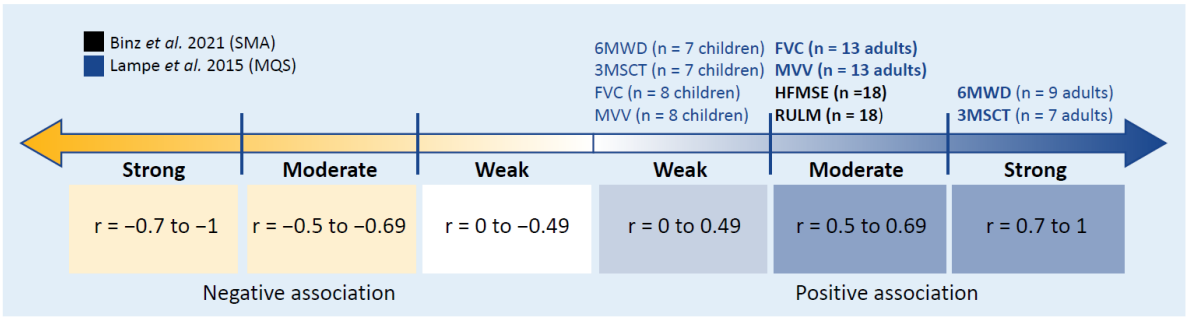
There are few studies that provide the long-term (5–10 years) progression of 6MWT/FVC and associated improvements in morbidity, mortality and HRQoL in patients with related neuromuscular and respiratory disorders (Amicus Therapeutics 2021a). Furthermore, Amicus Therapeutics is currently conducting a real-world evidence study in Sweden, which aims to provide insight on the disease burden, treatment patterns, and resource use utilisation associated with Pompe disease in the Nordics (See section 7.1.1.1).

Figure 1: Correlations between functional measures and SF-36-PCS in Pompe disease



Note: Reported associations are based on regression coefficients. Bold indicates a statistically significant indication.
Abbreviations: 6MWT, 6-minute walk test; FVC, forced vital capacity; HHD, hand-held dynamometry; MMT, manual muscle test; SF-36 PCS, 36-item Short-Form Health Survey Physical Component Summary.
Source: (Shohet 2021)

Figure 2: Correlations between functional measures and EQ-5D-5L in spinal muscular atrophy and Morquio syndrome (MPS IV)



Abbreviations: 3MSCT, 3-minute stair/climb test; 6MWT, 6-minute walk test; EQ-5D-5L, 5-dimension, 5-level EuroQol questionnaire; FVC, forced vital capacity; HFMSE, Hammersmith Functional Motor Scale Expanded; MVV, maximum voluntary velocity; RULM, Revised Upper Limb Module.
Source: (Shohet 2021)

5.1.1.4.2. Clinical meaningfulness of parameters

Minimal clinically important difference (MCID) in relation to 6MWD and % predicted FVC is not established in Pompe disease. Additionally, thresholds for clinically relevant changes in 6MWD and % predicted FVC are not established in Pompe disease. In addition, data reported in other conditions often do not take into account the differences expected due to previous treatment or baseline values. In the absence of established thresholds for clinically meaningful within-patient change used, the parameters for MCID were defined based on the literature for comparable instruments in similar disease populations: 6MWD in patients with MPS IV syndrome (Schrover 2017); FVC in patients with idiopathic pulmonary fibrosis (du Bois 2011) and Pompe disease (Lachmann 2013); and MMT in patients with myopathy (Baschung Pfister 2018).

Amicus has incorporated input from clinical experts and adults with Pompe disease to ensure that the PROPEL study investigated patient-centric and clinically meaningful endpoints, while remaining scientifically robust and highly relevant for cost-effectiveness decision making. For example, in patient advisory boards, people with Pompe disease noted that improvements in muscle strength, respiratory function, and QoL were most important to them, with motor and muscle function endpoints being transferrable to the ability to carry out daily tasks (Amicus Data on file 2015, Amicus Data on file 2018). Motor, respiratory and muscle function, were therefore measured in the trials (Amicus data on file 2019).

The clinical expert consulted in Denmark confirmed that 6MWD and % predicted FVC are important outcome measures in Pompe disease, which should also be used when assessing long-term efficacy of therapy; patients with Pompe have also considered these outcomes relevant. The clinical expert in Sweden also pointed out that small changes in the short-term can extrapolate to an important change long-term: even a 1% annual

improvement or stabilization of symptoms long-term (over a decade) can impact delaying the need for ventilation and or motor support (List of experts, section 11). The parameters for MCID in the PROPEL trial are outlined in Table 3.

Table 3: Thresholds for clinically meaningful within-patient change used in PROPEL SAP/CSR

Clinical outcome	Declining	Stable	Improving
6MWD	< −6%	−6 to < +6%	≥ +6%
% predicted FVC	< −3%	−3 to < +3%	≥ +3%
MMT lower extremity score	< −7%	−7 to < +7%	≥ +7%

Abbreviations: 6MWD, 6-minute walk distance; CSR, clinical study report; FVC, forced vital capacity; MMT, manual muscle testing; SAP, statistical analysis plan.
Source: (du Bois 2011, Lachmann 2013, Schrover 2017, Baschung Pfister 2018)

5.1.1.4.3. Validation of clinical measures

The reliability and validity of the 6-minute walk test (6MWT) has been assessed by evaluating correlation of 6MWT with other outcomes—e.g., MMT scores and FVC—and has been confirmed in patients with similar diseases to Pompe disease including ambulatory spinal muscular atrophy (Dunaway Young 2016), hypophosphatasia (Phillips 2019), and Duchenne muscular dystrophy (DMD) (McDonald 2013). Additionally, patient-reported outcomes (PROs) that can be widely applicable for use in patient-focused drug development or clinical trials are not yet validated for all diseases. The construct and content validity of selected PROs used in Pompe disease have been outlined below.

The Rasch-built Pompe-specific Activity (R-PAct) scale was constructed as a patient-based interval scale using Rasch analysis, specifically suited to quantify the effects of Pompe disease on patients' ability to carry out daily life activities and on their social participation (van der Beek 2013). The scale was tested by 186 patients with Pompe disease 16 years of age and older between 2005 and 2011, and was externally validated through correlation with the Medical Research Council sum score, the Rotterdam Handicap Scale (RHS) and test-retest reliability in a subgroup of 44 patients (van der Beek 2013). The MCID standard error (SE) was calculated at each assessment for each participant. The cut-off for a clinically important change (both in improvement and deterioration) was defined as ± 1.96 SE, as previously determined in patients with multiple sclerosis, and used to show clinically meaningful changes over time (van der Beek 2013). The value of R-Pact in estimating disease progression, the most appropriate time to initiate treatment and to evaluate therapeutic efficacy has also been indicated.

The construct and validity of five Patient-Reported Outcomes Measurement Information System (PROMIS®) questionnaires were compared with clinically relevant outcome measures in 30 patients with LOPD, including 6MWD, FVC and MMT (Harfouche 2020). The findings of this comparison alongside reports from the Amicus Pompe Disease Patient Advisory Board suggested that clinical outcome measures assess concepts important to patient-reported experiences and are meaningful to the patient (Harfouche 2020). However, further longitudinal studies including other PROMIS questionnaires, other measures of motor function and HRQoL, and a larger patient sample should be conducted (Harfouche 2020).

The RHS applicability for use in Pompe disease has been evaluated in a study investigating the impact of LOPD on participation in daily life activities in 257 adult patients from different countries (Hagemans 2007a). The RHS correlated significantly with all subscales of the SF-36, except for the mental health domain, and the internal consistency of the RHS was good with a Cronbach's α of 0.87 in the overall group, suggesting that the RHS is suitable for measuring the impact of LOPD on patients' lives (Hagemans 2007b).

The Subject Global Impression of Change (SGIC) identifies a patient-reported change that has clinical relevance for the individuals receiving treatment. Studies have found that the patient global impression is sensitive to change and correlates with patient satisfaction (Hui 2016). The SGIC has also been used in recent Pompe studies

(Berger 2019), including as an anchor to estimate patient-relevant change in % predicted FVC (Berger 2019), although it has not been validated in Pompe.

5.1.2. Epidemiology

Pompe disease is rare, with a globally estimated predicted prevalence of approximately 1 in 27 800 people (Scott 2013), resulting in an orphan drug designation in the EU and in other countries with Committee for Orphan Medicinal Products (COMP) designation (European Commission 2021): the maximum prevalence threshold in the EU is 1 in 2000 people (European Medicines Agency 2021b) (TGA 2021).

To date, there are no published global studies of the incidence of Pompe disease, and Pompe disease prevalence estimates by region are limited and vary by ethnicity, geography, and diagnostic approach.

It is also reasonable to assume that the actual prevalence of LOPD may be higher, possibly owing to delays in diagnosis as well as misdiagnosis (Hobson-Webb 2012). Symptoms related to LOPD, such as slowly progressive limb-girdle and/or respiratory muscle weakness, are often not easily distinguishable from other myopathies with proximal weakness and may be misdiagnosed as limp-girdle dystrophy or facioscapulohumeral dystrophy (Hobson-Webb 2012, Pérez-López 2015, Chu 2016).

5.1.2.1. Incidence and prevalence

A low incidence of LOPD has been reported in studies conducted in the Nordic region—in Western Sweden, Western Denmark, and Finland—possibly stemming from the ethnic stratification (Meznaric 2019).

In Denmark, it is estimated that there are currently around 20 patients diagnosed with Pompe disease (both LOPD and IOPD), of which almost all are treated with enzyme replacement therapy (Lægehåndbogen 2021). [redacted] patients from Denmark were enrolled in the market authorization study (PROPEL) for cipaglucosidase alfa/miglustat and have transferred to an open label long-term follow-up study.

Clinical experts in Denmark (List of experts, Section 11) estimated that there are 15-20 patients with LOPD disease living in Denmark today (as of November 2022).

5.1.3. Patient populations relevant for this application.

The relevant patient population for this application is adult patients (age 18 years and older) with a confirmed diagnosis of LOPD.

5.1.3.1. Estimated number of patients eligible for treatment in Denmark

Table 4: Estimated number of patients eligible for treatment with cipaglucosidase alfa/miglustat

Year	2023	2024	2025	2026	2027
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.1.4. Disease burden

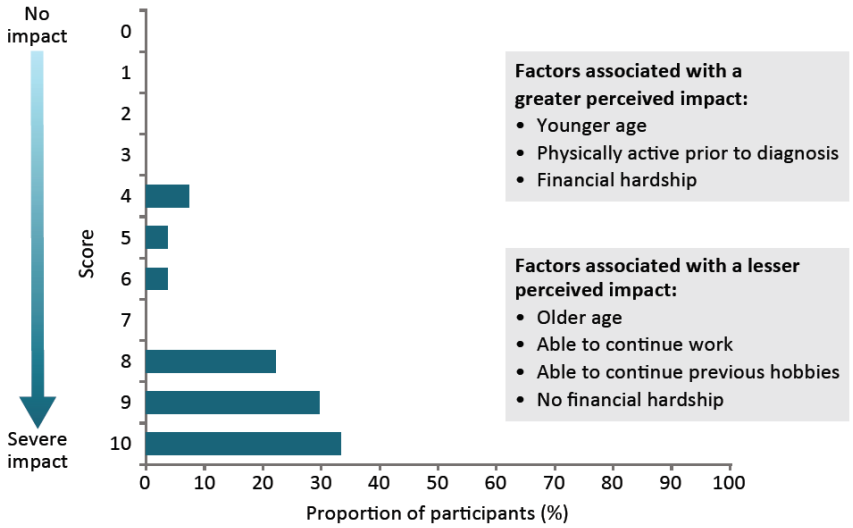
5.1.4.1. Health-related quality of life in patients living with Pompe disease is worse than the general population

Patients with LOPD experience debilitating symptoms, including respiratory, limb and trunk weakness, fatigue, pain and exercise intolerance that impacts their participation in daily activities, resulting in reduced social participation and an impaired sense of general well-being (Güngör 2011, Toscano 2013, Chan 2017, Iolascon 2020, Yuan 2020). When compared with the general population in several international and country-specific studies, patients with untreated LOPD reported a significantly worse HRQoL with regard to physical functioning, physical role functioning, general health, vitality and social functioning, leading to an increased risk of depression

and anxiety, as measured by instruments including the World Health Organization Quality of Life: Brief Version (WHOQOL-BRE) and the Nottingham Health Profile (Güngör 2013, Aslan 2016, van der Ploeg 2017, Schoser 2019, Chen 2021).

Muir *et al.* (2021) conducted in-depth interviews with patients living with LOPD in the UK to elucidate the psychological and emotional impact of the diagnostic process and of living with LOPD. When patients were asked to score the impact of Pompe disease on their lives on a scale of 0–10 (0, no impact; 10, severe impact), the mean (SD) score was 8.5 (1.8) for the interim analysis (Figure 3) (Muir 2019).

Figure 3: Perceived impact of LOPD on patients' lives



Abbreviations: LOPD, late-onset Pompe disease
N = 27 patients
Source: (Muir 2019)

5.1.4.2. Utility values

See Appendix U – Utility values.

5.1.4.3. Symptoms impact patients' health-related quality of life

Owing to deteriorating physical conditions, especially in those without treatment, it is highly probable that patients living with Pompe disease become disconnected from social life and experience psychological barriers and stress that prevent them from actively engaging with others (Chen 2021). The painful process of learning, coping and adapting to disease-related psychology could induce humanistic burden on the patient and caregivers and lead to reduced family roles (Chan 2017, Chen 2021).

Fatigue caused by chronic respiratory insufficiency can have a profound and disabling impact on the lives of patients with LOPD, increasing the risk of depression (Toscano 2013, Chan 2017). In an international study involving 265 adult patients with LOPD, approximately two-thirds (65%) reported that fatigue was one of their most disabling symptoms, demonstrated by a statistically significantly higher mean score on the FSS reported by patients living with LOPD than the general population (5.2 vs 2.9, respectively; $p < 0.001$) (Hagemans 2007b).

5.1.4.4. Impact of Pompe disease on day-to-day living

Work and study are substantially affected in patients living with Pompe disease. In a large international study of 257 patients with LOPD, the ability of patients to fulfil their work or study was hampered, with 40% of patients indicating they were not able to return to their prior job or study, and 9% could only work partially (Hagemans 2007a). This can lead to psychiatric challenges resulting from having to cope with potential financial issues (Chan 2017). Patients may also experience difficulties with communication and social interactions owing to speech

impairments, including articulation and phonation (Kishnani 2006). Furthermore, the need for physical support, including invasive/non-invasive ventilation and wheelchair use, substantially impacts the lifestyle of the patient as well as that of their carers, family and friends.

Real-life stories from Danish patients living with Pompe disease can be found on the Danish Pompe Association website (Pompeforeningen i Danmark 2023).

5.1.4.4.1. Pompe patient testimonials captured in patient advisory boards and from patient group insight

Medical advisory boards and patient advisory boards were conducted to solicit feedback from adults with Pompe disease on study design and endpoints throughout the development programme. In patient advisory boards, people with Pompe disease noted that improvements in muscle strength, respiratory function and QoL were most important to them, with motor and muscle function endpoints being transferrable to the ability to carry out daily tasks (Amicus Data on file 2015, Amicus Data on file 2018). Participants also noted that muscle weakness and fatigue are markers of disease progression and can result in a decline in the ability to perform daily activities. Motor, respiratory and muscle function, were therefore measured in the trial (Amicus data on file 2019). The secondary endpoint of change from Baseline in FVC % predicted in the PROPEL trial reflects adults' with LOPD priority for a treatment that preserves their pulmonary function:

"*I think for me, one of the most important things for therapy is preserving pulmonary function, because that is tied in with so many things that one does from talking and being able to sleep comfortably, to being able to move and to exercise and to just enjoy everything about life. So for me, that's one of the daunting things about Pompe disease is thinking about the loss of pulmonary function*."– Woman living with LOPD (Byrne 2022).

5.1.4.4.1.1. About living with Pompe disease and its wider impacts

About the impact on carers and the pain associated with Pompe disease:

"It must be said that I get an enormous amount of help from my sweet husband and our family. Without them, I don't know what I would do. Because I don't have much energy and I get pain very easily if I overuse my strength." – Danish patient reporting on patient advocacy organisation website (See Figure 3 above on how UK patients scored the impact on LOPD on their lives) (Pompeforeningen i Danmark 2023).

About the downstream effects of reduced muscle strength:

"My legs and core are the most impacted. I struggle with steps, bending over and picking things up. Picking up something from the floor is almost impossible for me." – May 2020 Patient Advisory Board.

Similar benefits noted by patients have been described in the UK where patients taking part in an early access program have reported reduced "brain fog" and reliance on pain medication [A Ochoa-Ferraro WORLD 2023].

5.1.4.5. Impact of Pompe disease on carers, families and friends

Pompe disease places a burden on both patients and families, resulting not only from the decline in mental and physical health associated with a chronic disease, but also social and relational issues, the impact of which is frequently underestimated by physicians (van der Ploeg 2017). Knowledge of the social consequences of the disease is extremely important with respect to therapeutic goals, cost estimation and reimbursement (Hagemans 2007a).

5.1.4.6. Comorbidities and complications

Patients with LOPD are also at risk of comorbidities/complications (Kishnani 2006), including respiratory infections such as atelectasis and pneumonia stemming from an inability to sufficiently clear pulmonary secretions (Kishnani 2006, Jones 2019). Additionally, difficulty chewing and swallowing can result in aspiration pneumonia and weight loss due to insufficient caloric intake (Kishnani 2006).

5.1.4.7. Monitoring

The need for close monitoring of disease progression in children and adults irrespective of the presence of symptomatic disease adds to the burden of the patient, carers and society (Hagemans 2006, Johnson 2016), with the requirement for frequent laboratory and functional outcome assessments, which contribute to the utilisation of healthcare resources (Echaniz-Laguna 2015, van der Ploeg 2017).

5.1.5. Unmet need

5.1.5.1. Patient and carer

The impact of Pompe disease on patients' HRQoL and social participation in daily life is substantial, and their physical health status is reduced compared with the general population (Hagemans 2004, van der Ploeg 2010, Vielhaber 2011). A disease characterised by progressive and debilitating weakening of the limbs and respiratory muscle, LOPD can result in an inability to function day to day without support such as invasive/non-invasive ventilation and wheelchair use (National Institute for Rare Disorders 2020). Patients often struggle with domestic tasks, indoor mobility and performing independent indoor leisure activities (Hagemans 2007a), and the painful process of learning, coping and adapting to disease contributes to the psychological burden faced by the patient and their caregivers (Chan 2017, Chen 2021), Fatigue caused by chronic respiratory insufficiency has a profound and disabling impact, increasing the risk of depression**,** with patients often experiencing the feeling of hopelessness, a sense of being marginalised and negative self-image (Chen 2021). Furthermore, many patients are limited in their ability to work or study (Hagemans 2007a), which can lead to psychiatric challenges due to having to cope with potential financial issues (Chan 2017). Their deteriorating physical condition also means patients become disconnected with social life and experience psychological barriers and stress that prevents them actively engaging with others, especially for those without treatment (Chen 2021).

In addition, a 2022 survey to UK Pompe patient support organisations (Association for Glycogen Storage Disease & Pompe Support Network) member, aimed at obtaining numerical data on key issues affecting UK LOPD patients, showed that [redacted].

[redacted]: [redacted]

[redacted]

5.1.5.2. Societal

Patients living with Pompe disease who are of working age either have to stop working or face a significant decline in productivity due to the symptom burden (Schoser 2019). Not only does this contribute significantly to indirect costs, but it is also likely to have wider societal implications in terms of reduced output. Furthermore, the need for support, including invasive/non-invasive ventilation, for patients with progressive disease symptoms not only impacts the patient themselves, but can require modifications to the patient's home and workplace, the impact of which extends to carers, family, friends and colleagues (Pompe Disease News 2018).

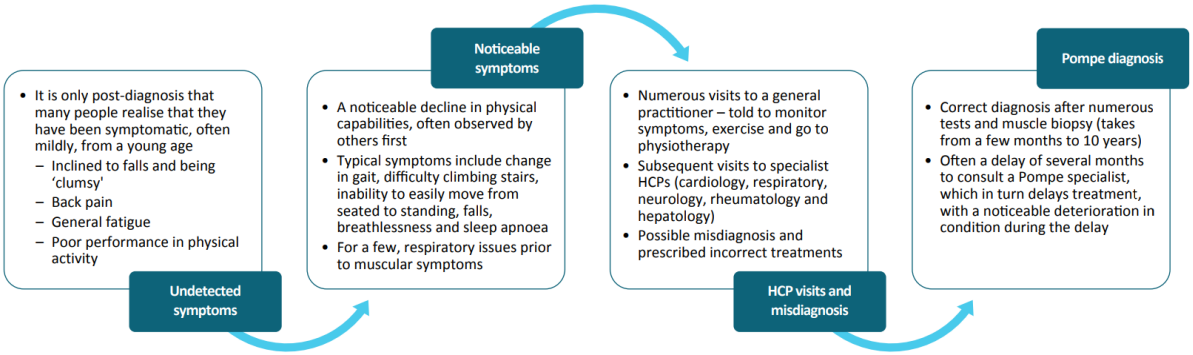
5.2. Current treatment options and choice of treatment

5.2.1. Diagnosis

Owing to the rarity of the condition and the relatively non-specific nature of the phenotypic features, diagnosis is challenging (Figure 5) and may only lead to suspicion of Pompe disease in aggregate (Kishnani 2006). In addition, the slow-evolving nature of LOPD means that there may be some indication in early adolescence before full disease onset that manifests as a spectrum of symptoms often overlapping with clinical features of other neurological diseases. Consequently, LOPD is often overlooked, with diagnosis delayed approximately 7–10 years, resulting in a lower baseline physical functioning level at diagnosis and subsequent treatment initiation

(Chu 2016, Lukacs 2016, Musumeci 2016, Chan 2017, McIntosh 2017, Semplicini 2018). Several key findings are suggestive of LOPD, including an at least a 10% drop in % predicted FVC from seated to supine position, proximal pattern of muscle weakness, electromyography (EMG) changes, and elevated CK and Hex4 (American Association of Neuromuscular & Electrodiagnostic Medicine 2009).

Figure 5: Typical stages of the diagnostic journey



Abbreviations: HCP, healthcare professional.
Source: (Muir 2021)

International monitoring and treatment guidelines recommend that diagnosis of Pompe disease is certified by genetic testing in Europe (van der Ploeg 2017). Current treatment options aim to delay or compensate for significant respiratory muscle weakness, both to improve overall HRQoL and avoid life-threatening complications; early diagnosis is therefore crucial to allow patients to receive treatment and slow disease progression (Boentert 2016b). This approach is supported by growing evidence that the early treatment of LOPD, prior to possible irreversible muscle damage, is more efficacious than later treatment (Kishnani 2009, van der Ploeg 2010, Chien 2015, Lukacs 2016, McIntosh 2017).

As with most rare genetic diseases, the feasibility and cost-effectiveness of new born screening (NBS) for Pompe disease remains a complicated issue, involving relatively high false-positive rates, the need for long-term follow-up and management of patients with a positive result, as well as genetic counselling for parents and carers (Chu 2016, Semplicini 2018). Consequently, there is a lack of universal consensus, and screening for LOPD is not practised worldwide (Chu 2016). Overestimation of prevalence of symptomatic disease-based genetic screening also poses an issue – it may therefore be more prudent to screen using enzymatic activity assays at first screening instead (McIntosh 2017, Semplicini 2018).

Table 5: International guidelines and consensus statements for the management of Pompe disease

Region/area (year of publication)	Diagnosis
Europe (van der Ploeg 2017, van Kooten 2020)	Diagnosis of Pompe disease must be performed by a certified laboratory and confirmed by enzyme analysis in leucocytes, fibroblasts or skeletal muscle and/or genetically by mutation analysis prior to treatment initiation To avoid the risk of initiating ERT in patients later found not to have Pompe disease, confirmation by both enzymatic and genetic testing is preferable. However, the authors note the need for accurate searching for mutation because it can be inconclusive owing to the detection of new variants of unknown pathogenicity Although DBS is available and is a good test for screening for Pompe disease, it always requires diagnostic confirmation

Abbreviations: DBS, dried blood spot; DNA, deoxyribonucleic acid; ERT, enzyme replacement therapy.

See Appendix P – Diagnostic path and disease management in Pompe disease Denmark, for a visual representation of the diagnostic journey for patients with Pompe disease in Denmark provided by a local expert in an Amicus steering committee (Section 11 List of experts).

5.2.2. Current treatment options

Alglucosidase alfa was the first ERT approved for use in Pompe disease by the EMA in 2006, and has since been considered the standard of care in Pompe disease (Section 5.2.2.3.1) (European Medicines Agency 2020). In August 2021, the ERT avalglucosidase alfa was approved as a treatment option by the USA FDA, and by the EMA in June 2022 as long-term ERT for the treatment of patients with Pompe disease (acid α-glucosidase deficiency) following receipt of a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in July 2021 (European Medicines Agency 2022). Avalgalucosidase alfa is not reimbursed in Denmark and therefore not considered as a comparator in this dossier (see Section 7.1.5 for a comparative analysis of avalglucosidase vs cipaglucosidase alfa/miglustat).

ERT is not curative – instead, the aim is to prolong survival and delay or address disease-specific and symptomatic complications, improving overall HRQoL (Section 5.2.2) (Boentert 2016a, Boentert 2016b). Furthermore, the effectiveness of alglucosidase alfa has been shown to diminish over time (Semplicini 2020). The reasons for the limited effectiveness of alglucosidase alfa are explained further in Section 5.2.2.3.1.

5.2.2.1. Supportive care

Additional supportive care is a fundamental feature of the treatment plan owing to the limited and non-curative nature of therapies currently available for Pompe disease. It is required to address disease-specific and symptomatic complications that affect activities of daily living (ADLs), including respiratory and cardiac problems, physical disability and difficulty swallowing. Auxiliary care is also the only available treatment pathway for patients who are unable to tolerate, or do not respond to, ERT. Frequently required supportive therapies are outlined in Figure 6. The management of Pompe disease involves the coordinated efforts of a team of specialists, including experts in metabolic diseases, cardiology, pulmonology, neurology, anaesthesiology, urology, immunology and nutrition (Kronn 2017).

Figure 6: Therapies and supportive measures

Patients with Pompe disease are at risk of requiring respiratory support during the course of their disease owing to varying degrees of respiratory failure. This may include physical therapy or mechanical ventilation (non-invasive or invasive) during the night and/or periods of the day, or during respiratory infections (National Institute for Rare Disorders 2020).

Non-invasive ventilation is required to relieve symptoms of LOPD such as morning headache, daytime somnolence and fatigue (Johnson 2016). prevent nocturnal hyperventilation and improve night-time saturation, sleep-related respiratory disorders and HRQoL. Although mechanical devices may improve survival, they do not treat the underlying progressive respiratory weakness; consequently, there is increasing interest in the use of respiratory muscle training to target the inspiratory and/or expiratory muscles directly in patients with Pompe disease (Jones 2019).

To improve the strength and mobility of patients, physiotherapy is often recommended as well as orthopaedic devices such as braces, and surgery for contractures or spinal deformities may be required in some patients. Patients living with Pompe disease experiencing progressive loss of muscle function will require ambulatory support, such as the use of canes and walkers. Eventually some patients will need to use a motorised wheelchair, and mechanical hoists (National Institute for Health and Care Excellence 2022). In the multinational long-term real-world STIG study, 3 patients (4.4%) already required use of a wheelchair at baseline and an additional 9 patients (13.2%) became non-ambulatory in the course of the 14-year follow-up (Gutschmidt 2021).

LOPD, although primarily treated with ERT, also benefits from concomitant diet and aerobic exercise therapy (Kishnani 2012, Kishnani 2014, Angelini 2021). Inspiratory muscle training has also been associated with a positive effect on patients with LOPD who are receiving ERT (Kishnani 2014, Aslan 2016).

A clinical expert in Denmark confirmed that supportive care may constitute, for example, physiotherapy, as well as ventilation, mobility, and dietary support as discussed above. In addition to equipment, also significant staff resources may be required. Nurse support during nighttime can be required for some patients (Section 11 List of experts).

5.2.2.2. International treatment guidelines

For details, see Appendix R – International treatment guidelines.

5.2.2.3. Current pharmacological treatments

5.2.2.3.1. Alglucosidase alfa

Alglucosidase alfa (Myozyme®) is approved for the treatment of both IOPD and LOPD (Cupler 2012a, Al Jasmi 2015, Tarnopolsky 2016, van der Ploeg 2017). It is indicated as follows by EMA: for long-term ERT in patients with a confirmed diagnosis of Pompe disease; alglucosidase alfa is indicated in adults and paediatric patients of all ages (European Medicines Agency 2020).

Alglucosidase alfa originally received EMA approval in 2006 for use in patients with LOPD. Approval was based on a superiority study of alglucosidase alfa versus placebo that demonstrated a *p*-value of 0.06 for the first hierarchal primary endpoint of 6MWD, and $p < 0.05$ for the second hierarchical endpoint of FVC (21 October 2008) (US Food and Drug Administration 2010).

5.2.2.3.1.1. Efficacy of alglucosidase alfa

Alglucosidase alfa is a recombinant human enzyme, designed to replace missing GAA in patients with Pompe disease. The efficacy and safety of alglucosidase alfa were demonstrated in a randomised, double-blind, placebo-controlled, multicentre study (NCT00158600; Late-onset Treatment Study (LOTS]) in 90 patients with LOPD (van der Ploeg 2010). After 78 weeks, alglucosidase alfa was associated with a significant increase in both the 6MWD (+25.1 m vs −3.0 m; $p = 0.03$) and % predicted FVC (1.2% vs −2.2%; $p = 0.006$) compared with placebo (van der Ploeg 2010). However, in the longer term (after 2–3 years, depending on analysis) (Semplicini 2020, Gutschmidt 2021), many patients experience a decline in these outcomes. In 2020, the US National Institute for Rare Disorders (NORD) broadly agreed that alglucosidase alfa extends the life expectancy of patients with classic IOPD and that most patients with LOPD also benefit; however, it does not represent a cure and efficacy remains suboptimal (National Institute for Rare Disorders 2020).

As previously described in Section 5.2.2, Gutschmidt et al. 2021, reported a statistically significant 14.9% decline in % predicted FVC ($P < 0.001$) over the course of 10 years on alglucosidase alfa accompanied by a 33% increase in non-invasive or invasive ventilation (Gutschmidt 2021). In addition to this, some patients do not experience the initial benefit or stabilisation associated with alglucosidase alfa: it has been reported that up to 24% of patients with LOPD do not demonstrate any initial benefit or stabilisation in 6MWD, and up to 30% do not demonstrate any initial benefit or stabilisation of FVC (van der Ploeg 2017). Interestingly, Semplicini *et al*. noted

that, in a real-world analysis of patients enrolled in the French Pompe Registry between 2007 and 2019 who received treatment with alglucosidase alfa, those with a higher FVC at baseline (> 80% of normal value) had a marked decrease in FVC compared with those with an FVC of 51–79% or less than 50% of normal value (both $p < 0.001$) (Semplicini 2020).

Patients with LOPD who received initial treatment with alglucosidase alfa initially reported an improvement in the physical domains of HRQoL questions, which then remained stable, while the mental domains of HRQoL remained largely unchanged before and during ERT (Yuan 2020). Although alglucosidase alfa can improve or stabilise motor function difficulties, fatigue, daily activities and breathing (especially in the early stages of treatment), there is substantial heterogeneity in disease progression and response to treatment, and patients still report a lower HRQoL than typical population norms, with pain being largely unaffected by alglucosidase alfa (Güngör 2011, van der Ploeg 2017, Schoser 2019).

5.2.2.3.2. Avalglucosidase alfa

Avalglucosidase alfa (Nexviadyme®[EU]; Nexviazyme®[US];) is an ERT that is designed with an approximate 15-fold increase in M6P content compared with alglucosidase alfa. The M6P moieties are chemically conjugated via an oxime bond, with the aim of improving cellular uptake of GAA. (European Medicines Agency , Sanofi) The FDA approved avalglucosidase alfa for the treatment of patients with LOPD 1 year of age or older in August 2021, and EMA and the UK Medicines and Healthcare products Regulatory Agency (MHRA) approvals were received in June 2022 and July 2022, respectively. In August 2022, avalglucosidase alfa was recommended by NICE , within its marketing authorisation, as an option for treating Pompe disease in infants, children, adolescents, and adults, in England and Wales. Avalglucosidase alfa is currently not recommended in Denmark.

COMET was a randomised, double-blind, non-inferiority, phase 3 trial conducted at 55 sites in 20 countries that assessed the safety and efficacy of avalglucosidase alfa compared with alglucosidase alfa only in naive patients (3 years of age or older) with LOPD (Diaz-Manera 2021). At week 49, avalglucosidase alfa was associated with a mean (least-squares) improvement in upright % predicted FVC of 2.89% (SE, 0.88) compared with 0.46% (SD, 0.93) with alglucosidase alfa (Diaz-Manera 2021). Although non-inferiority to alglucosidase alfa was shown ($p = 0.0074$), superiority was not reached ($p = 0.063$) (Diaz-Manera 2021). Improvements were also seen in the secondary endpoint, 6MWD, with avalglucosidase alfa compared with alglucosidase alfa, with greater increases in distance covered (difference 30.01 m [95% CI, 1.33, 58.69]) and percent predicted (4.71% [95% CI, 0.25, 9.17]) (Diaz-Manera 2021). The results of the study provide evidence of clinically meaningful improvement with avalglucosidase alfa therapy over alglucosidase alfa in respiratory function, ambulation and functional endurance. An open-label extended-treatment period investigated the long-term safety and efficacy of avalglucosidase alfa (Diaz-Manera 2021).

5.2.2.3.3. Cipaglucosidase alfa/miglustat

Cipaglucosidase alfa/miglustat is a two-component therapy for LOPD that was granted EMA approval in March 2023 and June 2023 respectively. It received Breakthrough Therapy Designation from the FDA in 2019 (Amicus Therapeutics 2019), highlighting it as a promising therapy for patients living with Pompe disease who currently have a significant unmet need. The indication for cipaglucosidase alfa/miglustat is for the treatment of adults 18 years of age and older living with LOPD disease. The two-component therapy consists of cipaglucosidase alfa (ATB200), a novel rhGAA enzyme with optimised carbohydrate structures (particularly bis-M6P) that enhances its uptake into cells, co-administered with miglustat (AT2221), an oral pharmacological enzyme stabiliser. Miglustat selectively and transiently binds cipaglucosidase alfa, stabilising it in the unfavourable physiological pH of the blood; this minimises the loss of enzyme activity while in circulation. Table 6 highlights how cipaglucosidase alfa/miglustat is designed to overcome the key mechanistic challenges in delivering an rhGAA to skeletal muscle.

The clinical efficacy and safety of cipaglucosidase alfa/miglustat was investigated in the phase 1/2, open-label, single-arm study ATB200-02 (NCT02675465) in 29 adult patients with Pompe disease and in the phase 3 RCT PROPEL (Amicus Therapeutics; NCT03729362) in adult patients with LOPD, who either have previously received at least 24 months of alglucosidase alfa treatment (**ERT-experienced**) or who have not received previous treatment with alglucosidase alfa (**ERT-naïve**), compared with alglucosidase alfa/placebo (Section 7.1.2).

Table 6: Cipaglucosidase alfa/miglustat is designed to overcome three key challenges to delivering an rhGAA to skeletal muscle

Challenges delivering an rhGAA to skeletal muscle	How cipaglucosidase alfa/miglustat addresses three key mechanistic challenges
Highly efficient CI-MPR-mediated uptake to muscle is required owing to the low interstitial concentrations of rhGAA that can be obtained post infusion (Do 2019)	**Cipaglucosidase alfa is a bis-M6P-enhanced rhGAA designed for high affinity CI-MPR-mediated cellular uptake**
	Cipaglucosidase alfa is a next-generation bis-M6P-enhanced rhGAA (1.3 mol of bis-M6P per mol of enzyme) The high affinity of bis-M6P N-glycans for the CI-MPR mediates transportation of cipaglucosidase to the lysosomes (Tong 1989) Cipaglucosidase alfa has more bis-M6P N-glycans than alglucosidase alfa, with 95% being competent for intracellular delivery to lysosomes compared with 27% for alglucosidase alfa (Amicus data on file , Do 2019)
rhGAA processing (both proteolytic and N-glycan trimming) is required to achieve maximal enzyme activity toward glycogen	**Cipaglucosidase alfa can be fully processed into the mature and most active form of GAA against the substrate glycogen**
	Cipaglucosidase alfa is a human acid α-glucosidase produced in CHO cells by recombinant DNA technology (Amicus data on file , Xu 2019, Tihanyi 2020) Given that cipaglucosidase alfa and the bis-M6P N-glycans are generated within CHO cells, cipaglucosidase alfa can undergo both proteolytic processing and N-glycan trimming to generate the mature form of the enzyme, which has 7−10-fold more activity than the precursor protein (Amicus data on file , Wisselaar 1993, Moreland 2005, Selvan 2021)
rhGAAs are rapidly inactivated in the blood following infusion	**Miglustat binds to, stabilises and minimises inactivation of cipaglucosidase alfa while in circulation following infusion (Xu 2019)**
	In the blood (pH 7.4), rhGAAs are significantly less stable than in the lysosome (pH 5.2) owing to the difference in pH between the two environments Miglustat is a small molecule with a similar structure to the terminal glucose on glycogen, which binds, stabilises and minimises inactivation of cipaglucosidase alfa following infusion Cipaglucosidase alfa pK: In the phase 1/2 ATB200-02 study, miglustat increased cipaglucosidase alfa area under the curve (260 mg dose) by approximately 35% (95% confidence interval 29–41) vs cipaglucosidase alfa alone (Johnson 2017)

Abbreviations: bis-M6P, bis-phosphorylated mannose 6-phosphate; CHO, Chinese hamster ovary, CI-MPR, cation-independent mannose 6-phosphate receptor; GAA, α-1,4-glucosidase; M6P, mannose 6-phosphate; rhGAA, recombinant human α-1,4-glucosidase.

5.2.2.4. Danish treatment guidelines for Pompe disease

As with international treatment guidelines, Danish treatment protocol (Lægehåndbogen 2021) focus on ERT and symptom relief. Clinical experts in Denmark (List of experts, Section 11) confirmed that care of Pompe disease is based on the European consensus for starting and stopping enzyme replacement therapy from the European Pompe Consortium (van der Ploeg 2017). As previous stated, LOPD requires a multidisciplinary approach to manage the various signs and symptoms of the disorder, which can include the following areas of therapy: physical, speech, respiratory, occupational, nutritional and dietary, psychosocial, and genetic counselling (Cupler 2012b). For patients who do not respond to ERT treatment, symptomatic support is currently the only treatment pathway. There are currently no available international or European recommendation criteria for switching Pompe-specific treatment, since until recently, there has only been one approved pharmaceutical treatment option. According to one Danish clinical expert—who is also a co-author—the European consensus is currently being revised based on recently authorised ERTs (Danish clinical expert, Section 11 List of experts).

The ERT, alglucosidase alfa (Myozyme®), was the first-approved ERT and is the current standard of care in LOPD in Denmark (Lægehåndbogen 2021). Alglucosidase alfa is associated with an initial improvement in physical and psychological symptoms (Kishnani 2009, Nicolino 2009, Hahn 2015, Kuperus 2017, van der Ploeg 2017, Gutschmidt 2021), and an approximate five-fold reduction in mortality compared with no treatment (van der Ploeg 2017). Death rates are improved, but substantial morbidity persists in most patients across the disease spectrum (van der Ploeg 2017), with complications from respiratory muscle weakness remaining the primary cause of morbidity and mortality in LOPD (Jones 2019). Many patients experience a decline in pulmonary function, muscle function, and muscle strength after 2–3 years of treatment with alglucosidase alfa (Semplicini 2020), and at a group level: 24% of patients with LOPD did not demonstrate improvement or stabilisation in 6-minute walk distance and 30% did not experience improvement or stabilisation of forced vital capacity (van der Ploeg 2017). This may result from poor cellular uptake of alglucosidase alfa due to inherent poor phosphorylation of the enzyme that is required for receptor-mediated cellular uptake and instability of the enzyme in circulation post-infusion (Do 2019).

Avalglucosidase alfa (Nexviadyme®) has been recently evaluated by the Danish Medicines Council (DMC) for treatment for the treatment of late-onset Pompe disease (LOPD). In August 2022, the DMC concluded they do not recommend the treatment (Medicinrådet 2022).

5.2.3. Choice of comparators

Head-to-head data on the efficacy of cipaglucosidase alfa/miglustat against alglucosidase alfa/placebo was available from the PROPEL randomised controlled trial. Alglucosidase alfa was considered as the main comparator in the health economic assessment of this submission, as alglucosidase alfa is the only current treatment option which would be replaced by cipaglucosidase alfa/miglustat, if it is introduced into the Danish health care system.

Clinical expert within Pompe disease in Denmark confirmed that essentially all Danish patients are on ERT treatment. Only in certain very exceptional cases (e.g., due to pregnancy, minimal disease manifestations, age or comorbidity) an LOPD patient would not be considered for active treatment using ERT (Section 11 List of experts).

However, a theoretical "BSC" scenario analysis was included in the health economic analysis at the request of Danish Medicines Council, based on an indirect treatment comparison (ITC) against the placebo arm in the LOTS study, see Results Section 8.7. Amicus would like to highlight that, based on the above, this scenario is purely theoretical and does not bear any clinical relevance in Denmark.

5.2.4. Description of the comparators

5.2.4.1. Alglucosidase alfa

Table 7: Product description for alglucosidase alfa

Product description	
Active ingredients	Alglucosidase alfa
Generic name and ATC code	Alglucosidase alfa: A16AB07
Pharmaceutical forms	Powder for concentrate for solution for infusion
Packaging	One vial contains 50 mg of alglucosidase alfa
Mode of action	It is postulated that alglucosidase alfa will restore lysosomal GAA activity resulting in stabilisation or restoration of cardiac and skeletal muscle function (including respiratory muscles); Due to the blood-brain barrier effect and the enzyme's size, uptake of alglucosidase alfa in the central nervous system is unlikely

Product description	
Dosing	The recommended dose regimen of Myozyme® (alglucosidase alfa) is 20 mg/kg of body weight administered once every 2 weeks
Methods of administration	Intravenous infusion Infusions 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, until a maximum rate of 7 mg/kg/h is reached
Should the intervention be used with other drugs?	No
Treatment duration/Criteria for end of treatment	In cases of unacceptable toxicity
Required monitoring, under administration or during treatment periods	Patient response to treatment should be routinely evaluated based on a comprehensive evaluation of all clinical manifestations of the disease
Requirements of diagnostics or other tests	Genetic testing for Pompe diagnosis

Source: *SmPC available at EMA

5.2.4.2. Best supportive care

Best supportive care consists of symptomatic relief, with no active treatment. For more details, please see Section 5.2.2.1. However, as discussed above, a scenario vs best supportive care is purely theoretical and does not bear any clinical relevance in Denmark.

5.3. The intervention

5.3.1. Summary

Table 8: Product description of cipaglucosidase alfa/miglustat

Product description	
Active ingredients	cipaglucosidase alfa/miglustat
Generic name and ATC code	Cipaglucosidase alfa: A16AB23 Miglustat: A16AX06
Pharmaceutical forms	Cipaglucosidase alfa: intravenous infusion Miglustat: oral hard capsule
Packaging	**Cipaglucosidase alfa** Vial containing 105 mg of cipaglucosidase alfa **Miglustat** 4 or 24 hard capsules of 65 mg (bottle)
Mode of action	Cipaglucosidase alfa/miglustat is an investigational ERT containing a rhGAA enzyme (cipaglucosidase alfa); cipaglucosidase alfa is co-administered with an enzyme stabiliser (miglustat). Miglustat binds selectively with cipaglucosidase alfa in the physiological pH of blood during infusion; thereby stabilizing the conformation of cipaglucosidase alfa and minimising the loss of enzyme activity while in circulation
Dosing	**Cipaglucosidase alfa** IV infusion every 2 weeks at 20 mg/kg, with an average of 4 hours infusion time **Miglustat** Orally administered 1 hour prior to IV infusion of cipaglucosidase alfa (fasting required prior to administration) to maximise occupancy and ensure enzyme stabilisation while in circulation

Product description	
	• For patients weighing ≥ 50 kg, four capsules of 65 mg (260 mg total) • For patients weighing ≥ 40 kg to < 50 kg, three capsules of 65 mg (195 mg total) The frequency of administration is once every 2 week Miglustat should be taken approximately 1 hour before the start of the cipaglucosidase alfa infusion; In the event of cipaglucosidase alfa infusion delay, the start of infusion should not exceed 3 hours from the oral administration of miglustat
Should the intervention be used with other drugs?	Cipaglucosidase alfa is administered in combination with miglustat
Treatment duration/Criteria for end of treatment	In cases of unacceptable toxicity
Required monitoring, under administration or during treatment periods	Patients should be monitored continuously for adverse reaction and disease progression
Requirements of diagnostics or other tests	Genetic testing for Pompe diagnosis

Source: (European Medicines Agency 2023)

5.3.2. Mode of action

Cipaglucosidase alfa/miglustat restores lysosomal GAA activity, promoting stabilisation or restoration of cardiac, skeletal and respiratory muscle function. It is a two-component therapy consisting of cipaglucosidase alfa, a novel recombinant human optimised form of the GAA enzyme, co-administered with an oral small molecule called miglustat, which acts as a pharmacological enzyme stabiliser.

Cipaglucosidase alfa compensates for the lack of natural GAA enzyme in patients living with LOPD. It has optimised levels of bis-phosphorylated N-glycans, including M6P, which increases its affinity and enhances binding to the CI-MPR, allowing effective uptake of the cipaglucosidase alfa/miglustat complex into the muscles (Xu 2019).

In the blood (pH 7.4), rhGAA is significantly less stable than in the lysosome (pH 5.2), due to the difference in pH between the two environments. Miglustat mimics the terminal glucose of glycogen, the natural substrate for GAA, allowing it to bind to cipaglucosidase alfa in human blood at 37°C. This increases the melting temperature of the active enzyme, enhancing structural stability and preventing denaturation (Xu 2019). This gives the enzyme longer time to reach and bind to the CI-MPR prior to uptake into the muscle.

The concentration of miglustat is in excess to cipaglucosidase alfa, ensuring 1:1 binding and stabilisation of the recombinant enzyme while in the circulatory system. The interaction of cipaglucosidase alfa and miglustat is transient (Amicus data on file) and dissociates after being trafficked into the lysosome, where cipaglucosidase alfa undergoes proteolytic cleavage and N-glycan trimming, which are both required for conversion into the mature, most active form of the enzyme (Selvan 2021). Non-clinical studies indicate that miglustat is cleared from the muscles within approximately 24 hours, while cipaglucosidase alfa has a much longer residence time in lysosomes of muscles, with an estimated half-life of approximately 7–10 days. Miglustat alone has no effect on glycogen reduction, primarily acting as a stabiliser of cipaglucosidase alfa. Preclinical studies in a genetically engineered GAA knock-out mouse model demonstrated that the two-component therapy results in higher GAA levels in the muscle (verified by immuno-histological staining) compared with alglucosidase alfa, resulting in a statistically significant reduction in glycogen accumulation as well as improvement or reversal of autophagic defects and muscle pathology (Xu 2019).

5.3.2.1. Use of enzyme stabilisers in the treatment of lysosomal storage disorders

The instability of rhGAA at blood pH is a significant aspect that encumbers ERT delivery to muscles and consequently hinders efficacy. The concept of coadministration of miglustat with cipaglucosidase alfa comes from preclinical studies that have reported improved glycogen clearance, stability of rhGAA and uptake of rhGAA into Pompe disease fibroblasts, in muscle of GAA-knockout mice cells and patients with Pompe disease when used in combination with an enzyme stabiliser compared with rhGAA alone (Parenti 2014, Kishnani 2017, Do 2019, Xu 2019).

5.3.3. Dosing and frequency

Cipaglucosidase alfa is provided in vials containing lyophilized powder for solution for intravenous infusion (each vial, 105 mg/mL). Miglustat is supplied as a hard gelatine capsule (each capsule, 65 mg).

It is anticipated that cipaglucosidase alfa/miglustat will be approved for at-home administration and infusion in addition to in-clinic and in-hospital dosing (Figure 7). The dose and frequency of each component in cipaglucosidase alfa/miglustat is outlined in Table 9.

Figure 7: The patients experience of cipaglucosidase alfa and miglustat

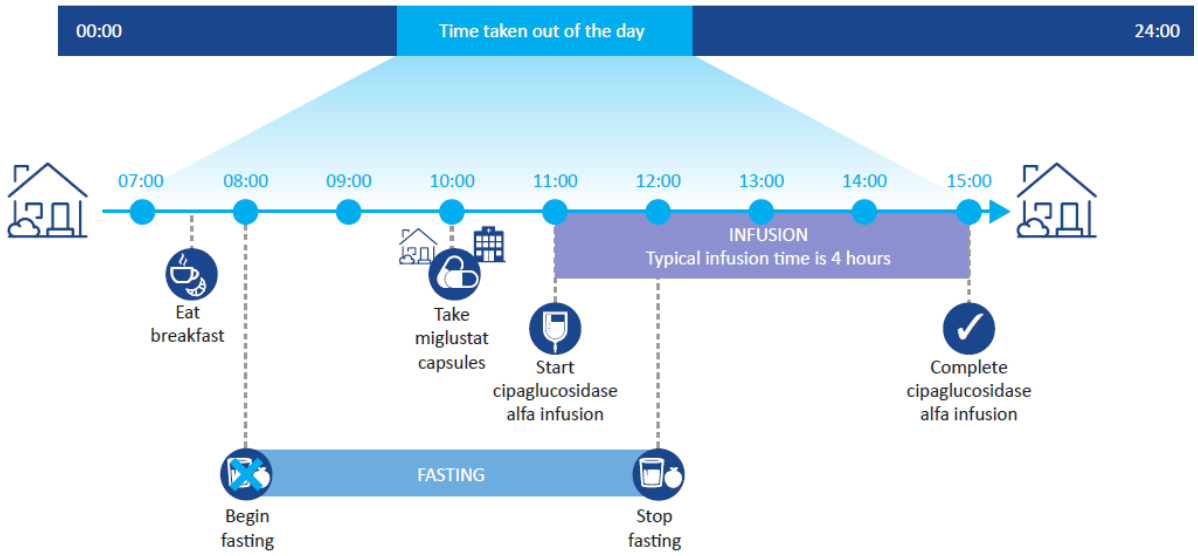


Table 9: Dose and frequency of cipaglucosidase alfa and miglustat

	Dosing	Administration
Cipaglucosidase alfa (ATB200)	20 mg/kg	IV infusion every 2 weeks
Miglustat (AT2221)	For patients weighing ≥ 50 kg, four capsules of 65 mg (260 mg total) For patients weighing ≥ 40 kg to < 50 kg, three capsules of 65 mg (195 mg total)	Orally administered 1 hour prior to IV infusion of cipaglucosidase alfa (fasting required prior to administration) to maximise occupancy and ensure enzyme stabilisation while in circulation

Abbreviations: IV, intravenous.

Literature search and identification of efficacy and safety studies

6.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify published evidence on the clinical efficacy and safety of cipaglucosidase alfa/miglustat and its relevant comparators in treatment of adults with LOPD. The SLR is relevant for the comparison of cipaglucosidase alfa/miglustat and BSC. The comparison of cipaglucosidase alfa/miglustat with alglucosidase alfa is available through in-trial, direct comparison in PROPEL. As such, no ITC nor SLR are required. While the SLR did capture other LOPD treatments outside of BSC, these are not relevant comparators for this health technology assessment and have not been considered; the full SLR strategy is presented for reference, with only the relevant studies outlined.

Additional insight into the SLR is presented in Appendix A.

6.2. List of relevant studies

Table 10 presents the studies that have been captured by the SLR and relevant to the comparison of cipaglucosidase alfa/miglustat against BSC and alglucosidase alfa: PROPEL, LOTS, and LOTS OLE. As no clinical study was found to include BSC, the placebo arm from LOTS was used as a proxy for BSC. Relevant for the comparison of cipaglucosidase alfa/miglustat to BSC, the LOTS OLE trial was needed to match the alglucosidase alfa to the placebo arm of LOTS.

Table 10: Relevant studies included in the assessment

Reference	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial (Schoser 2021a)	PROPEL	NCT03729362	Start: December 2018 Completion: January 2021	cipaglucosidase alfa/ miglustat versus BSC cipaglucosidase alfa/ miglustat versus alglucosidase alfa
A randomised study of alglucosidase alfa in late-onset Pompe's disease (van der Ploeg 2010)	LOTS	NCT03729362	Start: September 2005 Completion: September 2007	cipaglucosidase alfa/ miglustat versus BSC
Open-label extension study following the Late-Onset Treatment Study (LOTS) of alglucosidase alfa (Van der Ploeg 2012)	LOTS OLE	NCT00455195	Start: March 2007 Completion: October 2008	cipaglucosidase alfa/ miglustat versus BSC

Abbreviations: BSC, best supportive care

Efficacy and safety

7.1. Efficacy and safety of cipaglucosidase alfa/miglustat compared to alglucosidase alfa and placebo for adult patients with LOPD

7.1.1. Relevant studies

An overview of Amicus Therapeutics' clinical programme in Pompe disease is given in Table 11.

Table 11: Summary of clinical programs in LOPD (adult)

Study	Study design	Population	Treatment	Objectives	Relevant section
Study ATB200-02 (NCT02675465)	Phase I/II Single arm Fixed sequence Ascending dose First in human	LOPD	Cipaglucosidase alfa/miglustat	Safety Tolerability PK/PD Efficacy	n/a
PROPEL (NCT03729362)	Phase 3 Randomised Double blinded Active controlled	LOPD	Cipaglucosidase alfa/miglustat vs alglucosidase alfa and placebo	Efficacy Safety PK/PD	Section 7.1.2
Study ATB200-07 (NCT04138277)	Open-label extension Single arm	LOPD (patients enrolled in PROPEL)	Cipaglucosidase alfa/miglustat	Long-term efficacy Long-term safety	n/a

Abbreviations: LOPD, late-onset Pompe disease; N/A, not applicable; PD, pharmacodynamics; PK, pharmacokinetics; TEAE, treatment-emergent adverse event.

For detailed study characteristics refer to Appendix B – Main characteristics of included studies. For baseline characteristics of patients included in each study refer to Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

7.1.1.1. Real-world evidence study in Sweden

Amicus Therapeutics is currently conducting a real-world evidence study in Sweden, which will provide insight on the disease burden, treatment patterns, and resource use utilisation associated with Pompe disease in the Nordics. The study is a longitudinal retrospective, observational study using secondary Swedish national registry data, and the first data are becoming available in Q2 2023. The study will consider both IOPD and LOPD patients, with an estimated 20 to 30 number of prevalent patients between 2005 to study close. Objectives include: estimating prevalence and incidence; describing patient characteristics; overall survival and other health outcomes (e.g., loss of ambulation, scoliosis development, cardiac complications, respiratory lung capacity, liver and metabolic endpoint); and describing treatment patterns of ERT use (Nordin 2023).

7.1.2. Efficacy and safety – PROPEL

All data presented in Section 7.1.2 will exclude Patient 4005-2511 unless otherwise stated (see Appendix section 14.2.6 for an explanation of the exclusion). All endpoints are presented for the overall population and for the ERT-experienced and ERT-naïve subpopulations, as predefined in the clinical study report (CSR). The ERT-experienced cohort represent the main subpopulation of the PROPEL trial and were initially the intended study population. For detailed PROPEL safety results, see Appendix E – Safety data for intervention and comparator.

Post-hoc robustness analysis carried out at the request of the CHMP

Due to the COVID-19 pandemic and restrictions on access to study centres, some visits could not be done at the scheduled times as per the PROPEL study protocol. At the request of the CHMP, a post-hoc robustness analysis based on the mixed-effect model for repeated measures (MMRM) method was performed, using the actual date of each visit as a continuous variable. As such, these results have been additonally presented as found in the EMA European Public Assessment Report (EPAR), and support the efficacy of cipaglucosidase alfa/miglustat (European Medicines Agency 2023). For a summary of the EMA analyses outcomes, see Section 34 Appendix V.

7.1.2.1. Primary endpoint: change from baseline in 6-minute walk distance at week 52

7.1.2.1.1. Change from baseline in 6-minute walk distance at week 52 in the overall population (ERT-experienced and ERT-naïve)

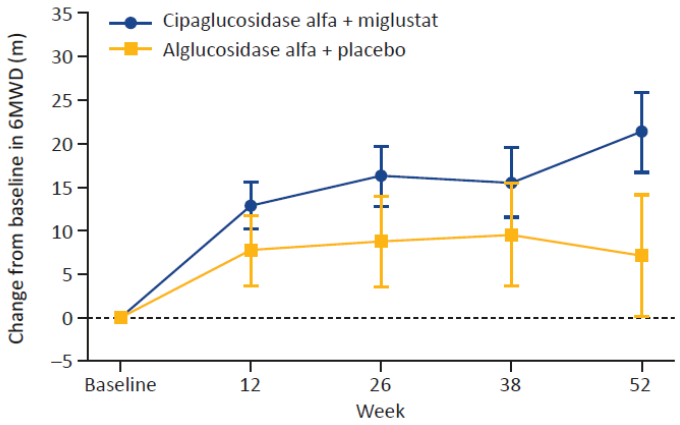
Cipaglucosidase alfa/miglustat was associated with an improvement in 6MWD (observed) compared with alglucosidase alfa/placebo but did not demonstrate statistical superiority in the overall population owing to testing at the one-side 0.025 significance level. Cipaglucosidase alfa/miglustat was associated with a mean 20.6-metre improvement in baseline 6MWD at 52 weeks, and alglucosidase alfa/placebo was associated with a mean improvement of 8.0 m (359.7 m [SD, 137.36]; Figure 8).

The MMRM least-squares (LS) mean treatment difference for observed 6MWD was 14.21 m (95% CI, −2.60, 31.02; two-sided p = [redacted]; Figure 8), which was consistent with the pre-specified analysis excluding the studentised residual > 3 in magnitude in the ITT population (Section 14.2.6). However, even with the exclusion of the outlier, the normality assumption was violated based on the diagnostic plot and Shapiro–Wilk test ($p < 0.01$); therefore, a non-parametric analysis using (last observation carried forward) LOCF 6MWD was performed. The non-parametric randomisation-based covariance analysis of LOCF 6MWD revealed an LS mean treatment difference of 13.66 m (95% CI, −1.17, 28.48; two-sided p = [redacted]; Figure 8).

Mean 6MWD at baseline was 357.9 m and 351.0 m in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and 376.4 m (SD, 122.93) and 359.7 m (SD, 137.36) at 52 weeks (observed), respectively (Figure 41 in Appendix M – Secondary endpoints).

Mean change from baseline 6MWD at week 26, a key secondary endpoint, and at week 52 LOCF was generally in agreement with observed data at week 52 (Figure 8). In the overall population, the ANCOVA LS mean treatment difference in 6MWD at 26 weeks was 8.2 (95% CI, −4.24, 20.57), with a nominal two-sided p value of [redacted].

Figure 8: PROPEL primary endpoint: LS mean change in baseline 6MWD at 52 weeks (overall population [ERT-experienced and ERT-naïve])



Abbreviations: LOPD, late-onset Pompe disease; N/A, not applicable; PD, pharmacodynamics; PK, pharmacokinetics; TEAE, treatment-emergent adverse event.

Figure 9: PROPEL primary endpoint: LS mean change in baseline 6MWD at 52 weeks (overall population [ERT-experienced and ERT-naïve])

Population	Treatment	n	Mean baseline 6MWD (SD), m	n	Mean 6MWD at week 52 (SD), m	Mean CFB 6MWD at 52 weeks (SD)	
Observed (primary endpoint)							
Overall	**Cipaglucosidase alfa/miglustat**	85	357.93 (111.84)	81	376.41 (122.93)	20.56 (42.27)	↑
	Alglucosidase alfa/placebo	37	350.95 (121.32)	36	359.70 (137.36)	8.02 (40.56)	↑
	MMRM difference in LS mean (95% CI)				14.21 (−2.60, 31.02); **nominal two-sided *p* =** [redacted]		
LOCF (sensitivity analysis of the primary endpoint)							
Overall	**Cipaglucosidase alfa/miglustat**	85	357.93 (111.84)	85	378.7 (123.3)	20.79 (42.77)	↑
	Alglucosidase alfa/placebo	37	350.95 (121.32)	37	358.19 (135.75)	7.24 (40.28)	↑
	ANCOVA difference in LS mean (95% CI)				13.66 (−1.17, 28.48); **nominal two-sided *p* =** [redacted]		

Note: ↑ denotes improvement from baseline.
Abbreviation: 6MWD, 6-minute walk distance; ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; LOCF, last observation carried forward; LS, least-squares; MMRM, mixed-effect model for repeated measures; SD, standard deviation.

7.1.2.1.2. Change in baseline 6MWD at 52 weeks stratified by ERT status

In the **ERT-experienced population** (95 patients), cipaglucosidase alfa/miglustat was associated with a 16.3-m improvement from baseline 6MWD (observed) at 52 weeks, compared with a 0.70 m improvement in the alglucosidase alfa/placebo arm (MMRM difference in LS mean, 16.45 m [95% CI, −1.86, 34.77]; nominal two-sided p = [redacted]; Figure 10). As in the overall population, the normality assumption for the MMRM analysis was violated; therefore, a pre-planned non-parametric randomisation-based ANCOVA of LOCF 6MWD was performed, yielding a nominally significant two-sided p value of [redacted] (Figure 10).

Mean baseline 6MWD was 346.9 m (SD, 110.21) and 334.6 m (SD, 114.02) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at 52 weeks (observed) was 359.8 m (SD, 122.49) and 335.7 m (SD, 131.67), respectively (Figure 10). Change from baseline at 52 weeks using LOCF was consistent with the observed data (Figure 10).

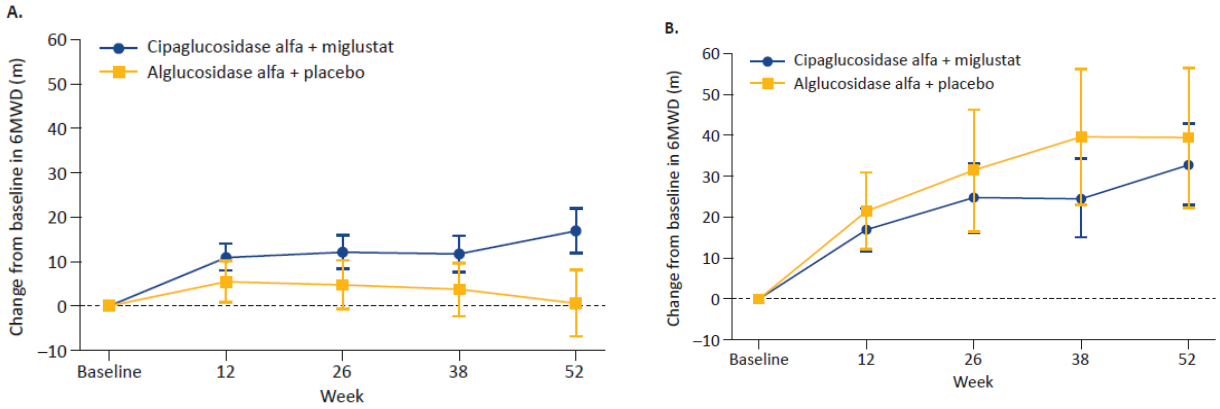
The primary endpoint (change in 6MWD from baseline to week 52) resulted in an estimated treatment difference of 14.9 m (95% CI 1.2, 28.6). A MCID for treatment experienced LOPD patients cannot be retrieved from literature. However, in this treatment-experienced population, some deterioration is to be expected after more than 7 years of treatment. Therefore, an observed improvement in this population should be considered clinically beneficial (European Medicines Agency 2023).

In the **ERT-naïve population** (27 patients), an improvement from baseline 6MWD at 52 weeks was recorded in both treatment arms: mean 6WMD at baseline was 393.6 m (SD, 112.4) and 420.9 m (SD, 135.8) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, which improved to 427.1 m (SD, 11.2.5) and 459.3 m (SD, 121.7), respectively, at week 52 (observed; Figure 10). This equated to a 33.4-m improvement in 6MWD in the cipaglucosidase alfa/miglustat arm, and a 38.3-m improvement in the alglucosidase alfa/placebo arm (MMRM difference in LS mean, −6.55 [95% CI, −48.2, 35.1]; nominal two-sided *p* = [redacted]; Figure 10). As with the overall and ERT-experienced populations, the normality assumption for the MMRM analysis was violated. Owing to the small sample size and differences in baseline characteristics between treatment arms (e.g. sex) (Appendix C – Baseline characteristics of patients in studies used for the comparative

analysis of efficacy and safety), a *post hoc* Wilcoxon rank sum test was performed. The location shift was −9.0 (95% CI, −46.5, 35.0) with a two-sided *p* value of 0.604 (Figure 10). Change from baseline at 52 weeks using LOCF was consistent with the observed data (Figure 10).

The ANCOVA LS mean treatment difference in 6MWD from baseline was 9.62 (95% CI, −3.82, 23.06) and −10.38 (95% CI, −49.27, 28.51) in the **ERT-experienced** and **ERT-naïve populations,** respectively.

Figure 10: PROPEL LS mean change from baseline 6MWD at 52 weeks stratified by ERT status. A. ERT-experienced population. B. ERT-naïve population



Population	Treatment	n	Mean baseline 6MWD (SD), m	n	Mean observed 6MWD at week 52 (SD), m	Mean CFB 6MWD at 52 weeks (SD)	
Observed							
ERT-experienced	**Cipaglucosidase alfa/miglustat**	65	346.94 (110.21)	61	359.79 (122.49)	16.34 (39.46)	↑
	Alglucosidase alfa/placebo	30	334.62 (114.02)	29	335.66 (131.67)	0.70 (39.84)	↑
	MMRM difference in LS mean (95% CI)				16.45 (−1.86, 34.77); two-sided *p* = [redacted]		
ERT-naïve	**Cipaglucosidase alfa/miglustat**	20	393.64 (112.39)	20	427.09 (112.47)	33.44 (48.70)	↑
	Alglucosidase alfa/placebo	7	420.94 (135.75)	7	459.28 (121.66)	38.34 (29.32)	↑
	MMRM difference in LS mean (95% CI)				−6.55 (−48.19, 35.08); two-sided *p* = [redacted]		
LOCF							
ERT-experienced	**Cipaglucosidase alfa/miglustat**	65	346.94 (110.21)	65	363.83 (123.52)	16.89 (40.39)	↑
	Alglucosidase alfa/placebo	30	334.62 (114.02)	30	334.60 (129.51)	–0.02 (39.35)	↓
	ANCOVA difference in LS mean (95% CI)				16.76 (0.24, 33.29); two-sided *p* = [redacted]		
ERT-naïve	**Cipaglucosidase alfa/miglustat**	20	393.64 (112.39)	20	427.09 (112.47)	33.44 (48.70)	↑
	Alglucosidase alfa/placebo	7	420.94 (135.75)	7	459.28 (121.66)	38.24 (29.32)	↑
	Location shift[a] (95% CI)				−9.00 (−46.50, 34.95); two-sided *p* = [redacted]		

Note: ↑ denotes improvement from baseline; ↓ worsening from baseline.
[a]Nonparametric Wilcoxon rank sum test; location shift and 95% CI were from Hodges-Lehmann estimation.
Abbreviation: 6MWD, 6-minute walk distance; ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; LOCF, last observation carried forward; LS, least-squares; MMRM, mixed-effect model for repeated measures; SD, standard deviation.

Post-hoc robustness analysis carried out at the request of the CHMP for 6MWD

For the 6MWD at 52 weeks, the results of the post-hoc robustness analysis were consistent with those of the main analysis (European Medicines Agency 2023):

- For the ITT population, least squares mean difference of +11.7 m (95% CI -1.0, 24.4) in favour of cipaglucosidase alfa/miglustat, but not statistically significant
- For the ERT-experienced population, least squares mean difference of +14.9 m (95% CI 1.2, 28.6) in favour of cipaglucosidase alfa/miglustat

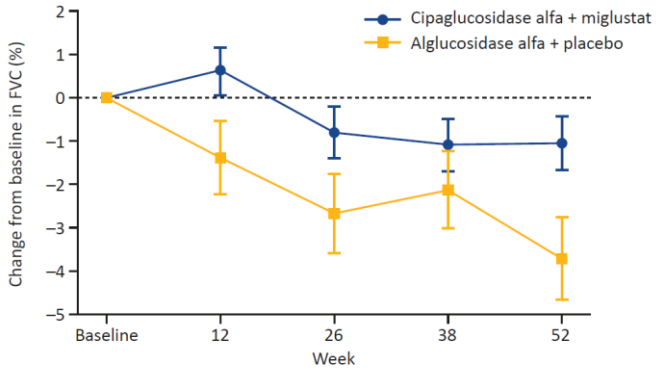
For a summary of the 6MWD analyses outcomes, see Section 34 Appendix V.

7.1.2.2. First key secondary endpoint: change from baseline in percent predicted sitting forced vital capacity at week 52

7.1.2.2.1. Change from baseline in percent predicted sitting FVC at week 52 in the overall population (ERT-experienced and ERT-naïve)

At 52 weeks, cipaglucosidase alfa/miglustat was associated with a clinically meaningful, according to the study investigators, and nominally statistically significant relative improvement in baseline % predicted sitting FVC compared with alglucosidase alfa/placebo. The key secondary endpoint (change in sitting % predicted FVC from baseline to week 52 in the overall population resulted in an estimated mean difference of -1.4 (95% CI -2.5, 0.3) in the cipaglucosidase alfa/miglustat group and of -3.7 (95% CI -5.4, -2.0) in the alglucosidase alfa/placebo group (ANCOVA LS mean treatment difference, 2.66% [95% CI, 0.37, 4.95]; nominal two-sided p = [redacted]; Figure 11). Mean baseline % predicted FVC was 70.7% (SD, 19.6) and 69.7% (SD, 21.5) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at 52 weeks (LOCF) was 69.8% (SD, 19.9) and 65.7% (SD, 21.1), respectively (Figure 11). As quoted in the EPAR: ”the change in the cipaglucosidase alfa/miglustat arm may indicate a stabilisation of disease as it cannot be considered a clinically relevant decline, whereas the difference in the alglucosidase alfa arm indicated some clinically relevant deterioration after 52 weeks of treatment”(EPAR 2023).

Figure 11: First key secondary endpoint: LS mean change from baseline to week 52 in percentage FVC (overall population [ERT-experienced and ERT-naïve])



Population	Treatment	n	Mean baseline % predicted FVC (SD)	n	Mean LOCF % predicted FVC at 52 weeks (SD)	Mean CFB at 52 weeks (SD)	
Overall	**Cipaglucosidase alfa/miglustat**	85	70.74 (19.57)	84[a]	69.81 (19.86)	-0.93 (6.23)	↓
	Alglucosidase alfa/placebo	37	69.68 (21.48)	37	65.73 (21.11)	−3.95 (4.89)	↓
	ANCOVA LS mean treatment difference (95% CI; EMA analysis)				[redacted]		

Note: ↑ denotes improvement from baseline; ↓ worsening from baseline.

[a]Patient 2301-1421 had a baseline result of 70.5% but subsequently withdrew consent (not willing to travel to treatment site) and was therefore excluded from the analysis.
Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; FVC, forced vital capacity; LOCF, last observation carried forward; LS, least-squares; SD, standard deviation.

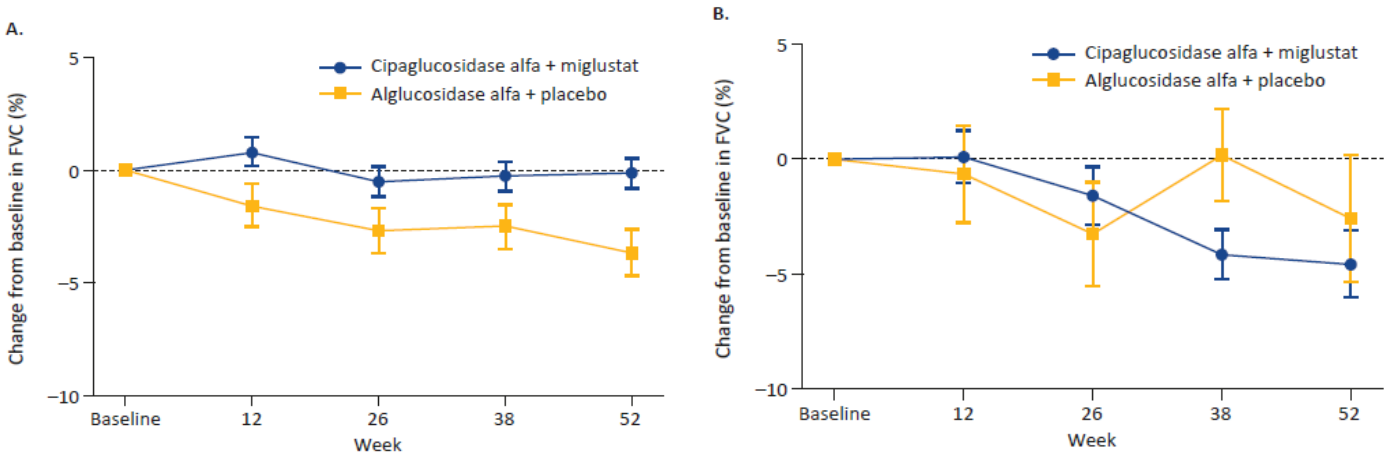
7.1.2.2.2. Change from baseline in percent predicted FVC stratified by ERT status

Cipaglucosidase alfa/miglustat demonstrated stabilisation of % predicted FVC over the 52-week study period, which was a clinically meaningful and nominally statistically significant relative improvement compared with the alglucosidase alfa/placebo group in the **ERT-experienced population** (95 patients), demonstrating stabilisation over the 52-week study period (Figure 12). Mean change from baseline in sitting % predicted FVC was 0.1% (SD, 5.84) in the cipaglucosidase alfa/miglustat arm and −4.0% (SD, 5.01) in the alglucosidase alfa/placebo arm (LS mean treatment difference, 3.51% [95% CI, 1.03, 5.99]; nominal two-sided p = [redacted]; Figure 12). At baseline, mean sitting % predicted FVCs were 67.9% (SD, 19.1) and 67.5% (SD, 21.0) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at 52 weeks (LOCF) were 67.9% (SD, 19.8) and 63.5% (SD, 20.5), respectively (Figure 12).

In the **ERT-naïve population** (27 patients), mean baseline sitting % predicted FVC was 80.2% (SD, 18.7) and 79.1% (SD, 22.6) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively (Figure 12). At 52 weeks (LOCF), mean sitting % predicted FVC was 76.1% (SD, 19.3) in the cipaglucosidase alfa/miglustat arm and 75.4% (SD, 22.6) in the alglucosidase alfa/placebo arm, which equates to a change from baseline of −4.1% (SD, 6.53) and −3.6% (SD, 4.71), respectively (Figure 12).

Extrapolation of the data from the ERT-experienced (generally more severe and difficult to treat patients) to ERT-naïve population in LOPD is considered justified, primarily since there is no biologically plausible argumentation that the expected benefit would be less in ERT-naïve LOPD population. Further, the number of patients in this subgroup is very limited and a random drift of the results cannot be excluded (European Medicines Agency 2023).

Figure 12: PROPEL LS mean change from baseline percentage FVC at week 52 stratified by ERT status. A. ERT-experienced population. B. ERT-naïve population



Population	Treatment	n	Mean baseline % predicted FVC (SD), m	n	Mean LOCF % predicted FVC at 52 weeks (SD), m	Mean CFB at 52 weeks (SD)	
ERT-experienced	**Cipaglucosidase alfa/miglustat**	65	67.85 (19.05)	64	67.86 (19.78)	0.05 (5.84)	↑
	Alglucosidase alfa/placebo	30	67.48 (20.99)	30	63.47 (20.48)	−4.02 (5.01)	↓
	ANCOVA difference in LS mean (95% CI)				3.51 (1.03, 5.99); **nominal two-sided *p* =** [redacted]		
ERT-naïve	**Cipaglucosidase alfa/miglustat**	20	80.15 (18.69)	20	76.05 (19.30)	−4.10 (6.53)	↓
	Alglucosidase alfa/placebo	7	79.07 (22.58)	7	75.43 (22.60)	−3.64 (4.71)	↓
	ANCOVA difference in LS mean (95% CI)				−1.95 (−8.93, 5.03); nominal two-sided *p* = [redacted]		

Note: ↑ denotes improvement from baseline; ↓ worsening from baseline.
Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; FVC, forced vital capacity; LOCF, last observation carried forward; LS, least-squares; SD, standard deviation.

Post-hoc robustness analysis carried out at the request of the CHMP for FVC

For the FVC at 52 weeks, the results of the post-hoc robustness analysis were consistent with those of the main analysis, showing stabilisation of FVC in percent predicted between baseline and Week 52 in the ITT and ERT-experienced populations, in favour of the cipaglucosidase alfa/miglustat group (European Medicines Agency 2023):

- For the ITT population, least squares mean difference of 2.3% (95% CI 0.2, 4.4)
- For the ERT-experienced population, least squares mean difference of 3.6% (95% CI 1.3, 5.9)

For a summary of the FVD analyses outcomes, see Section 34 Appendix V.

7.1.2.3. Post hoc global test on the primary and first key secondary endpoints

A global post hoc test was performed on the 6MWD (primary endpoint) and % predicted FVC (first key secondary endpoint). Individual patient response was ranked individually for each endpoint from least to greatest improvement. The two ranks were summed for each patient and analysed using a Wilcoxon rank sum test (Wang 2019). As summarised in Table 12, the Wilcoxon rank sum test based on 6MWD and % predicted FVC further supported the significance and consistency of the treatment effect of cipaglucosidase alfa/miglustat over alglucosidase alfa/placebo in the overall population (two-sided p = 0.010).

Table 12: PROPEL post hoc analysis: Wilcoxon rank sum test based on sum of ranks for the primary and first key secondary endpoints (overall population)

Population	Treatment	n	Sum of scores	Mean score	Two-sided *p* value
Overall population	**Cipaglucosidase alfa/miglustat**	84[a]	5587.5	66.5	0.010
	Alglucosidase alfa/placebo	37	1793.5	48.5	

[a]For % predicted FVC, Patient 2301-1421 had a baseline result of 70.5% but subsequently withdrew from the study (not willing to travel to the study site), and their data were thus excluded from the study.
Abbreviations: FVC, forced vital capacity.

7.1.2.4. Secondary endpoints

Other secondary endpoints, including those assessing motor function, pulmonary function, muscle strength, PROs and biomarkers, are presented in detail along with the primary and key secondary endpoints in Appendix M – Secondary endpoints. A brief summary of the main secondary efficacy outcomes is outlined below.

As stated in the EPAR: ”for the remaining key secondary endpoints (MMT, PROMIS-Physical Function, PROMIS-fatigue and GSGC), results reported are more or less in line with the results of the 6MWT and the sitting %FVC and further support the conclusion that the effects obtained with cipaglucosidase alfa/miglustat appeared to be reasonably robust and consistent" (European Medicines Agency 2023).

Percent predicted FVC

- Cipaglucosidase alfa/miglustat demonstrated a nominally significant and clinically meaningful 2.7%-difference in % predicted FVC over alglucosidase alfa/placebo across all patients (n = 123, with a reduction from baseline of −0.93% [SD, 6.23] and −3.95% [4.89], respectively; two-sided p = [redacted])

Change from baseline in MMT score for lower extremities at 52 weeks in the overall population (ERT-experienced and ERT-naïve)

- An improvement in motor function was reported in both treatment arms of the overall population at 52 weeks, as demonstrated by change from baseline MMT lower extremities score at 52 weeks
- At week 52, cipaglucosidase alfa/miglustat was associated with a mean improvement in baseline MMT lower extremities score of 1.56 points (SD, 3.78), compared with a mean 0.9-point (SD, 2.58) improvement in the alglucosidase alfa/placebo arm

Mean changes from baseline 6MWD at week 26 in the ERT-experienced and ERT-naïve populations

- The ANCOVA LS mean treatment difference was 9.62 (95% CI, −3.82, 23.06) and −10.38 (95% CI, −49.27, 28.51) in the ERT-experienced and ERT-naïve populations, respectively

Change from baseline in PROMIS–Physical Function score at week 52 in the overall population (ERT-experienced and ERT-naïve)

- Cipaglucosidase alfa/miglustat was associated with a numerically greater improvement in PROMIS–Physical Function score than alglucosidase alfa/placebo; however, these improvements were not considered clinically significant
- Mean improvement from baseline PROMIS–Physical Function score at week 52 was 1.9 points (SD, 7.50) in the cipaglucosidase alfa/miglustat arm and 0.2 points (SD, 10.82) in the alglucosidase alfa/placebo arm (ANCOVA LS mean treatment difference, 1.87 [95% CI, −1.51, 5.25]; nominal two-sided p = [redacted])

Change from baseline in PROMIS–Fatigue score at week 52 in the overall population (ERT-experienced and ERT-naïve)

- Improvement in PROMIS–Fatigue score was reported in both treatment arms. Patients allocated to the cipaglucosidase alfa/miglustat arm reported a −2.0-point (SD, 5.8) improvement from baseline in PROMIS–Fatigue score at week 52 compared with a −1.7-point (SD, 6.6) improvement in the alglucosidase alfa/placebo arm (ANCOVA treatment difference in LS mean, 0.04 [95% CI, −2.12, 2.20]; nominal two-sided p = [redacted])

Change from baseline in GSGC score at week 52 in the overall population (ERT-experienced and ERT-naïve)

- Cipaglucosidase alfa/miglustat was associated with a nominally statistically significant improvement in GSGC score compared with alglucosidase alfa/placebo; note, a lower score represents better functionality
- Mean change from baseline GSGC score was −0.53 (SD, 2.54) in the cipaglucosidase alfa/miglustat arm and 0.77 (SD, 1.81) in the alglucosidase alfa/placebo arm

Table 13: PROPEL summary of key secondary endpoints in the overall (ERT-experienced and ERT-naïve), ERT-experienced and ERT-naïve populations

Endpoints	Overall population			ERT-experienced			ERT-naïve		
	CFB at week 52 (SD)		LS mean treatment difference (95% CI)	CFB at week 52 (SD)		LS mean treatment difference (95% CI)	CFB at week 52 (SD)		LS mean treatment difference (95% CI)
	Cipaglucosidase alfa/miglustat (n = 85)	Alglucosidase alfa/ placebo (n = 37)		Cipaglucosidase alfa/miglustat (n = 65)	Alglucosidase alfa/ placebo (n = 30)		Cipaglucosidase alfa/miglustat (n = 20)	Alglucosidase alfa/ placebo (n = 7)	
Key secondary endpoint									
% predicted FVC	−0.93 (6.23)	−3.95 (4.89)	2.66 (0.37, 4.95)	0.05 (5.84)	−4.02 (5.01)	3.51 (1.03, 5.99)	−4.10 (6.53)	−3.64 (4.71)	−1.95 (−8.93, 5.03)
	One-sided p = 0.012 Two-sided p = 0.023 ↑			One-sided p = 0.003 Two-sided p = 0.006 ↑			One-sided p = 0.717 Two-sided p = 0.566 ↓		
Additional key secondary endpoints ordered by statistical hierarchy									
MMT lower extremity score	1.56 (3.78)	0.88 (2.58)	0.96 (−0.48, 2.40)	1.63 (4.13)	0.85 (2.81)	0.70 (−1.08, 2.49)	1.36 (2.55)	1.00 (1.53)	0.78 (−1.79, 3.34)
	One-sided p = 0.095 Two-sided p = 0.191 ↑			One-sided p = 0.218 Two-sided p = 0.436 ↑			One-sided p = 0.267 Two-sided p = 0.534 ↑		
6MWD (at 26 weeks), m	17.44 (32.74)	9.19 (26.93)	8.2 (−4.24, 20.57)	12.95 (30.37)	4.67 (26.58)	9.62 (−3.82, 23.06)	32.23 (36.75)	30.31 (17.94)	−10.38 (−49.27, 28.51)
	One-sided p = 0.097 Two-sided p = 0.195 ↑			One-sided p = 0.079 Two-sided p = 0.158 ↑			One-sided p = 0.708 Two-sided p = 0.584 ↑		
PROMIS–Physical Function total score	1.94 (7.50)	0.19 (10.82)	1.87 (−1.51, 5.25)	1.76 (7.18)	−0.97 (11.20)	3.14 (−0.73, 7.02)	2.50 (8.62)	5.14 (7.82)	−5.09 (−14.04, 3.85)
	One-sided p = 0.138 Two-sided p = 0.276 ↑			One-sided p = 0.055 Two-sided p = 0.110 ↑			One-sided p = 0.876 Two-sided p = 0.249 ↓		
PROMIS–Fatigue total score	−2.02 (5.76)	−1.67 (6.62)	0.04 (−2.12, 2.20)	−1.87 (5.84)	−0.27 (5.27)	−0.84 (−3.16, 1.49)	−2.50 (5.63)	−7.70 (8.77)	3.29 (−3.69, 10.27)
	One-sided p = 0.515 Two-sided p = 0.970 ↑			One-sided p = 0.238 Two-sided p = 0.476 ↓			One-sided p = 0.831 Two-sided p = 0.338 ↑		
GSGC total score	−0.53 (2.54)	0.77 (1.81)	−1.41 (−2.46, −0.36)	−0.53 (2.53)	0.61 (1.83)	−1.19 (−2.38, 0)	−0.56 (2.64)	1.29 (1.80)	−1.32 (−4.03, 1.39)
	One-sided p = 0.004 Two-sided p = 0.009 ↓			One-sided p = 0.025 Two-sided p = 0.050 ↓			One-sided p = 0.160 Two-sided p = 0.320 ↓		

Note: Blue shading indicates that **cipaglucosidase alfa/miglustat** is directionally favoured over alglucosidase alfa/placebo. Yellow shading indicates that **alglucosidase alfa/placebo** is directionally favoured over cipaglucosidase alfa/miglustat. ↑ denotes improvement from baseline; ↓ worsening from baseline. Wording in **bold** and purple shading indicates nominal significance.

Abbreviations: 6MWD, 6-minute walk distance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; FVC, forced vital capacity; GSGC, gait, stairs, Gower's manoeuvre, chair; LOCF, last observation carried forward; LS, least-squares; MMT, manual muscle test; NR, not reported; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.

7.1.2.5. Patient-reported outcomes

In addition to PROMIS–Physical Function and PROMIS–Fatigue, differences in PROMIS–Dyspnoea, PROMIS–Upper Extremity, R-PAct, EQ-5D-5L, subject global impression of change (SGIC) and physician's global impression of change (PGIC) outcomes were assessed between treatment arms. A similar improvement in PROMIS–Dyspnoea, PROMIS–Upper Extremity, R-PAct and EQ-5D-5L was reported in both treatment arms, but SGIC and PGIC demonstrated a consistently greater improvement favouring cipaglucosidase alfa/miglustat over alglucosidase alfa/placebo in the overall population.

See Appendix N – Patient-reported outcomes for further details.

7.1.2.6. Biomarkers

Efficacy outcomes for values of key biomarkers are summarised in brief below. For further details, see Appendix O – Biomarkers: change in baseline absolute values of key biomarkers at 52 weeks.

7.1.2.6.1. Change from baseline in absolute values of key biomarkers at 52 weeks in the overall population (ERT-experienced and ERT-naïve)

Levels of biomarkers representative of muscle damage (CK) and disease substrate (Hex4) were significantly reduced ($p < 0.001$) in the cipaglucosidase alfa/miglustat arm compared with the alglucosidase alfa/placebo arm.

Mean change from baseline absolute CK value was −130.5 U/L (SD, 231.2) in the cipaglucosidase alfa/miglustat arm and 60.2 U/L in the alglucosidase alfa/placebo arm (ANCOVA LS mean treatment difference, −176.0 U/L [95% CI, −244.4, −107.6]; nominal one-sided $p < 0.001$).

7.1.2.6.2. Change from baseline in absolute values of key biomarkers at 52 weeks stratified by ERT status

As reported for the overall population, a nominally statistically significant reduction in CK and Hex4, a marker of muscle damage and a disease-specific marker, was observed in both the ERT-experienced and ERT-naïve populations.

In the ERT-experienced population, mean changes in absolute CK and Hex4 values were −118.0 U/L (SD, 228.8) and −1.69 mmol/mol creatinine (SD, 2.41) in the cipaglucosidase alfa/miglustat arm, respectively, and 79.6 U/L (SD, 147.5) and 1.89 mmol/mol creatinine (SD, 4.61) in the alglucosidase alfa/placebo arm, respectively (ANCOVA LS mean treatment difference, CK: −179.7 (−253.9, −105.5); nominal one-sided $p < 0.001$; HEX4: −2.68 (−4.0, −1.33); nominal one-sided $p < 0.001$).

7.1.2.7. Safety and tolerability

All data presented in this section pertain to the safety population, defined as patients who received at least one dose of study treatment. Additional safety data are presented in Appendix E – Safety data for intervention and comparator.

7.1.2.7.1. Summary of treatment-emergent adverse events and serious treatment-emergent adverse events

Almost all patients in the safety population experienced a TEAE (cipaglucosidase alfa/miglustat, 95.3% vs alglucosidase alfa/placebo, 97.4%). The number of patients discontinuing treatment owing to TEAEs was low, and no patients died because of a TEAE. A summary of safety data is given in Table 14.

As discussed in Section 14.2.5, five patients in the cipaglucosidase alfa/miglustat arm discontinued study treatment, three owing to TEAEs: one patient discontinued owing to COVID-19-related pneumonia and two

patients because of IARs. A single patient in the alglucosidase alfa/placebo arm discontinued treatment, owing to a cerebrovascular accident that was considered by the investigator as unrelated to study drug.

Table 14: PROPEL summary of safety data (safety population)

	Number of patients, n (%)			
	Cipaglucosidase alfa/miglustat (n = 85)		Alglucosidase alfa/placebo (n = 38)	
Any TEAE	**81 (95.3)**		**37 (97.4)**	
Any TEAE leading to discontinuation of study drug	2 (2.4)[a]		1 (2.6)	
Any TEAE potentially related to treatment	**Cipaglucosidase**	**Miglustat**	**Alglucosidase alfa**	**Placebo**
	24 (28.2)	18 (21.2)	10 (26.3)	11 (28.9)
Discontinuation of study drug owing to potentially drug-related TEAEs	2 (2.4)	0	0	0
Any serious TEAEs	**8 (9.4)**		**1 (2.6)**	
Any serious TEAE leading to discontinuation of study drug	1 (1.2)		1 (2.6)	
Any serious TEAEs potentially related to treatment	**Cipaglucosidase**	**Miglustat**	**Alglucosidase alfa**	**Placebo**
	1 (1.2)	0	0	0
Discontinuation of study drug owing to potentially drug-related TEAEs	1 (1.2)	0	0	0
TEAEs leading to death	0		0	

Note: [a]A further patient discontinued treatment owing to COVID-19-related pneumonia.
Five subjects in the cipaglucosidase alfa/miglustat group discontinued from the study as follows: 3 subjects discontinued due to an AE (discontinued due to COVID-19-related pneumonia [classified as other], withdrew consent due to an IAR [classified as withdrawn consent], and was withdrawn due to an IAR [classified as investigator's decision]); 1 subject withdrew due to the COVID-19 pandemic (did not want to visit site for infusion due to the COVID-19 pandemic); and 1 subject withdrew consent due to not wanting to travel to the site. In the alglucosidase alfa/placebo group, 1 subject discontinued from the study due to a cerebrovascular accident AE that was considered by the investigator to be unrelated to study drug.
The details re: the COVID pneumonia AE is that it started >30 days after the patient's last dose of study medication, and was not considered treatment-emergent based on prespecified analysis rules. Of the 5 subjects in the cipaglucosidase alfa/miglustat group who discontinued, 3 subjects discontinued due to an AE: discontinued due to an SAE of COVID-19-related pneumonia ("Other" was checked by the Principal investigator (PI) for reason of premature discontinuation); withdrew consent due to an SAE of IAR/anaphylactic event ("Withdrawal of consent by subject" was checked by the PI for reason of premature discontinuation); withdrawn due to an IAR/chills ("Investigator's decision" was checked by the PI for reason of premature discontinuation). One subject withdrew due to the COVID-19 pandemic (did not want to visit site for infusion due to the COVID-19 pandemic); and 1 subject withdrew consent due to not wanting to travel to the site
Abbrevations: TEAE, treatment-emergent adverse event.

7.1.2.7.2. Treatment-emergent adverse events

The incidence of TEAEs occurring in at least 10% of patients in either treatment arm of the safety population is summarised in Table 15.

The most frequently reported TEAEs in the cipaglucosidase alfa/miglustat arm were fall (29.4%), headache (23.5%), nasopharyngitis (22.4%) and myalgia (16.5%), and in the alglucosidase alfa/placebo arm were fall (39.5%), headache (23.7%), nausea (21.1%) and back pain (18.4%; Table 15).

Table 15: PROPEL incidence of TEAEs in at least 10% of patients (safety population)

TEAE	Number of patients, n (%)	
	Cipaglucosidase alfa/miglustat (n = 85)	Alglucosidase alfa/placebo (n = 38)
Any	81 (95.3)	37 (97.4)
Fall	25 (29.4)	15 (39.5)
Headache	20 (23.5)	9 (23.7)
Nasopharyngitis	19 (22.4)	3 (7.9)
Myalgia	14 (16.5)	5 (13.2)
Arthralgia	13 (15.3)	5 (13.2)

Nausea	10 (11.8)	8 (21.1)
Back pain	9 (10.6)	7 (18.4)
Diarrhoea	11 (12.9)	4 (10.5)
Urinary tract infection	12 (14.1)	2 (5.3)
Fatigue	8 (9.4)	5 (13.2)
Pain in extremity	11 (12.9)	2 (5.3)
Oropharyngeal pain	10 (11.8)	2 (5.3)

Abbreviations: TEAE, treatment-emergent adverse event.

The most frequently reported drug-related TEAEs were headache (7.1%) and diarrhoea (5.9%) in the cipaglucosidase alfa/miglustat arm (considered related to cipaglucosidase alfa or miglustat), and nausea (13.2%) and fatigue (10.5%) in the alglucosidase alfa/placebo arm (considered related to alglucosidase alfa/placebo alfa or placebo). Study drug-related TEAEs, including system organ class groupings, are summarised in Table 16.

Table 16: PROPEL incidence of study drug-related TEAEs in at least 5% of patients (safety population)

Study drug-related TEAE	Cipaglucosidase alfa/miglustat (n = 85)		Alglucosidase alfa/placebo (n = 38)	
	Cipaglucosidase alfa	Miglustat	Alglucosidase alfa/placebo	Placebo
Any	24 (28.2)	18 (21.2)	10 (26.3)	11 (28.9)
Gastrointestinal disorders	**7 (8.2)**	**11 (12.9)**	**3 (7.9)**	**8 (21.1)**
Abdominal distension	3 (3.5)	3 (3.5)	0	2 (5.3)
Abdominal pain	0	0	1 (2.6)	3 (7.9)
Abdominal pain upper	1 (1.2)	1 (1.2)	1 (2.6)	2 (5.3)
Diarrhoea	2 (2.4)	5 (5.9)	0	2 (5.3)
Flatulence	1 (1.2)	1 (1.2)	0	2 (5.3)
Nausea	0	2 (2.4)	2 (5.3)	5 (13.2)
General disorders and administration site conditions	**8 (9.4)**	**2 (2.4)**	**5 (13.2)**	**3 (7.9)**
Fatigue	1 (1.2)	0	4 (10.5)	3 (7.9)
Musculoskeletal and connective tissue disorders	**3 (3.5)**	**4 (4.7)**	**2 (5.3)**	**1 (2.6)**
Nervous system disorders	**14 (16.5)**	**7 (8.2)**	**6 (15.8)**	**2 (5.3)**
Dizziness	4 (4.7)	0	2 (5.3)	0
Headache	6 (7.1)	2 (2.4)	2 (5.3)	1 (2.6)
Skin and subcutaneous tissue disorders	**5 (5.9)**	**0**	**2 (5.3)**	**1 (2.6)**
Pruritus	2 (2.4)	0	2 (5.3)	1 (2.6)

Abbreviations: TEAE, treatment-emergent adverse event.

7.1.2.7.3. Severe TEAEs

Most TEAEs were mild or moderate in severity. Severe TEAEs were reported in eight patients (13 severe TEAEs in total) in the cipaglucosidase alfa/miglustat arm and two patients (three severe TEAEs) in the alglucosidase alfa/placebo arm. The incidence of severe TEAEs is summarised in Table 17.

Table 17: PROPEL incidence of severe TEAEs (safety population)

Severe TEAE	Number of patients, n (%)	
	Cipaglucosidase alfa/miglustat (n = 85)	Alglucosidase alfa/placebo (n = 38)
Any	**8 (9.4)**	**2 (5.3)**
Gastrointestinal disorders	**1 (1.2)**	**0**

Abdominal pain	1 (1.2)	0
Enteritis	1 (1.2)	0
Vomiting	1 (1.2)	0
General disorders and administration site conditions	**1 (1.2)**	**0**
Chills	1 (1.2)	0
Immune system disorders	1 (1.2)	0
Anaphylactoid reaction	1 (1.2)	0
Infections and infestations	0	1 (2.6)
Diverticulitis	0	1 (2.6)
Injury, poisoning and procedural complications	**2 (2.4)**	**0**
Accidental overdose	1 (1.2)	0
Fall	1 (1.2)	0
Investigations	**1 (1.2)**	**0**
Heart rate irregular	1 (1.2)	0
Nervous system disorders	0	1 (2.6)
Cerebrovascular accident	0	1 (2.6)
Renal and urinary disorders	**0**	**1 (2.6)**
Glycosuria	0	1 (2.6)
Respiratory, thoracic and mediastinal disorders	**1 (1.2)**	**0**
Dyspnoea	1 (1.2)	0
Skin and subcutaneous tissue disorders	**1 (1.2)**	**0**
Pruritus	1 (1.2)	0
Urticaria	1 (1.2)	0
Vascular disorders	**2 (2.4)**	**0**
Aortic aneurysm	1 (1.2)	0
Flushing	1 (1.2)	0

Abbreviations: TEAE, treatment-emergent adverse event.

7.1.3. Supporting study ATB200-02 – phase 1/2 single-arm trial

For details, see Appendix Q – Supporting studies ATB200-02 and ATB200-07.

7.1.4. Supporting study ATB200-07 – open-label extension of the PROPEL study

For details, see Appendix Q – Supporting studies ATB200-02 and ATB200-07.

7.1.5. Comparative analyses of efficacy and safety

7.1.5.1. Cipaglucosidase alfa/miglustat vs. Alglucosidase alfa/placebo

As direct head-to-head evidence is available for the comparison of cipaglucosidase alfa/miglustat with alglucosidase alfa/placebo for long-term treatment of adults with a confirmed diagnosis of Pompe disease, the outcomes from the PROPEL trial are considered (see Section 7.1.2).

7.1.5.2. Cipaglucosidase alfa/miglustat vs. best supportive care

There is no head-to-head evidence comparing cipaglucosidase alfa/miglustat with BSC for treatment of adults with a confirmed diagnosis of Pompe disease; hence, an indirect treatment comparison (ITC) analysis is needed and presented.

Best supportive care was assessed as best informed by the placebo arm in the LOTS trial (van der Ploeg 2010). This patient group would function as a proxy for 'BSC', being reliant on other supportive measures in the absence of any available ERT at the time. This is in contrast to the 'ERT naïve' arms of more recent clinical trials, which likely included patients considered for pharmaceutical treatments early in their patient journey, and therefore not necessarily on 'BSC'. However, as discussed in Section 5.2.3, Amicus would like to highlight that this scenario is purely theoretical and does not bear any clinical relevance in Denmark.

7.1.5.2.1. Objective

The aim of this ITC study was to report relative effects for three ERTs using an indirect treatment comparison. A multi-level network meta regression (ML-NMR) was considered the most suitable approach in an LOPD population that includes a mix of ERT-naïve and ERT-experienced patients, similar to the pivotal Phase III trial comparing cipaglucosidase alfa/miglustat with alglucosidase alfa (PROPEL). To do this analysis most effectively, RCT data were compared with the addition of single-arm and extension-trial data matched to comparator arms. In addition, we also report the analysis with RCT-only data.

7.1.5.2.1.1. Rationale

The COMET trial (N=100) (Diaz-Manera 2021) compared avalglucosidase alfa to alglucosidase alfa in exclusively ERT-naïve patients, while the PROPEL trial (N=123) (Schoser 2021a) compared cipaglucosidase alfa/miglustat to alglucosidase alfa in primarily ERT-experienced patients with a smaller cohort of naïve patients (77% ERT-experienced, 23% ERT-naïve). This is more closely aligned with the real-world population of LOPD patients as demonstrated by ongoing registry studies in which approximately 78–80% of patients have received ERT previously (Byrne 2011, Semplicini 2020).

In the absence of head-to-head trials comparing cipaglucosidase alfa/miglustat with avalglucosidase alfa with , an indirect treatment comparison (ITC) is a suitable approach to better understand the clinical differentiation of the three treatments available or potentially forthcoming for LOPD.

If the trial populations had comparable naïve and experienced populations, a simple network meta-analysis (NMA) could be conducted, as COMET and PROPEL were RCT sharing the two key endpoints of 6MWD and FVC.

As mentioned, BSC was informed by the placebo arm in the LOTS trial (van der Ploeg 2010); see Section 7.1.5.2 for further details and rational.

7.1.5.2.2. Methods

A systematic literature review (SLR) was conducted to identify relevant published clinical studies of ERTs in LOPD. Outcomes assessed were change from baseline in 6-minute walking distance (6MWD) (m) and in forced vital capacity (FVC; % predicted) at week 52, acknowledged by clinicians, HTA agencies and payers as key LOPD trial endpoints (Raza 2022b). Aggregate results on 6MWD and FVC change from baseline over time and baseline characteristics (age, gender, ethnicity, previous ERT duration, baseline 6MWD and baseline FVC) were extracted from included studies.

A multi-level network meta regression (ML-NMR) was performed, which is an extension of standard network meta-analyses (NMAs) that take into account the effect of study-level covariates, and that can be applied to any connected network with any mixture of individual patient-level data (IPD) and aggregate data (Phillippo 2020). ML-NMR is an accepted method by the National Institute for Health and Care Excellence (NICE) (Phillippo 2020, Welton 2020) in support of cost effectiveness analysis.

Single-arm study results were matched to appropriate comparator arms of the comparative studies to allow for inclusion into the network (Leahy 2019). Mean treatment differences with associated 95% credible intervals (CrIs) were calculated for 6MWD and FVC change from baseline at week 52.

A base-case scenario was evaluated in which all covariates were set to the target population of the PROPEL trial. To study the impact of previous ERT duration on relative effects, ERT duration value was varied, keeping remaining covariate values as in the base-case scenario. A sensitivity analysis was performed by excluding all matched single-arm evidence from the network to assess its impact on the results.

Both fixed effects (FE) and random effects (RE) ML-NMR models were applied and the deviance information criteria (DIC) was used to assess goodness-of-fit of the models and to identify the appropriate model (FE or RE model) for the data. Models were implemented in a Bayesian framework using Stan with help of the R package multinma (Phillippo 2020).

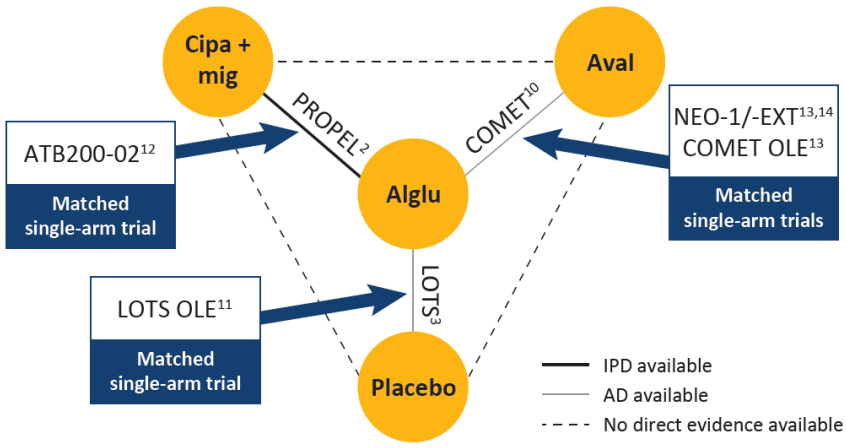
7.1.5.2.3. Network

The SLR identified seven clinical studies (see Figure 13). These studies included but were not limited to three randomised clinical trials - LOTS: alglucosidase alfa versus Placebo (van der Ploeg 2010); COMET: avalglucosidase alfa vs alglucosidase alfa (Diaz-Manera 2021); PROPEL: cipaglucosidase alfa/miglustat vs alglucosidase alfa (Schoser 2021a). Each share 6MWD and FVC as key primary or secondary endpoints (see Figures 1 and 2), but differ in their trial populations (PROPEL is the only randomised controlled trial [RCT] that comprised both ERT-naïve and -experienced subjects).

For both endpoints, the network is the same and shown in Figure 13.

Evidence from the single-arm studies LOTS OLE, NEO-1/-EXT, COMET OLE and ATB200- 02 was included into the network, as shown in the blue boxes, by matching the single arm results to appropriate comparator results from the head-to-head trials.

Figure 13: Network for 6MWD (meters) and sitting FVC (% predicted)



Abbreviations: 6MWD, 6-minute walking distance; AD, aggregate data; alglu, alglucosidase alfa; aval, avalglucosidase alfa; cipa+mig, cipaglucosidase alfa/miglustat; FVC, forced vital capacity; IPD, individual patient data; RCT, randomised controlled trial
Note: sources associated with the trials COMET (Diaz-Manera 2021), PROPEL (Schoser 2021a); NEO-1/-EXT (Center for Drug Evaluation and Research 2020, Dimachkie 2022b), COMET OLE (Kishnani 2023), ATB200-02 (Schoser 2022), and PROPEL OLE (Schoser 2023)
Source: (Fu 2022). Figure number source: 2: (Schoser 2021a) 3: (van der Ploeg 2010) 10: (Diaz-Manera 2021) 11: (Van der Ploeg 2012) 12: (Byrne 2022) 13: (Center for Drug Evaluation and Research) 14: (Dimachkie 2022a)

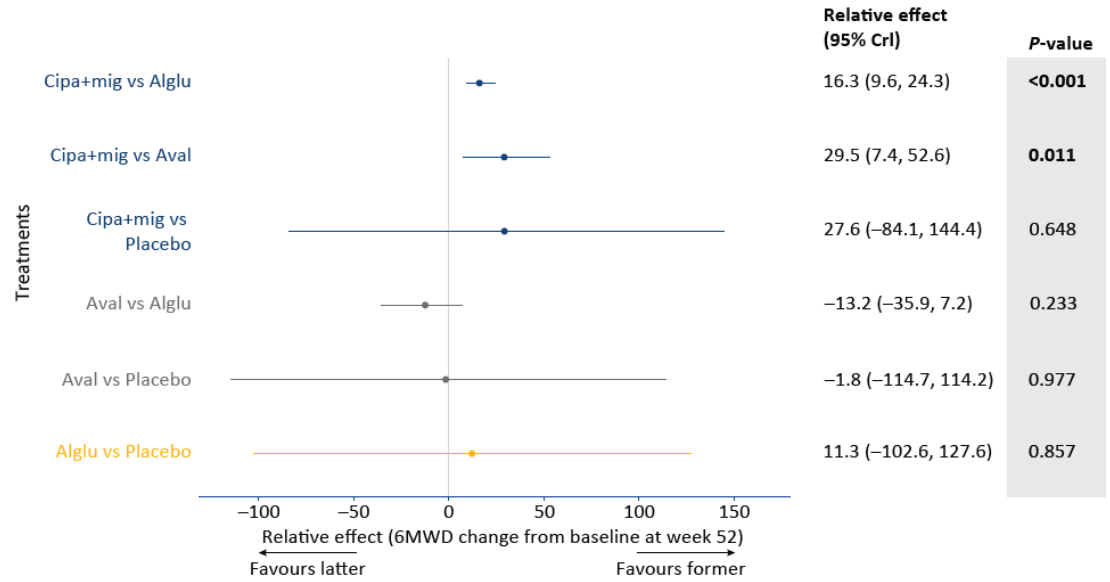
Note, for the PROPEL trial, the data as published in Schoser 2021 (Schoser 2021a) was considered, which is consistent with the CSR data presented in Section 7.1.2.

7.1.5.2.3.1. Multi-level network meta regression (ML-NMR) results

7.1.5.2.3.1.1. Results for main analysis

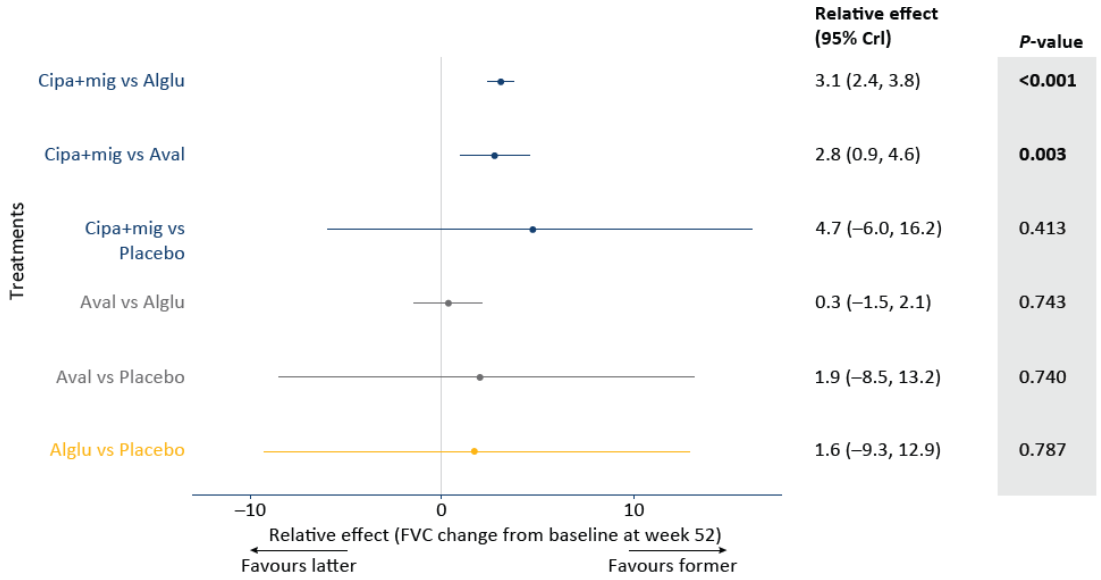
Based on the DIC, an RE model was chosen for 6MWD and an FE model for FVC. For both endpoints (Figure 14 and Figure 15) cipaglucosidase alfa/miglustat showed a statistically significant favourable effect versus avalglucosidase alfa and alglucosidase, and a numerically favourable effect versus placebo.

Figure 14: Forest plot of relative effect estimates with 95% credible intervals for 6MWD in the base-case scenario (main analysis)



Abbreviations: 6MWD, 6-minute walking distance; alglu, alglucosidase alfa; aval, avalglucosidase alfa; cipa+mig, cipaglucosidase alfa/miglustat; CrI, credible interval; RCT, randomised control trial.
Source: (Fu 2022)

Figure 15: Forest plot of relative effect estimates with 95% credible intervals for FVC in the base-case scenario (main analysis)



Abbreviations: alglu, alglucosidase alfa; aval, avalglucosidase alfa; cipa+mig, cipaglucosidase alfa/miglustat; CrI, credible interval; FVC, forced vital capacity; RCT, randomised control trial.
Source: (Fu 2022)

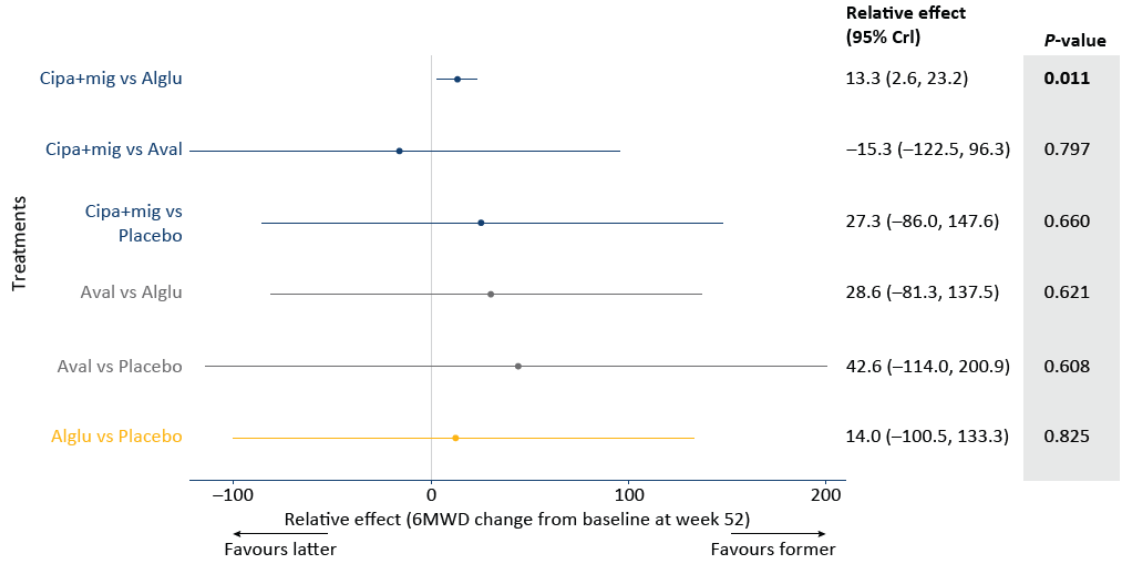
Note that the 95% CrIs of the relative effect estimates versus placebo are generally much wider than those versus Alglu or versus Aval. This reflects the larger uncertainty of those estimates, since data on placebo were only available for ERT naïve subjects and previous ERT duration of the base-case scenario is relatively long (5.7 years).

7.1.5.2.3.1.2. Sensitivity analysis (only RCTs included in the network)

RE models were chosen for both 6MWD and FVC based on the DIC. Figure 16 and Figure 17 provide an overview of the relative effect estimates with 95% CrIs for the base-case scenario using the sensitivity analysis and show:

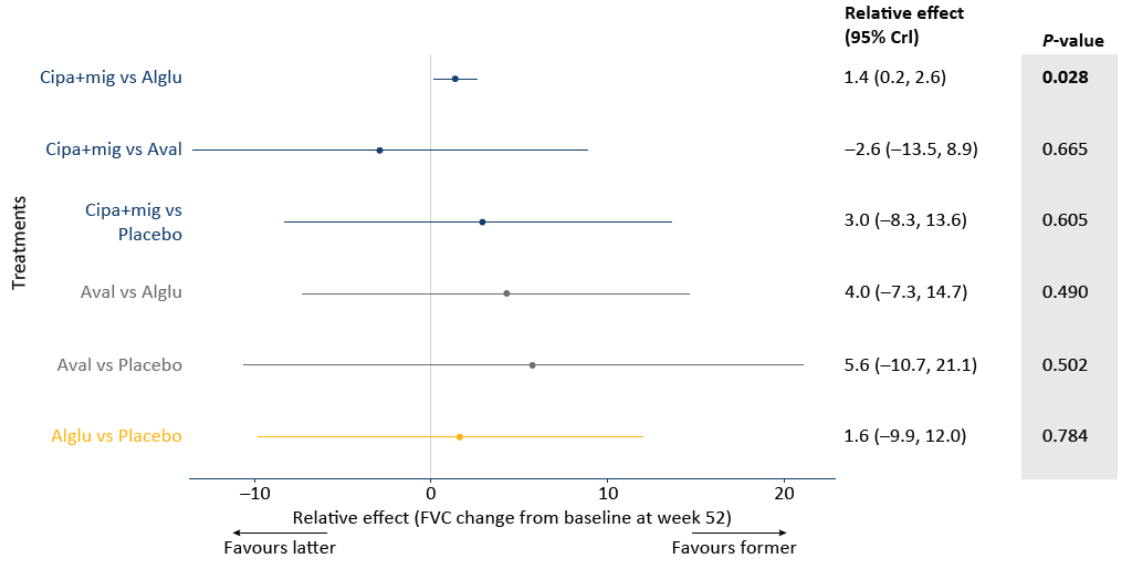
- Inclusion of matched single-arm evidence into the network for the main analysis reduces uncertainty of the relative effect estimates
- Cipaglucosidase alfa/miglustat: statistically favourable versus alglucosidase alfa; numerically unfavourable versus avalglucosidase alfa; numerically favourable versus placebo (6MWT and FVC)
- Avalglucosidase alfa: numerically favourable versus alglucosidase alfa and placebo (6MWT and FVC)
- Alglucosidase alfa: numerically favourable versus placebo

Figure 16: Forest plot of relative effect estimates with 95% credible intervals for 6MWD in the base-case scenario (sensitivity analysis)



Abbreviations: 6MWD, 6-minute walking distance; alglu, alglucosidase alfa; aval, avalglucosidase alfa; cipa+mig, cipaglucosidase alfa/miglustat; CrI, credible interval; RCT, randomised control trial.
Source: (Fu 2022)

Figure 17: Forest plot of relative effect estimates with 95% credible intervals for FVC in the base-case scenario (sensitivity analysis)



Abbreviations: alglu, alglucosidase alfa; aval, avalglucosidase alfa; cipa+mig, cipaglucosidase alfa/miglustat; CrI, credible interval; FVC, forced vital capacity RCT, randomised control trial.
Source: (Fu 2022)

7.1.5.2.4. Limitations of the analysis

Although matching of single-arm trials increases the precision and the number of data points it can result in biased relative effect estimates when there is high heterogeneity between the single and the matched arm. The consequences of removing matched single-arm trials from the network were explored in the sensitivity analysis, yielding mainly an increase in uncertainty of the relative effect estimates since the single-arm trials contributed evidence on treatment effects in ERT-experienced patients who were part of the target population of interest. Hence, there is a trade-off between a potential bias in the relative effect estimates and an increase in uncertainty of those estimates. The ML-NMR method can adjust the relative effect estimates for any observed effect modifier available; unobserved effect modifiers or effect modifiers not available in the data cannot be accounted for.

Health economic analysis

8.1. Model

The cost-effectiveness model was built using Microsoft Excel® and was designed in a flexible, user-friendly format whereby the user could access a full range of input sheets and run various scenarios by choosing from the options provided in an initial set-up sheet. The model was built to allow all major inputs to be easily changed by the model user, including but not limited to, the treatment and comparator efficacy data, cost/resource use inputs and utility inputs. This flexibility was deemed to be important given the need for the model to be easily adapted in the future.

The key elements of the modelling approach adopted are summarised in Table 18. Please note that further detail regarding each element of the model is provided within the methods sections below.

Table 18: Summary of economic modelling approach

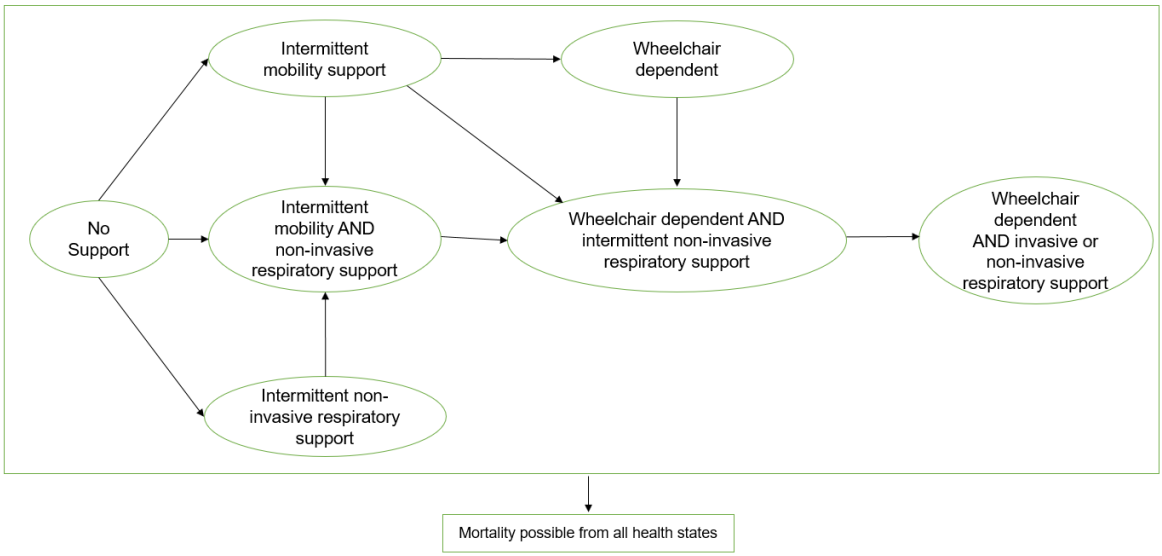
Model element	Description	Source
Population	The base case applies to the overall population (ERT naïve and experienced)	Amicus
Perspective	Limited societal perspective	Per DMC guidelines
Model design	Patient-level simulation	Amicus
Discount rate	3.5% years 0-35, 2.5% years 36-70	The current discounting rate from the Ministry of Finance (Finansministeriet 2021)
Intervention	AT-GAA: cipaglucosidase alfa (ATB200) combined with miglustat (AT2221)	Amicus
Comparator(s)	1. Alglucosidase alfa: standard enzyme replacement therapy [ERT, Myozyme®] (20mg/kg) 2. Best supportive care [BSC] (symptom management with no active treatment)	Amicus
Time horizon	Lifetime	Amicus
Key outcomes of the model	Incremental cost-effectiveness ratio (ICER), net monetary benefit (NMB) and incremental budget impact	Amicus
Sensitivity analysis	Deterministic, probabilistic and scenario analyses	Amicus

A patient-level simulation model was produced to estimate the cost-effectiveness of cipaglucosidase alfa/miglustat for the treatment of LOPD over a lifetime time horizon. The model structure was based upon the cipaglucosidase alfa/miglustat Phase III PROPEL study. Therefore, the primary and key secondary outcomes from the trial, the 6MWT and %pred FVC, were used to determine the muscular and respiratory deterioration of patients throughout the model time horizon respectively. Such outcomes are often presented as a percentage of predicted normal values to account for age, height, weight and sex (Quanjer 2012).

The final model structure, which was updated following a consultation with the Preliminary Independent Model Advice (PRIMA) service offered by NICE, is presented in Figure 18. Patients were stratified into specific health

states based on whether they required no mobility support, intermittent mobility support (a variety of mobility aids and the occasional use of a 'manual' wheelchair) or were wheelchair dependent (patients within this health state were expected to require the use of powered wheelchairs and no longer able to use alternative mobility aids). Patients were also stratified by whether they required no respiratory support, intermittent respiratory support, or were dependent on respiratory support (either non-invasive or invasive ventilation). Following clinical advice, it was assumed that intermittent respiratory support should be considered a proxy for nocturnal ventilation only (i.e. no daytime support) and respiratory dependent a proxy for when both daytime and nocturnal ventilation was required.

Figure 18 Schematic of model structure



The transitions between the health states presented in Figure 18 were determined by the main outcomes described above. More precisely, the 6MWT score was used to model the decline in mobility and, therefore, the point by which intermittent mobility support would be required and the point at which each patient became wheelchair dependent. Similarly, the %pred FVC was used to model the decline in lung function and, therefore, the point at which intermittent and permanent respiratory support would be required.

One clinical expert in the UK advised that patients would not receive invasive ventilation until they were dependent on respiratory support. Therefore, it was assumed that all patients would receive non-invasive respiratory support whilst intermittent support was required. In the base case analysis, all patients that were dependent on ventilation were assumed to receive invasive ventilation. However, the model included functionality for the user to determine the proportion of patients receiving non-invasive and invasive ventilation within the dependent health state (with a weighted cost and utility applied).

To predict the 6MWT and %pred FVC decline, each patient that entered the patient-level simulation model was randomly assigned baseline 6MWT and %pred FVC values, based on pre-defined distributions. Next, that patient was assigned a rate of change in 6MWT and %pred FVC, again based on relevant distributions, which generally led to a long-term decline in these outcomes. When that patient's 6MWT and %pred FVC had declined by a sufficient amount this then caused them to move to an alternative health state. For example, if their 6MWT declined to the point of being unable to walk more than a short distance then it was assumed that intermittent mobility support would be required. Therefore, that patient would enter the relevant mobility support health state (dependent on whether they also required respiratory support or not).

The point at which a patient's condition had declined to the point of requiring intermittent mobility support/wheelchair dependence and/or respiratory support was determined by specific threshold values for the 6MWT and %pred FVC respectively. Due to a lack of precedence on the most valid values to adopt for these thresholds within current practice, and in the published literature, the values for both outcomes were again informed and validated by the UK Pompe disease clinical experts. These Pompe clinical experts advised that a LOPD patient would need to use mobility support once they were unable to walk more than 250m within the 6MWT. Furthermore, the experts indicated patients would become wheelchair dependent once their 6MWT score fell below 150m (this result would indicate the patient was not stable enough to walk unassisted for six minutes).These threshold values were confirmed by Danish experts (Section 11).

The UK clinicians were unable to indicate the %pred FVC threshold at which patients would require intermittent and permanent respiratory support. Instead, the clinicians recommended using literature from Duchenne Muscular Dystrophy as a proxy for LOPD. A previous NICE submission for Duchenne Muscular Dystrophy indicated that patients require ventilation assistance once their %pred FVC falls below 30% (National Institute for Health and Care Excellence 2016). Evidence from idiopathic pulmonary fibrosis indicates that patients with this disease require ventilation support once their %pred FVC falls below 50%. Therefore, for the current model, the mid-point of these two values was utilised (i.e. 40%) as the threshold for intermittent respiratory support. It was also assumed that patients would become dependent on ventilation support once their %pred FVC fell by a further 10%.

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

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

Table 19: Input data used in the model:

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Important baseline characteristics			
Percentage male	45.5% (N/A)	45.5% (N/A)	PROPEL (Amicus Therapeutics 2021b)
Average patient age	46.80 (13.270)	46.80 (13.270)	PROPEL (Amicus Therapeutics 2021b)
Average patient weight (kg)	74.71 (14.696)	74.71 (14.696)	PROPEL (Amicus Therapeutics 2021c)
Average patient height (cm)	171.45 (9.634)	171.45 (9.634)	PROPEL (Amicus Therapeutics 2021c)
Baseline 6MWT	Overall: 356 (113.915) ERT naïve: 398 (115.578) ERT experienced: 343 (110.970)	Overall: 356 (113.915) ERT naïve: 398 (115.578) ERT experienced: 343 (110.970)	PROPEL (Amicus Therapeutics 2021b)
Baseline %pred FVC (sitting)	Overall: 70.5% (0.200) ERT naïve: 80.2% (0.190) ERT experienced: 67.9% (0.196)	Overall: 70.5% (0.200) ERT naïve: 80.2% (0.190) ERT experienced: 67.9% (0.196)	PROPEL (Amicus Therapeutics 2021b)
Posology			
Intervention			
Cipaglucosidase alfa	Every 2 weeks at 20 mg/kg	Every 2 weeks at 20 mg/kg	PROPEL SmPC

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Miglustat	Every 2 weeks, 4 capsules of 65 mg (260 mg total)	Every 2 weeks, 4 capsules of 65 mg (260 mg total)	PROPEL SmPC
Comparator			
Alglucosidase alfa	Every 2 weeks at 20 mg/kg	Every 2 weeks at 20 mg/kg	PROPEL SmPC
Best supportive care	No active treatment	No active treatment	Danish clinical experts (Section 11 List of experts)
Length of treatment			
Intervention			
Cipaglucosidase alfa	Life long	Life long	PROPEL SmPC
Miglustat	Life long	Life long	PROPEL SmPC
Comparator			
Alglucosidase alfa	Life long	Life long	PROPEL SmPC
Best supportive care	Life long	Life long	Hypothetical comparison. Patients would receive active treatment upon diagnosis (Section 11 List of experts)

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Clinical efficacy outcome			
6MWT (absolute m)	Baseline to year one 20.79	20.79	PROPEL (Amicus Therapeutics 2021b)
	Year one to year two 12.39	12.39	Weighted average experienced and naïve (Byrne 2020)
	Year two to year three 11.93	11.93	
%pred FVC	Baseline to year one -0.9%	-0.9%	PROPEL (Amicus Therapeutics 2021b)
	Year one to year two 3.0%	3.0%	Weighted average experienced and naïve (Byrne 2020)
	Year two to year three 0.1%	0.1%	
Adverse events	-	-	Assumed to not differ between treatments. See Section 8.2.2.5.
Alglucosidase alfa long term efficacy inputs			
All populations: %pred 6MWT	-2.3%	-2.3%	(Semplicini 2020)
All populations: %pred FVC	-0.9%	-0.9%	
Cipaglucosidase Alfa/Miglustat long term efficacy inputs			See Section 8.3.2.
Health state utility values used in the model			Estimated according to DMC guidelines using Jensen et al. 2021. See Section 8.4.

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Drug acquisition costs			
Cipaglucosidase alfa	-	[redacted]	AMICUS
Miglustat	-	[redacted]	AMICUS
Alglucosidase alfa	-	3 105.10 DKK	Produktvisning - www.medicinpriser.dk
Drug administration costs			
Hospital: cost per administration		1 386.34 DKK	Kommunernes og Regionernes Løndatakontor 2023, Chief physician. Bruttoløn February 2023 available from: https://krl.dk/#/sirka, Accessed May 2023. Calculated monthly salary/hours per month (DKK 130 316 divided by 94 hours) according to Medicines Council 2023 guideline Resource used based on Danish clinical experts (Section 11 list of clinical experts)
Home (nurse administration): cost per hour		1 386.34 DKK	
Home (self administration, nurse time for required for reconstitution (hours))		1 386.34 DKK	
Patient management costs			
Consultant neurologist appointment		1 386.34 DKK	Kommunernes og Regionernes Løndatakontor 2023, Chief physician. Bruttoløn February 2023 available from: https://krl.dk/#/sirka, Accessed May 2023. Calculated monthly salary/hours per month (DKK 130 316 divided by 94 hours) according to Medicines Council 2023 guideline Resource used based on Danish clinical experts (Section 11 list of clinical experts)
Non-invasive ventilation support assessment		1 386.34 DKK	
Respiratory physiology consultant appointment		1 386.34 DKK	

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Physiotherapist visit		1 386.34 DKK	
Non-invasive ventilation		Annual costs: 36 150 DKK	Sundhedsdatastyrelsen (2022). Interactive DRG: 01MA15 - Andre specifikke sygdomme i nervesystemet, pat. mindst 18 år. Available at: http://interaktivdrg.sundhedsdata.dk/
Invasive ventilation		Upfront unit cost: 1 137 431 DKK Annual costs: 858 427 DKK	No relevant DK cost identified. Approach decribed below: **Upfront cost** NEO-GAA NICE submission (2022): https://www.nice.org.uk/guidance/gid-ta10876/documents/committee-papers, Accessed May 2023 Table 36: Health state costs for ventilation and wheelchair states. Ventilation: Invasive ventilation (home): One -off cost. Converted to DKK using oanda.com Inflated to April 2023 based on Statistics Denmark KPI April 2022 to April 2023, https://www.dst.dk/da/Statistik/emner/oekonomi/prisindeks/forbrugerprisindeks, Accessed May 2023 **Annual costs** Sundhedsdatastyrelsen (2023). Interactive DRG: 01MA15 long term (>12hrs) (BGDA61) Manuel ventilation gennem trakealtube (DG728) Anden myopati. Available at: http://interaktivdrg.sundhedsdata.dk/ Costs consider per 1 year of 365 days
Intermittent mobility: Manual wheelchair		4995 DKK	Hjaelpemiddelbasen Dolphin kørestol med ledsagerbremse Dolphin kørestol med ledsagerbremse fra FNP Hjælpemidler - Hjælpemiddelbasen (hmi-basen.dk)

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Wheelchair dependent:		**Powered wheelchair:** 34 990 DKK **Home adjustments:** 263 084 DKK **Hoist:** 80 264 DKK	**Powered wheelchair** Hjaelpemiddelbasen. Eloflex D2. https://hmi-basen.dk/r11x.asp?linkinfo=72534 **Home adjustments** NEO-GAA NICE submission: https://www.nice.org.uk/guidance/gid-ta10876/documents/committee-papers Table 36: Health state costs for ventilation and wheelchair states; home adjustments and hoist (converted to DKK on 3 May 2023, oanda.com) **Hoist** Hjaelpemiddelbasen. Esense Line Drive. https://hmi-basen.dk/r11x.asp?linkinfo=72534
Patients time costs			
Unit cost for transportation	140 DKK	140 DKK	Cost unit (140 DKK per visit of transportation) is sourced from Medicinrådet (2023), Værdisætning af enhedsomkostninger-vers. 1.2 (medicinraadet.dk)
Patient time cost per visit	812 DKK	812 DKK	Assumption of 4 hours for administration of infusion at hospital. Cost unit (203 DKK per hour of patient/caregiver time) is sourced from Medicinrådet (2023), Værdisætning af enhedsomkostninger-vers. 1.2 (medicinraadet.dk)
Caregiver time costs	812 DKK	812 DKK	

Abbreviations: 6MWT, six minute walk test; ERT, enzyme replacement therapy; FVC, forced vital capacity; NA: not applicable

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

8.2.2.1. Patient population

The economic model estimated results for the following three separate populations, which were chosen to align with the inclusion criteria for the phase III PROPEL study (Amicus Therapeutics 2021b):

- Overall population: All adults with a confirmed diagnosis of LOPD (based on documentation of a deficiency of the GAA enzyme or GAA genotyping).
- ERT naïve: Adults with a confirmed diagnosis of LOPD that have never received alglucosidase alfa.
- ERT experienced: Adults with a confirmed diagnosis of LOPD that have received alglucosidase alfa for ≥ 24 months.

All baseline characteristics (as presented in Table 20) were based upon the overall average of the PROPEL study and stratified by the patient population, where possible. Where available, baseline data were obtained from the clinical study report from the PROPEL study (Amicus Therapeutics 2021b). However, the average weight and height of patients were estimated using individual patient-level data from the PROPEL trial, because these were not reported within the product dossier (Amicus Therapeutics 2021c). All baseline characteristics were varied using a normal distribution within each simulation of the model.

Table 20: Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison (including source)	Used in the model (number/value including source) (SD)	Danish clinical practice (including source)
Percentage male	PROPEL (Amicus Therapeutics 2021b)	45.5% (N/A)	Confirmed by Danish clinical experts (Section 11)
Average patient age	PROPEL (Amicus Therapeutics 2021b)	46.80 (13.270)	Confirmed by Danish clinical experts (Section 11)
Average patient weight (kg)	PROPEL (Amicus Therapeutics 2021c)	74.7 (14.696)	Confirmed by Danish clinical experts (Section 11)
Average patient height (cm)	PROPEL (Amicus Therapeutics 2021c)	171.45 (9.634)	Confirmed by Danish clinical experts (Section 11)
Baseline 6MWT	PROPEL (Amicus Therapeutics 2021b)	Overall: 356 (113.915) ERT naïve: 398 (115.578) ERT experienced: 343 (110.970)	Confirmed by Danish clinical experts (Section 11)
Baseline %pred FVC (sitting)	PROPEL (Amicus Therapeutics 2021b)	Overall: 70.5% (0.200) ERT naïve: 80.2% (0.190) ERT experienced: 67.9% (0.196)	Confirmed by Danish clinical experts (Section 11)

Abbreviations: 6MWT, six minute walk test; ERT, enzyme replacement therapy; FVC, forced vital capacity; NA: not applicable

8.2.2.2. Intervention

Table 21: Intervention

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology			
Cipaglucosidase alfa	PROPEL SmPC	Every 2 weeks at 20 mg/kg	Every 2 weeks at 20 mg/kg

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Miglustat	PROPEL SmPC	Every 2 weeks, 4 capsules of 65 mg (260 mg total)	Administered 1 hour before cipaglucosidase alfa, every 2 weeks For patients weighing ≥ 50 kg, four capsules of 65 mg (260 mg total) For patients weighing ≥ 40 kg to < 50 kg, three capsules of 65 mg (195 mg total)
Length of treatment			
Cipaglucosidase alfa	PROPEL SmPC	Life long	In cases of unacceptable toxicity, or diminished efficacy, treatment can be terminated (Section 11 List of experts)
Miglustat	PROPEL SmPC	Life long	In cases of unacceptable toxicity, or diminished efficacy, treatment can be terminated (Section 11 List of experts)

8.2.2.3. Comparators

Table 22: Comparator

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology			
Alglucosidase alfa	PROPEL SmPC	Every 2 weeks at 20 mg/kg	Every 2 weeks at 20 mg/kg
Best supportive care	Danish clinical experts (Section 11 List of experts)	No active treatment	No active treatment
Length of treatment			
Alglucosidase alfa	PROPEL SmPC	Life long	In cases of unacceptable toxicity, treatment can be terminated
Best supportive care	Danish clinical experts (Section 11 List of experts)	Life long	Hypothetical comparison. Patients would receive active treatment upon diagnosis (Section 11 List of experts)

8.2.2.4. Relative efficacy outcomes

Data from the PROPEL study were used to inform the treatment progression associated with cipaglucosidase alfa/miglustat for each of the patient populations within the model from baseline to year one (as presented in Table 23 (Amicus Therapeutics 2021b). The open-label Phase I/II study was used to inform the change for the first two years within the ERT experienced and naïve populations (Byrne 2020).

A weighted average of the ERT experienced and naïve populations were used to inform the change from years one to two, and two to three within the overall population, due to an absence of alternative information.

Data from the OLE were available for two years only. Therefore, long-term efficacy data was used to inform treatment progression from year two onward (Semplicini 2020).

Danish clinical practice:

Alglucosidase alfa is used in clinical practice in Denmark today, as confirmed by Danish experts (Section 11). Therefore, the comparator used in PROPEL is relevant and transferable to the Danish clinical practice.

Table 23: Initial annual change from baseline (cipaglucosidase alfa/miglustat)

Clinical efficacy outcome	Used in the model				Clinical documentation
Overall Population	**Time period**	**N**	**Mean**	**SE**	**Source**
6MWT (absolute m)	Baseline to year one	85	20.79	4.639	PROPEL (Amicus Therapeutics 2021b)
	Year one to year two	-	12.39	18.283	Weighted average experienced and naïve (Byrne 2020)
	Year two to year three	-	11.93	19.417	
%pred FVC	Baseline to year one	85	-0.9%	0.007	PROPEL (Amicus Therapeutics 2021b)
	Year one to year two	-	3.0%	0.026	Weighted average experienced and naïve (Byrne 2020)
	Year two to year three	-	0.1%	0.023	

Abbreviations: 6MWT, six minute walk test; FVC, forced vital capacity; SE, standard error

Table 24: Summary of text regarding *relevance*

Clinical efficacy outcome	Clinical documentation	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study: 6MWT (absolute m)	PROPEL	Relevant, used in clinical practice as confirmed by Danish experts (Section 11).	Relevant, used in clinical practice as confirmed by Danish experts (Section 11).
Secondary endpoint: %pred FVC	PROPEL	Relevant, used in clinical practice as confirmed by Danish experts (Section 11).	Relevant, used in clinical practice as confirmed by Danish experts (Section 11).

Abbreviations: 6MWT, six minute walk test; FVC, forced vital capacity

8.2.2.5. Adverse reaction outcomes

A targeted literature search was conducted to identify any adverse events associated with the treatment of LOPD.

A randomised, placebo-controlled trial estimating the efficacy and safety of alglucosidase alfa (20mg/kg) in 90 patients with LOPD across America and Europe over 78 weeks was considered the most appropriate source to obtain adverse event rates associated with alglucosidase alfa (van der Ploeg 2010). This study was considered most appropriate because it recruited a greater number of patients, over the longest time horizon, than the alternative trials reporting the frequency of alglucosidase alfa treatment-related adverse events in LOPD patients identified from the burden of illness review conducted by YHEC (Case 2015, Koeberl 2018, Koeberl 2020). Most adverse events were reported to be mild or moderate in severity and were not considered to be related to the study drug, with the frequency of the most commonly frequently events (falls, nasopharyngitis, and headache) considered similar between treatment groups.

The study reported that the rate of serious adverse events was similar between patients in the alglucosidase alfa and placebo arms, and that all serious adverse events had a frequency below 3%. Therefore, no adverse events specific to alglucosidase alfa were included in the base case analysis.

Two serious treatment-related adverse events leading to treatment discontinuation from cipaglucosidase alfa/miglustat (urticaria and skin and subcutaneous tissue disorders) were reported within the phase II study (Table 14.3.1.11.2 CSR). The frequency of these events was less than 5% and, therefore, these particular adverse events were also not included within the model.

The two UK Pompe disease clinical experts commented that, whilst infusion reactions associated with treatment are relatively common, it is rare that they will cause a patient to cease treatment. Furthermore, the costs associated with the treatment of these reactions are relatively low (generic low-cost medications such as paracetamol and steroids are used). Therefore, it is proposed that such reactions are not accounted for within the model due to the anticipated minor impact they will have on the cost-effectiveness results. This was also reflected in the avalglucosidase NICE submission, which stated that adverse events were consistent across both arms and, therefore, excluded from the model (National Institute for Health and Care Excellence 2022). However, placeholders for the frequency, treatment costs and disutility associated with three adverse events were built into the model to allow the future incorporation of adverse event data, if applicable, when available.

8.3. Extrapolation of relative efficacy

8.3.1. Alglucosidase Alfa (Myozyme®)

Sufficient long-term data were only available to estimate the long-term deterioration of patients receiving alglucosidase alfa. This evidence indicates that patients will experience a gradual deterioration in %pred FVC over time whilst receiving alglucosidase alfa (Semplicini 2020). Alternatively, patients will experience an initial improvement in the 6MWT upon commencement of treatment, which would then be followed by a decline after two to three years.

Due to considerations of the short-term efficacy data available, it was expected that patients who received cipaglucosidase alfa/miglustat would experience an initial improvement in both 6MWT and %pred FVC, followed by a gradual decline, to match the available data for alglucosidase alfa. However, it was anticipated that the magnitude of initial improvement, and rate of progression, would differ depending on the treatment received (feedback from clinical experts in Denmark, Section 11). For example, as observed in the first 52 weeks of the PROPEL trial, it was anticipated that patients receiving cipaglucosidase alfa/miglustat would experience a greater improvement in 6MWT and %pred FVC than with alglucosidase alfa during the first one to two years of treatment, followed by a slower rate of decline in the longer-term. If this prediction were to occur then cipaglucosidase alfa/miglustat patients should remain ambulatory, with no need for respiratory support, for a longer period. Due to long-term data limitations, following the application of the initial improvement, it was necessary to assume a linear, or constant, rate of progression throughout the time horizon of the model. This was a conservative approach because it was anticipated that, in reality, the rate of decline could increase throughout the model time horizon. Scenarios were validated with Danish Pompe clinical experts (Section 11).

The long-term change in %pred FVC and 6MWT associated with alglucosidase alfa in the overall population was informed by a prospective analysis from the French Pompe Registry (Semplicini 2020). This study was considered the most appropriate source of efficacy data for alglucosidase alfa because it reported data on 197 patients with LOPD over a maximum of 13 years (the largest study, over the longest time period, identified from the burden of illness review). Patients receiving alglucosidase alfa within this study had a baseline percentage predicted 6MWT of 56.95 (SD: 23.64) and a baseline %pred FVC of 64.38 (SD: 26.22).

The changes in 6MWT and %pred FVC recorded within the study are presented graphically in [redacted] and [redacted] respectively (these figures have been reproduced from the Semplicini et al., study (Semplicini 2020). In both figures, the thick black line indicates the average change in the outcome over time, based on trend lines that were fitted to the patient-level data. More specifically, two types of linear mixed-effects models

were fitted to assess the trends over time. Firstly, a mixed linear model with a constant slope was fitted – this included a single-phase (i.e. the trend was fixed for the full-time horizon). Secondly, a more complex two-phase mixed linear discontinuous model was fitted. This two-phase model was based on a polynomial growth curve and included different effects of baseline, short-term and long-term treatment. More information on the linear mixed-effects models is provided in the Semplicini et al., study (Semplicini 2020).

The authors judged that a two-phase model better described the changes observed for the %pred 6MWT within the study. Based on the fitting of this two-phase model, the data indicates there was an initial improvement over the first two years of alglucosidase alfa, followed by a steady decline from approximately two years. More precisely, an initial improvement of 1.4% over the first 2.2 years of treatment with alglucosidase alfa was reported and patients then experienced an annual reduction of -2.3% (± 0.6%) for the remainder of the time horizon.

The authors judged that a single-phase model was more appropriate for outcomes related to FVC. The outcomes from this single-phase model indicate that for sitting %pred FVC there was not an initial increase, but rather a steady decline was observed, straight from treatment initiation. This equated to an average annual reduction in predicted sitting %pred FVC of -0.9% (95 CI: -0.8%, -1.0%). Moreover, as discussed in section 5.1.1.4.2, clinical experts pointed out that small changes in the short-term can extrapolate to an important change long-term: even a 1% annual improvement or stabilization of symptoms long-term (over a decade) can impact delaying the need for ventilation and or motor support.

The study cohort in Semplicini et al., (Semplicini 2020) was based upon an overall population with no stratification dependent on whether patients were ERT naïve or experienced. Therefore, it was not possible to stratify the long-term progression by patient population. Instead, the long-term efficacy data reported for the overall population were applied to all three populations. However, it should be straightforward to update the model should alternative long-term data become available for the other sub-groups.

All efficacy data used to inform the %pred FVC and 6MWT values for alglucosidase alfa patients are reported in Table 25.

Table 25: Alglucosidase alfa long term efficacy inputs

Subsequent annual percentage change	N	Mean	SE	Source
All populations: %pred 6MWT	158	-2.3%	0.003	(Semplicini 2020)
All populations: %pred FVC	158	-0.9%	0.001	

Abbreviations: 6MWT, six minute walk test; CI, Confidence interval; ERT, enzyme replacement therapy; FVC, forced vital capacity; NA, not applicable; SE, standard error

[redacted]

[redacted]

[redacted]

[redacted]

8.3.2. Cipaglucosidase Alfa/Miglustat

It is not yet possible to determine the long-term effectiveness (change in 6MWT and %pred FVC scores) of cipaglucosidase alfa/miglustat beyond 48 month data presented as poster (Byrne 2022). Therefore, the model was designed to enable the comparison of multiple scenarios relating to the long-term changes in these

progression outcomes. This scenario could be varied via an input that was used to determine the relative rate of long-term progression compared to alglucosidase alfa. For example, if the relative rate was set to one, a pessimistic scenario could be modelled in which the rate of decline in 6MWT and FVC% after one year matches the long-term data that are available for alglucosidase alfa. Alternatively, a more optimistic scenario could be modelled (for example, a relative rate of 0.5) in which these parameters decline at half the rate of alglucosidase alfa after one year. In the base case analysis, it was assumed (based on consultation with clinical experts in Denmark, Section 11) that the progression rates of both %pred FVC and 6MWT would be [redacted] slower with cipaglucosidase alfa/miglustat, versus alglucosidase alfa, which means a relative rate of [redacted] was applied in the model.

For illustrative purposes, a hypothetical scenario was plotted ([redacted] and [redacted]). These figures show the potential changes in 6MWT and FVC% with cipaglucosidase alfa/miglustat, based on cipaglucosidase alfa/miglustat having a similar long-term effect when compared to alglucosidase alfa. In this scenario, cipaglucosidase alfa/miglustat led to larger initial improvements during the first two years of therapy and a similar rate of decline for both outcomes compared to alglucosidase alfa. Hence, it would take longer for cipaglucosidase alfa/miglustat patients to decline to the point of requiring ambulatory and/or respiratory support. When translated into the model structure presented in Figure 18, this would mean patients remain in the 'no support' health state for longer, which would result in higher overall QALYs and lower background costs. However, the treatment costs would also be higher in this scenario due to the extension of life.

[redacted]

[redacted]

[redacted]

[redacted]

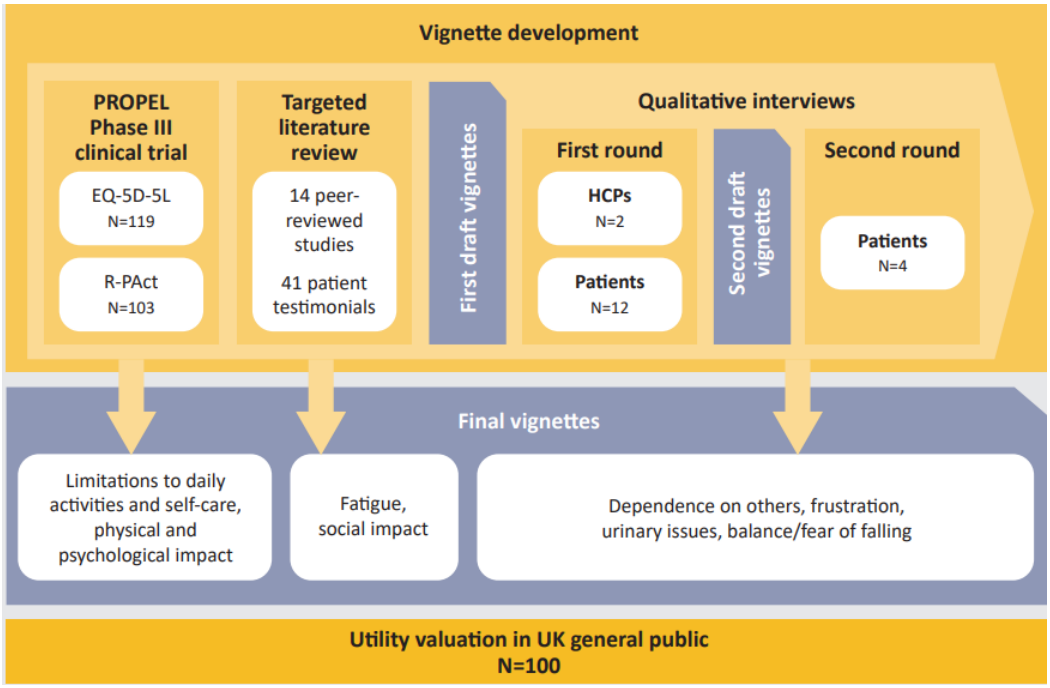
[redacted]

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

Although EQ-5D-5L was collected within the PROPEL clinical trial (Amicus data on file), it was not possible to use these data to inform the additional disutility because the majority of patients within the trial had not yet reached the later severe health states due to the short follow-up period. Although confirming that such health states would be associated with a significant decrement to quality of life, predominantly caused by an inability to perform usual activities and anxiety associated with machine reliance, clinicians were also unable to estimate the relative reduction in disutility.

In the absence of published evidence available to describe the full set of health states in the health economic analysis, Amicus developed a vignette study (Hubig 2023). Vignettes are often derived from information available in published literature or a small sample of qualitative interviews, which provides limited evidence on the content validity of the health state descriptions. The study developed by Amicus used patient-reported outcome (PRO) data to develop the vignette content. The draft vignettes were evaluated in interviews with patients and healthcare professionals (HCPs) and applied in valuation studies conducted to estimate utility values for LOPD health states. A total of 100 people provided utility valuation in UK general population. See Figure 23 for an overview of the methodology applied.

Figure 23: Vignette development methodology overview



Abbreviations: EQ-5D-5L: EuroQol-5 dimension-5 level; HCP, healthcare practitioner; R-PAct, Rasch-built Pompe-specific activity

Phase III trial (PROPEL) participants were classified into health states based on their documented use of mobility and respiratory support. Item-level response data from the Rasch-built Pompe-specific activity measure (R-Pact) and EQ-5D-5L were summarised (item level: count, percentage; item: mode, median) stratified by participants' health state classification. The first draft vignettes were developed using the most reported PRO item responses; missing health states and additional vignette items were supported by a targeted literature review.

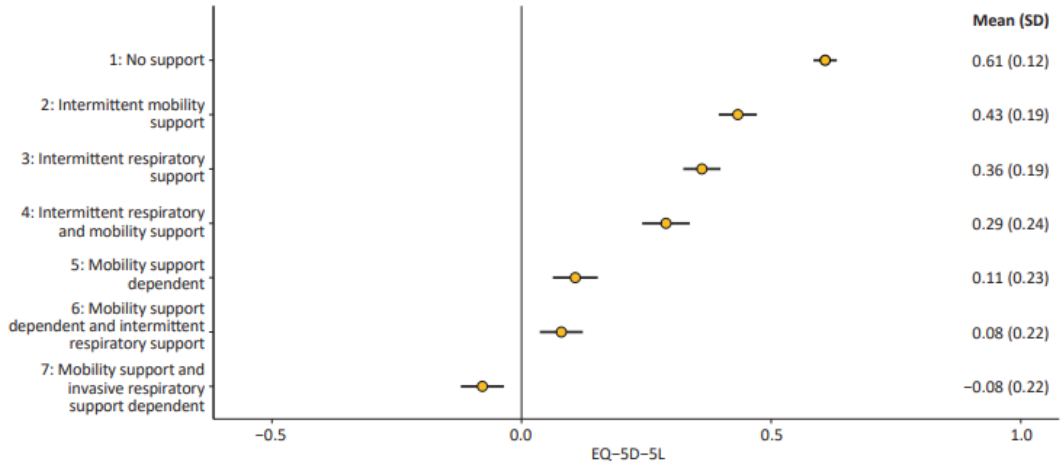
Participants were recruited via Pompe Support UK and the Association for Glycogen Storage Disease UK (AGSD) with experience of different health states, where possible. Qualitative, 1-hour semi-structured interviews were conducted with patients who had a self-reported diagnosis of LOPD, were 18 or older, fluent in English, and consented to participate. First, participants described their experience of living with LOPD, and then provided feedback on the draft vignettes for their own current and previously experienced health states.

All vignettes were reviewed by patients with experience of the health state except for HS7 (mobility support dependent and invasive respiratory support dependent). The first draft vignettes were reviewed by HCPs experienced in the treatment and management of LOPD in 1-hour semi-structured interviews. The vignettes were revised and finalised following HCP feedback and two rounds of patient review.

The health state vignettes were valued by members of the UK general public using standard utility assessment techniques (EQ-5D-5L, Visual Analogue Scale [VAS] and Time Trade-Off [TTO] assessment). The R package "eq5d" was used to calculate EQ-5D-5L utility values using Danish population weights.

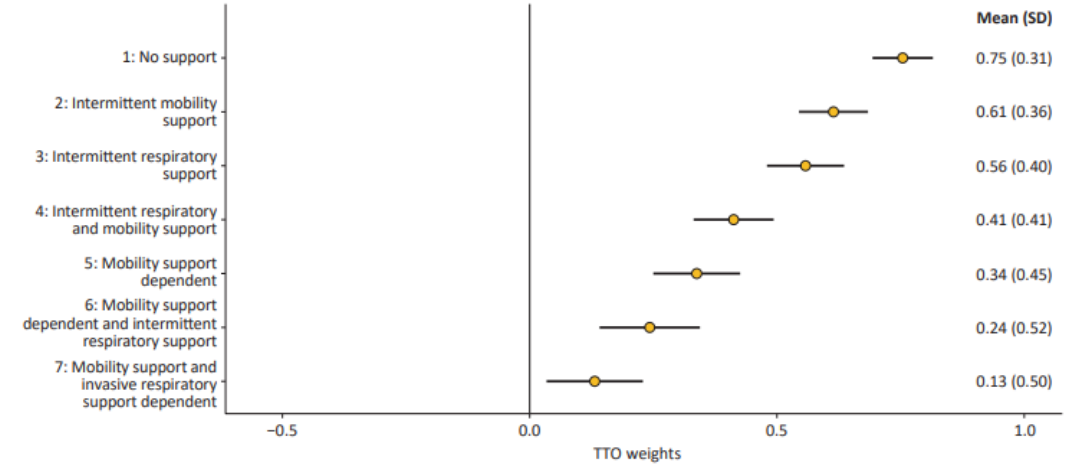
Both the TTO and EQ-5D-5L generated similar results as described in Figure 24 and Figure 25 (UK weights). EQ-5D-5L using Danish preference weights was applied in the health economic model and is presented in Table 26.

Figure 24: Mean (95% CI) EQ-5D-5L index scores



Abbreviations: CI, confidence interval; EQ-5D-5L: EuroQol-5 dimension-5 level; SD, standard deviation

Figure 25: Mean (95% CI) TTO weights



Abbreviations: CI, confidence interval; TTO; time trade-off; SD, standard deviation

The health state utilities were age-adjusted to account for the fact that as people age their quality of life decreases and to prevent the overestimation of quality of life. Each year in the model age-specific general population EQ-5D-3L utilities were derived using the following formula (Ara 2010).

$$Utility = 0.9508566 + 0.0212126 * Male - 0.0002587 * Age - 0.0000332 * age\text{^}2$$

The average age and gender of respondents were obtained from each source and combined with the health-state specific utilities presented below using the multiplicative method.

8.4.1. Health state utility values (HSUV)

Table 26: Summary of the HSUV

	HSUV mean	SD	Source
Health state			
No wheelchair use or respiratory support (0-5) years	0.608	(0.12)	

	HSUV mean	SD	Source
No wheelchair use or respiratory support (6-15) years	0.608	(0.12)	Vignette development and utility valuation study (HM de Freitas 2022, Hubig 2023)
No wheelchair use or respiratory support (>15) years	0.608	(0.12)	
Intermittent mobility support	0.433	(0.12)	
Wheelchair dependent	0.108	(0.23)	
Intermittent respiratory support (non-invasive ventilation)	0.361	(0.19)	
Intermittent mobility support and intermittent respiratory support (non-invasive ventilation)	0.289	(0.24)	
Intermittent respiratory support and wheelchair dependent (non-invasive ventilation)	0.0800	(0.22)	
Wheelchair and respiratory support dependent (non-invasive ventilation)	0.0800	(0.22)	
Wheelchair and respiratory support dependent (invasive ventilation)	-0.078	(0.22)	

Abbreviations: CI, confidence interval; HSUV; health state utility value; SD, standard deviation

8.4.2. Danish utility used in the model

The EQ-5D-5L index score of participants' ratings for each health state were obtained by weighting each level in each dimension using the Danish preference weights (Jensen et al. 2021). The index values range between -0.757 and 1, where 1 represents full health and 0 death; values less than 0 are considered worse than death.

The analysis was performed in R 4.1.2 using the R package 'eq5d' to calculate the utility values.

Table 27 EQ-5D-5L index scores (N = 100) scored using the Danish EQ-5D-5L value set

	HSUV mean (SD)	95% C.I.	Source
Health state			
No support	0.720 (0.152)	0.690, 0.749	Vignette development and utility valuation study (HM de Freitas 2022, Hubig 2023)
Intermittent mobility support	0.506 (0.265)	0.454, 0.558	
Intermittent respiratory support	0.449 (0.277)	0.394, 0.503	
Intermittent respiratory and mobility support	0.355 (0.342)	0.288, 0.422	
Mobility support dependent	0.140 (0.318)	0.077, 0.202	
Mobility support dependent and intermittent respiratory support	0.108 (0.305)	0.048, 0.168	
Mobility support and invasive respiratory support dependent	-0.041 (0.327)	-0.105, 0.023	

Abbreviations: CI, confidence interval; HSUV; health state utility value; SD, standard deviation

8.5. Resource use and costs

Cost input values for the analysis was obtained through interviews with Danish clinical experts (Section 11 list of clinical experts). The experts were allowed to see the estimated resource usage for LOPD treatment in the UK but could freely estimate the frequencies they deemed appropriate for a Danish clinical setting. They were also asked to list any other health care resources that they thought may be applicable in Denmark.

Different sources were used to obtain the unit cost for all resource types. All costs were updated to 2023 prices.

8.5.1. Health care resource utilization

8.5.1.1. Drug acquisition costs

Drug acquisition costs were based upon pharmacy purchasing price (PPP) excluding VAT. Drug costs were obtained from Medicinpriser.dk, using the lowest available price per mg for the package size. The input values for drug costs in this analysis are presented in Table 28.

Table 28.

Table 28: Drug acquisition costs

Subtype	Vial / package information				Cost per pack (DKK) PPP excl. VAT	Reference for unit costs
	Strength	Unit	Size	Unit		
Cipaglucosidase alfa	105	mg	1	unit	[redacted]	[redacted]
Miglustat	65	mg	4	tablets	[redacted]	[redacted]
Alglucosidase alfa	50	mg	1	unit	3 105.10	Medicinpriser.dk

Abbreviations: DKK, Danish Kroner; VAT, value added tax; PPP, Pharmacy purchasing price

8.5.1.2. Drug administration costs

The administration costs associated with drug infusion is presented in Table 29. The same infusion costs were applied for both the cipaglucosidase alfa/miglustat and alglucosidase alfa treatment arms. Note, as no administration costs are expected for miglustat, as is it an oral treatment taken by the patient at home, and the costs for the treatment administration are solely based on the in-hospital costs for cipaglucosidase alfa.

The frequency of administrations were based upon the SmPC of each drug. Nurse hours are expected to differ between the treatments, and have been captured.

Table 29: Administration cost per included treatment

Resource	Frequency		Unit cost (DKK)	Reference for unit cost
	Cipaglucosidase alfa/miglustat	Alglucosidase alfa		
Hospital: cost per administration	Every 2 weeks	Every 2 weeks	1 386.34	Kommunernes og Regionernes Løndatakontor 2023, Chief physician. Bruttoløn February 2023 available from: https://krl.dk/#/sirka, Accessed May 2023. Calculated monthly salary/hours per month (DKK 130 316 divided by 94 hours) according to Medicines Council 2023 guideline Resource used based on Danish clinical experts (Section 11 list of clinical experts)
Home (nurse administration): cost per hour	4.7 hours/ administration	5.2 hours/ administration	1 386.34	
Home (self administration, nurse time for required for reconstitution (hours))	0.88 hours/administration	1.38 hours/administration	1 386.34	

Abbreviations: DKK, Danish kroner

8.5.1.3. Patient management costs

Table 30 presents the patient management costs for patients regarding follow-up visits. The disease management costs are presented as resource use required every year to provide care to adult patients with Pompe disease regardless of treatment. Frequency estimates were provided by Danish clinical experts (Section 11 list of clinical experts).

Table 31 presents equipment costs that may be required for treatment of Pompe disease. The equipment can capture differences in costs with respect to disease progression, as more progressive stages of Pompe disease can require variations and additions in treatment equipment. As such, the type of equipment needs has been divided per patient medical needs. The equipment types and treatment needs have been informed by Danish clinical experts (Section 11 list of clinical experts), as well as Pompe diseases resourced from the UK setting.

Table 30: Patient management costs follow-up visits

Resource name	Yearly resource use	Unit cost (DKK)	Reference for unit costs
Consultant neurologist appointment	1.75	1 386.34	Kommunernes og Regionernes Løndatakontor 2023, Chief physician. Bruttoløn February 2023 available from: https://krl.dk/#/sirka, Accessed May 2023. Calculated monthly salary/hours per month (DKK 130 316 divided by 94 hours) according to Medicines Council 2023 guideline Resource used based on Danish clinical experts (Section 11 list of clinical experts)
Non-invasive ventilation support assessment	1	1 386.34	
Respiratory physiology consultant appointment	1.25	1 386.34	

Physiotherapist visit	20	1 386.34

Abbreviations: DKK, Danish Kroner; PD, Progressive disease; PF, Progression-free

Table 31: Equipment costs per patient medical needs

Medical needs	Upfront unit costs (DKK)	Annual costs (DKK)	Reference for unit costs
Non-invasive ventilation	n/a	36 150	Sundhedsdatastyrelsen (2022). Interactive DRG: 01MA15 - Andre specifikke sygdomme i nervesystemet, pat. mindst 18 år. Available at: http://interaktivdrg.sundhedsdata.dk/
Invasive ventilation	1 137 431	858 427	No relevant DK cost identified. Approach decribed below: **Upfront cost** NEO-GAA NICE submission (2022): https://www.nice.org.uk/guidance/gid-ta10876/documents/committee-papers, Accessed May 2023 Table 36: Health state costs for ventilation and wheelchair states. Ventilation: Invasive ventilation (home): One -off cost. Converted to DKK using oanda.com Inflated to April 2023 based on Statistics Denmark KPI April 2022 to April 2023, https://www.dst.dk/da/Statistik/emner/oekonomi/prisindeks/forbrugerprisindeks, Accessed May 2023 **Annual costs** Sundhedsdatastyrelsen (2023). Interactive DRG: 01MA15 long term (>12hrs) (BGDA61) Manuel ventilation gennem trakealtube (DG728) Anden myopati. Available at: http://interaktivdrg.sundhedsdata.dk/ Costs consider per 1 year of 365 days
Intermittent mobility: Manual wheelchair	4 995	No additional costs considered	Hjaelpemiddelbasen Dolphin kørestol med ledsagerbremse Dolphin kørestol med ledsagerbremse fra FNP Hjælpemidler - Hjælpemiddelbasen (hmi-basen.dk)
Wheelchair dependent : Powered wheelchair Home adjustments Hoist	34 990 263 084 80 264	No additional costs considered	**Powered wheelchair** Hjaelpemiddelbasen. Eloflex D2. https://hmi-basen.dk/r11x.asp?linkinfo=72534 **Home adjustments** NEO-GAA NICE submission: https://www.nice.org.uk/guidance/gid-ta10876/documents/committee-papers Table 36: Health state costs for ventilation and wheelchair states; home adjustments and hoist (converted to DKK on 3 May 2023, oanda.com) **Hoist** Hjaelpemiddelbasen. Esense Line Drive. https://hmi-basen.dk/r11x.asp?linkinfo=72534

Abbreviations: DKK, Danish Kroner

8.5.1.4. Patient costs

Costs for patients' time and transportation were included in the base case in line with Danish guidelines (Lægehåndbogen 2021). These items aimed to cover the cost paid by patients and their time in regards to each treatment administration (Table 32). These costs were applied to each visit in the model and were excluded in the budget impact analysis, as recommended in the Danish medicines council guidelines.

Table 32: Patient costs included in the model for time spent on treatment and transportation

Resource	Cost per treatment administration cipaglucosidase alfa/miglustat (DKK)	Cost per treatment administration alglucosidase alfa (DKK)	Source/Comment
Unit cost for transportation	140	140	Cost unit (140 DKK per visit of transportation) is sourced from Medicinrådet (2023), Værdisætning af enhedsomkostninger-vers. 1.2 (medicinraadet.dk)
Patient time cost per visit	954.1	1055.6	Assumption of 4 hours for administration of infusion at hospital. Cost unit (203 DKK per hour of patient/caregiver time) is sourced from Medicinrådet (2023), Værdisætning af enhedsomkostninger-vers. 1.2 (medicinraadet.dk)
Caregiver time costs	954.1	1055.6	
Patient costs for time spent on treatment and transportation, total	2048.2	2251.2	-

Abbreviations: DKK, Danish Kroner.

8.6. Scenario vs best supportive care

The DMC have requested an analysis comparing cipaglucosidase alfa/miglustat with best supportive care (BSC).

Insufficient data were available to model the outcomes associated with BSC after one year. The predominant cause for this lack of data was because alglucosidase alfa has been available as a treatment option for many years and, therefore, it is understood that very few patients receive treatment with BSC. However, a systematic review and meta-analysis by Schoser et al., indicated that the rate of mortality was five times higher for patients receiving BSC as opposed to alglucosidase alfa. Mortality is not directly impacted by the treatment choice (see Section 5.1). Instead, the impact is indirect because the treatment choice affects the rate of disease progression and later health states are associated with higher mortality rates. For example, if a patient requires wheelchair support and invasive ventilation their mortality rate will be five times higher than a Pompe disease patient with no support. Therefore, it has been assumed the data reported by Schoser et al., can be applied to the disease progression parameters, such that the mean annual rate of decline for patients receiving BSC was five times faster than patients receiving alglucosidase alfa (as determined from (Semplicini 2020).

A randomised study comparing the efficacy of alglucosidase alfa versus placebo (considered a proxy for BSC) over 78 weeks was identified during the project [47]. It was judged that it would not be appropriate to use the data from this study directly in the model, due to the relatively short follow-up and low patient numbers. Hence, the approach described above was adopted. Nevertheless, the outputs from this study do indicate that patients in the placebo arm (assumed to be equivalent to BSC) declined at a significantly faster rate than those receiving alglucosidase alfa (Figure 26). Therefore, this is seen as justification for the approach used.

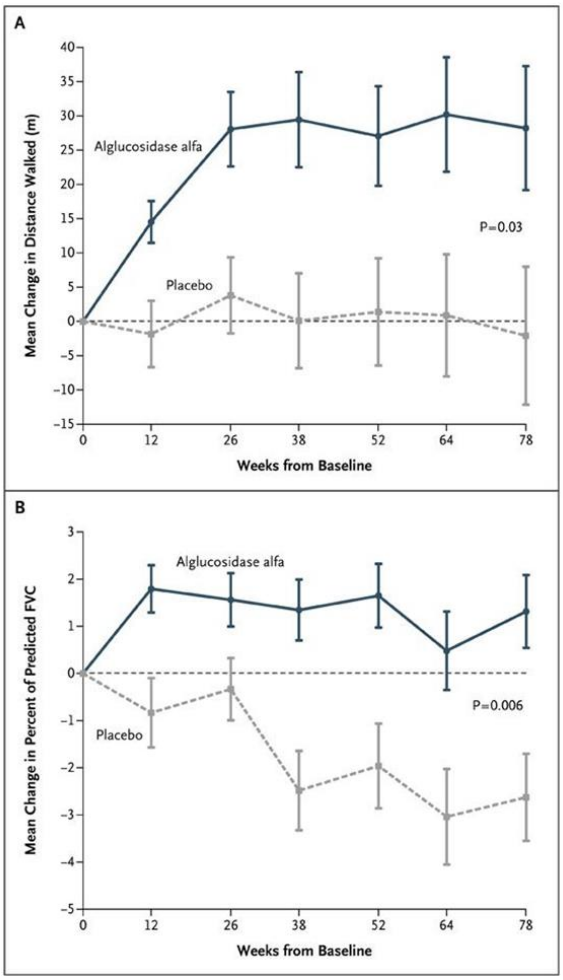
Please note that efficacy data used to inform the initial change from baseline following the commencement of BSC was only available within the ERT naïve population. However, the long-term efficacy data reported in Semplicini et al., are based upon the overall population due to an absence of alternative information. Therefore, it was conservatively assumed that the efficacy of BSC is equivalent across all populations. The efficacy inputs for BSC is presented in Table 33.

Table 33 Best supportive care efficacy inputs

Subsequent annual percentage change:	N	Mean	SE	Source
ERT naïve: %pred 6MWT	158	-11.5%	0.003	Assumption (200% of Semplicini 2020)
ERT naïve: %pred FVC	158	-4.5%	0.001	

Abbreviations: 6MWT, 6 minute walk test; BSC, best supportive care; FVC, forced vital capacity

Figure 26 Mean change in 6MWT and %pred FVC for best supportive care (placebo) versus alglucosidase alfa



Abbreviations: 6MWT, 6 minute walk test; BSC, best supportive care; FVC, forced vital capacity
Source: (van der Ploeg 2010)

8.7. Results

8.7.1. Base case overview

Table 34: Base case overview

Comparator	Alglucosidase alfa: standard enzyme replacement therapy [ERT, Myozyme®] (20mg/kg)
Type of model	Individual patient simulation model
Time horizon	Lifetime
Treatment line	1st line

Measurement and valuation of health effects	Health-related quality of life measured with vignette study using EQ-5D-5L Danish population weights were used to estimate health-state utility values
Included costs	Pharmaceutical costs Hospital costs Patient costs
Dosage of pharmaceutical	Based on weight
Rate of decline relative comparator	[redacted]
Thresholds for required support	Intermittent mobility support (max m in 6MWT): 250 m Wheelchair dependent (max m in 6MWT): 150 m Intermittent respiratory support (%pred FVC): 40% Respiratory support dependent (%pred FVC): 30%
Efficacy data	Length of time clinical trial data is applied for (before application of Semplicini): 4 years Source of cipaglucosidase alfa w. miglustat data (before application of Semplicini): PROPEL phase III OLE study (two years)

Abbreviations: 6MWT, 6 minute walk test; EQ-5D-5L: EuroQol-5 dimension-5 level; ERT, enzyme replacement therapy; FVC, forced vital capacity

8.7.2. Base case results

Table 35: Base case results

Per patient	Intervention	Comparator	Difference
Life years gained			
Total life years gained (discounted)	[redacted]	[redacted]	[redacted]
Total life years gained (undiscounted)	[redacted]	[redacted]	[redacted]
QALYs			
Total QALYs	[redacted]	[redacted]	[redacted]
Costs			
Total costs (DKK)	[redacted]	[redacted]	[redacted]
Treatment costs (DKK)	[redacted]	[redacted]	[redacted]
Drug administration (DKK)	3 487 676	3 804 964	-317 288
Patient management (DKK)	1 230 043	1 778 212	-548 169
End of life (DKK)	0	0	0
Productivity loss (DKK)	0	0	0
Adverse events (DKK)	0	0	0
Incremental results	Intervention vs. Comparator		
ICER (per QALY) (DKK)	[redacted]		

Abbreviations: DKK, Danish kronor; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year

8.7.3. Scenario results

Table 36: Results vs best supportive care

Per patient	Intervention	Comparator	Difference
Life years gained			
Total life years gained (discounted)	[redacted]	[redacted]	[redacted]
Total life years gained (undiscounted)	[redacted]	[redacted]	[redacted]
QALYs			
Total QALYs	[redacted]	[redacted]	[redacted]
Costs			
Total costs (DKK)	[redacted]	[redacted]	[redacted]
Treatment costs (DKK)	[redacted]	[redacted]	[redacted]
Drug administration (DKK)	3 572 767	0	3 572 767
Patient management (DKK)	703 499	6 846 242	-6 142 744
End of life (DKK)	0	0	0
Productivity loss (DKK)	0	0	0
Adverse events (DKK)	0	0	0
Incremental results	Intervention vs. Comparator		
ICER (per QALY) (DKK)	[redacted]		

Abbreviations: DKK, Danish kronor; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year

8.8. Sensitivity analyses

8.8.1. Deterministic sensitivity analyses

In order to account for first-order uncertainty around the data used for all input parameter values, all cost, utility and mortality parameters should be tested in deterministic sensitivity analysis (DSA). DSA involves altering the value used for individual parameters, within realistic ranges, to see the impact on the model results. The main output from the DSA is a tornado diagram, which summarises the impact of changes to each parameter on the model results. The tornado diagram is presented in [redacted]. Parameters are varied using the 95% confidence intervals or errors presented within the literature for each input. The detailed DSA results are presented in Appendix [redacted] in [redacted].

[redacted]

[redacted]

8.8.2. Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) was included in the model to account for second-order uncertainty around parameter values. The inputs described in Table 37: PSA distributions included in the model were each selected from a distribution rather than using just one fixed value for each input. The model used a recommended minimum sample of 1,000 iterations (10 first order x 100 second order), each iteration using a different set of

values for the inputs, to ensure stable results. The ICER generated from each iteration was collected and the spread could be examined. This provided information on the robustness of the results in the model. If the ICERs from all of the iterations were very tightly clustered together, then this would suggest that the results of the model did not change greatly when the inputs were varied with plausible ranges.

PSA can also provide an estimate of the level of confidence in the direction of results in the model by looking at the spread of results and what proportion of iterations the ICER is below the threshold and, therefore, in what proportion of iterations the new intervention was estimated to be cost-effective. The model reports the mean costs and QALY outcomes per person (and hence an ICER). The uncertainty associated with each parameter varied within the PSA was estimated using the standard errors reported from the relevant published sources. The distributions used to model the uncertainty associated with each parameter category were informed by Briggs et al., (Briggs A 2006).

Table 37: PSA distributions included in the model

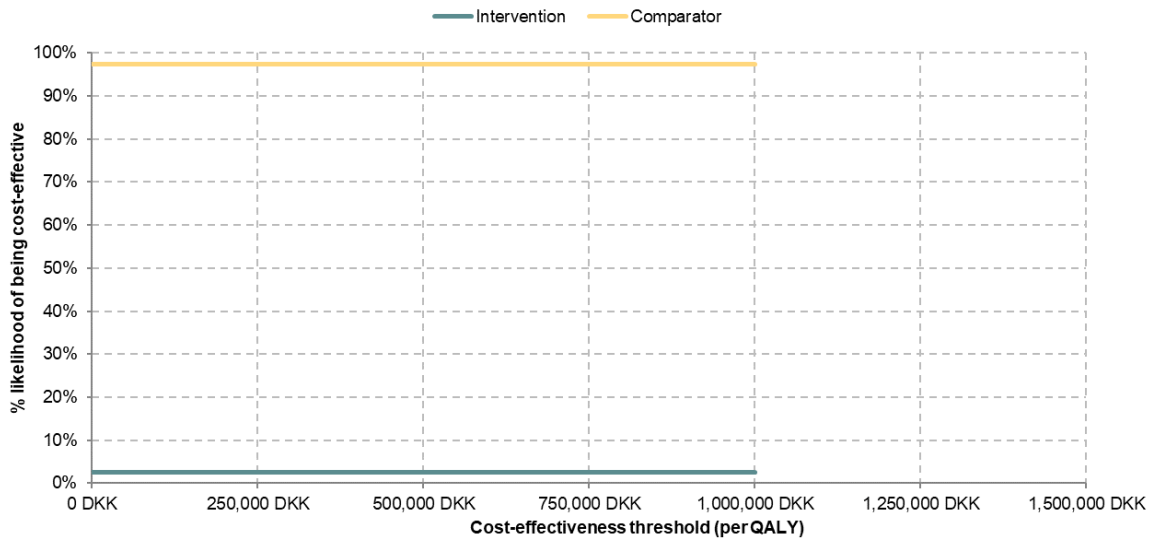
Parameter Group	Distribution
Baseline patient characteristics	Normal
Efficacy values: 6MWT and %pred FVC	Lognormal
Mortality	Lognormal
Health state utility	Beta
Costs and resource use	Gamma

Abbreviations: 6MWT, 6 minute walk test; FVC, forced vital capacity

[redacted]

[redacted]

Figure 27: Cost effectiveness acceptability curve (CEAC) placeholder



Abbreviations: CEAC; cost-effectiveness acceptability curve; DKK, Danish kronor; QALY, quality adjusted life year

Budget impact analysis

To assess the budgetary impact of cipaglucosidase alfa/miglustat it was necessary to model two separate scenarios and compare the results across them. The first scenario was the current cost of treatment for each case of LOPD in which only current standard of care was available (i.e., cipaglucosidase alfa/miglustat was unavailable). This was then compared to a scenario following the introduction of cipaglucosidase alfa/miglustat.

The model considered a five-year time horizon, as is standard practice for budget impact models. Annual costs were not discounted in the base case analysis.

It should be noted that the annual costs per patient, used to inform the budget impact results, were determined by outputs from the patient level simulation cost-effectiveness model (CEM). These costs were, therefore, dependent on the effectiveness, cost and mortality data used within the CEM that have been described in the earlier sections of this report.

Number of patients

The number of patients eligible for treatment with cipaglucosidase alfa/miglustat in Denmark was estimated to be [redacted] patients annually, with the number of eligible patients increasing to [redacted] in years 4 and 5.

Table 38 describes the number of patients expected to be treated with cipaglucosidase alfa/miglustat and alglucosidase alfa if cipaglucosidase alfa/miglustat receives approved reimbursement. If approval is not granted, the number of patients expected to be treated with alglucosidase alfa is presented in Table 39.

Table 38: Number of LOPD patients expected to be treated over the next five-year period – if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Cipaglucosidase alfa/miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LOPD, late onset Pompe disease

Table 39: Number of LOPD patients expected to be treated over the next five-year period – if the pharmaceutical is NOT introduced (Currently 6 Danish patients are receiving cipaglucosidase alfa/miglustat as part of an OLE study)

	Year 1	Year 2	Year 3	Year 4	Year 5
Cipaglucosidase alfa/miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LOPD, late onset Pompe disease; OLE, open label extension

Budget impact results

The budget impact is estimated directly in the health economic model and, thus, takes into consideration patients survival over time. This means that patients that are initiated on treatment year 1 are expected to incur costs in the budget impact analysis over time, due to treatment length and progression related costs. Patient time and transport is not included in the budget impact.

The total annual budget impact of the introduction of cipaglucosidase alfa/miglustat is estimated to [redacted] in year 5. Detailed budget impact results per year are presented in Table 40, Table 41, and Table 42.

Table 40: Total expenditure per year – if cipaglucosidase alfa/miglustat is approved for reimbursement

	Year 1	Year 2	Year 3	Year 4	Year 5
Cipaglucosidase alfa/miglustat (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alglucosidase alfa (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish Kroner

Table 41: Total expenditure per year – if cipaglucosidase alfa/miglustat is not approved for reimbursement

	Year 1	Year 2	Year 3	Year 4	Year 5
Cipaglucosidase alfa/miglustat (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alglucosidase alfa (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish Kroner

Table 42: Expected budget impact of recommending cipaglucosidase alfa/miglustat

	Year 1	Year 2	Year 3	Year 4	Year 5
Cipaglucosidase alfa/miglustat (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alglucosidase alfa (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (impact) (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish Kroner

Discussion on the submitted documentation

The improved efficacy of cipaglucosidase alfa in combination with miglustat compared to alglucosidase alfa has been demonstrated in the PROPEL trial, across a range of endpoints relevant to people with LOPD, covering motor function, respiratory function, muscle strength and patient-reported outcomes (PROs). In the total population of the PROPEL trial, 6MWD (the primary efficacy endpoint) showed greater improvement with cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa but did not demonstrate statistical superiority. However, the clinical expert consulted in Denmark confirmed that 6MWD and % predicted FVC are the most important outcome measures in Pompe disease, which should also be used when assessing long-term efficacy of therapy. The clinical expert also pointed out that small changes in the short-term can extrapolate to an important change long-term: even a 1% annual improvement long-term (e.g., over a decade) can impact delaying the need for ventilation and or motor support.

Head-to-head data on the efficacy of cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo was available from the PROPEL randomised controlled trial. Alglucosidase alfa was considered as the main comparator in the health economic assessment of this submission, as alglucosidase alfa is the only current treatment option which would be replaced if cipaglucosidase alfa/miglustat were introduced into the Danish health care system.

A clinical expert within Pompe disease in Denmark confirmed that essentially all Danish patients are on ERT treatment. Only in certain very exceptional cases (e.g., due to pregnancy, minimal disease manifestations, age or comorbidity) would an LOPD patient not be considered for active treatment using ERT.

The health economic results shows that the incremental cost between cipaglucosidase alfa in combination with miglustat and alglucosidase alfa was around [redacted], the incremental QALY gain was [redacted] in favour of cipaglucosidase alfa in combination with miglustat. The associated ICER was estimated to [redacted]. The scenario comparing vs best supportive care estimated [redacted] in incremental costs and a QALY gain of [redacted]. The associated ICER vs best supportive care was [redacted].

List of experts

[redacted]

[redacted]

[redacted]

References

Al Jasmi, F., M. Al Jumah, F. Alqarni, N. Al-Sanna'a, F. Al-Sharif, S. Bohlega, E. J. Cupler, W. Fathalla, M. A. Hamdan, N. Makhseed, S. Nafissi, Y. Nilipour, L. Selim, N. Shembesh, R. Sunbul and S. H. Tonekaboni (2015). "Diagnosis and treatment of late-onset Pompe disease in the Middle East and North Africa region: consensus recommendations from an expert group." BMC Neurol **15**: 205.

American Association of Neuromuscular & Electrodiagnostic Medicine (2009). "Diagnostic criteria for late-onset (childhood and adult) Pompe disease." Muscle Nerve **40**(1): 149–160.

American Thoracic Society (2002). "Guidelines for the six-minute walk test." Am J Respir Crit Care Med **166**(1): 111–117.

Amicus data on file "Amicus Therapeutics, Cranbury, NJ, USA (Non-clinical report RRB200–043 ATB200: Comparison of CI-MPR binding of ATB200 and alglucosidase alfa by CI-MPR affinity chromatography); 6. Do H et al. Ann Transl Med 2019;7:291)."

Amicus data on file "File Ado. ATB200-03, Functional Assessment Manual."

Amicus data on file "Module 2.6.4 Pharmacokinetics written summary ".

Amicus Data on file (2015). "Patient Advisory Board 2015."

Amicus Data on file (2018). "Patient Advisory Board 2018."

Amicus data on file (2019). "Patient Advisory Board 2019."

Amicus data on file (2021a). ATB200-02 Interim CSR. Data on file.

Amicus data on file (2021b). "Proposed Pompe disease guidelines analysis; December 2021."

AMICUS data on file (2022a). Nordics Pompe Disease Advisory Board.

Amicus data on file (2022b). "Pompe online patient survey."

Amicus Therapeutics (2019). "U.S. FDA grants Breakthrough Therapy Designation ("BTD") to Amicus' AT-GAA in late onset Pompe disease. Accessed on 2 November 2021 from: https://ir.amicusrx.com/news-releases/news-release-details/us-fda-grants-breakthrough-therapy-designation-btd-amicus-gaa."

Amicus Therapeutics (2021a). "Functional evidence development for AT-GAA in Pompe disease to support HTA submission."

Amicus Therapeutics (2021b). A Phase 3 Double-blind Randomised Study to Assess the Efficacy and Safety of Intravenous ATB200 Co-Administered with Oral AT2221 in Adult Subjects with Late-Onset Pompe Disease Compared With Alglucosidase Alfa/Placebo.

Amicus Therapeutics (2021c). Phase III PROPEL patient level data. Data on file.

Angelini, C. (2021). "Exercise, nutrition and enzyme replacement therapy are efficacious in adult Pompe patients: report from EPOC Consortium." Eur J Transl Myol.

Angelini, C., C. Semplicini, S. Ravaglia, M. Moggio, G. P. Comi, O. Musumeci, E. Pegoraro, P. Tonin, M. Filosto, S. Servidei, L. Morandi, G. Crescimanno, G. Marrosu, G. Siciliano, T. Mongini and A. Toscano (2012). "New motor outcome function measures in evaluation of late-onset Pompe disease before and after enzyme replacement therapy." Muscle Nerve **45**(6): 831–834.

Angelini, C., C. Semplicini, P. Tonin, M. Filosto, E. Pegoraro, G. Sorarù and M. Fanin (2009). "Progress in enzyme replacement therapy in glycogen storage disease type II." Ther Adv Neurol Disord **2**(3): 143–153.

Ara, R. and J. E. Brazier (2010). "Populating an economic model with health state utility values: moving toward better practice." Value in Health **13**(5): 509-518.

Arber, M., S. Garcia, T. Veale, M. Edwards, A. Shaw and J. Glanville (2016). "Performance of Search Filters to Identify Health State Utility Studies." Value in Health **19**(7): A390-A391.

Arias, E. (2014). "United States life tables, 2009." Natl Vital Stat Rep **62**(7): 1–63.

Aslan, G. K., B. E. Huseyinsinoglu, P. Oflazer, N. Gurses and E. Kiyan (2016). "Inspiratory muscle training in late-onset Pompe disease: the effects on pulmonary function tests, quality of life, and sleep quality." Lung **194**(4): 555–561.

Baschung Pfister, P., E. D. de Bruin, I. Sterkele, B. Maurer, R. A. de Bie and R. H. Knols (2018). "Manual muscle testing and hand-held dynamometry in people with inflammatory myopathy: An intra- and interrater reliability and validity study." PLoS One **13**(3): e0194531.

Bay, L. B., I. Denzler, C. Durand, H. Eiroa, J. Frabasil, A. Fainboim, C. Maxit, A. Schenone and N. Spécola (2019). "Infantile-onset Pompe disease: Diagnosis and management." Arch Argent Pediatr **117**(4): 271–278.

Berger, K., P. DasMahapatra, E. Baranowski, K. A. Haack, S. Sparks, N. Thibault, C. Gwaltney, C. Ivanescu, G. Flore and L. Pollissard (2021). "POMPE DISEASE: EP. 200 Patient relevant change in forced vital capacity% predicted in late onset Pompe disease (LOPD) in the COMET trial." Neuromuscular Disorders **31**: S110.

Berger, K. I., S. Kanters, J. P. Jansen, A. Stewart, S. Sparks, K. A. Haack, A. Bolzani, G. Siliman and A. Hamed (2019). "Forced vital capacity and cross-domain late-onset Pompe disease outcomes: an individual patient-level data meta-analysis." Journal of Neurology **266**(9): 2312-2321.

Boentert, M., B. Dräger, C. Glatz and P. Young (2016a). "Sleep-disordered breathing and effects of noninvasive ventilation in patients with late-onset Pompe disease." J Clin Sleep Med **12**(12): 1623–1632.

Boentert, M., H. Prigent, K. Várdi, H. N. Jones, U. Mellies, A. K. Simonds, S. Wenninger, E. Barrot Cortés and M. Confalonieri (2016b). "Practical Recommendations for Diagnosis and Management of Respiratory Muscle Weakness in Late-Onset Pompe Disease." Int J Mol Sci **17**(10).

Briggs A, C. K., Sculpher M (2006). Decision Modelling for Health Economic Evaluation, Oxford University Press.

Byrne, B. J., P. S. Kishnani, L. E. Case, L. Merlini, W. Müller-Felber, S. Prasad and A. van der Ploeg (2011). "Pompe disease: design, methodology, and early findings from the Pompe Registry." Mol Genet Metab **103**(1): 1-11.

Byrne, B. J. S., B. Kishnani, P. Bratkovic, D. Clemens, P. Goker-Alpan, O. Ming, X. Robets, R. Vorgerd M, Sivakumar, K. Van der Ploeg, A. Goldman, M. Wright, J. Holdbrook., F. Jain, V. Sitaraman, S. Wasfi, Y. Mozaffar, F. . (2020). "Long-term follow-up of cipaglucosidase alfa/miglustat in ambulatory patients with Pompe disease: an open-label Phase I/II study (ATB200-02)." from https://ir.amicusrx.com/static-files/7b65de4a-227a-41aa-a3ef-cded1a7b819d.

Byrne, S., Kishnani, Bratkovic, Clemens, Goker-Alpan, Ming, Roberts, Vorgerd, Sivakumar, van der Ploeg, Goldman, Wright, Holdbrook, Jain, Sitaraman, Wasfi, Mozaffar (2022). Long-term follow-up of cipaglucosidase alfa/miglustat in ambulatory patients with Pompe disease: an open-label Phase I/II study (ATB200-02). Muscular Dystrophy Association (MDA) Clinical & Scientific Conference, Nashville, USA.

CADTH. (2022). "CADTH Search Filters Database." Retrieved 30th September 2022

from https://searchfilters.cadth.ca.

Casanova, C., B. R. Celli, P. Barria, A. Casas, C. Cote, J. P. de Torres, J. Jardim, M. V. Lopez, J. M. Marin, M. Montes de Oca, V. Pinto-Plata and A. Aguirre-Jaime (2011). "The 6-min walk distance in healthy subjects: reference standards from seven countries." European Respiratory Journal **37**(1): 150.

Case, L. E., C. Bjartmar, C. Morgan, R. Casey, J. Charrow, J. P. Clancy, M. Dasouki, S. DeArmey, K. Nedd, M. Nevins, H. Peters, D. Phillips, Z. Spigelman, C. Tifft and P. S. Kishnani (2015). "Safety and efficacy of alternative alglucosidase alfa regimens in Pompe disease." Neuromuscul Disord **25**(4): 321-332.

Castelli (2023). "Jeff Castelli, Shuai Fu, Noemi Hummel, Tahseen Mozaffar, Brian Fox, Ian Keyzor, Syed Raza, Sheela Sitaraman Das, Simon Shohet. Indirect treatment comparison of three enzyme replacement treatments for late-onset Pompe disease: a network meta-analysis with patient-level and aggregate data

– cipaglucosidase alfa plus miglustat shows favorable results when both ERT-naïve and ERT-experienced patient data are incorporated. Poster no. 63. Presented at the 19th Annual WORLDSymposium™; Orlando, FL, USA; February 22–26, 2023."

Castro-Jaramillo, H. E. (2012). "The cost-effectiveness of enzyme replacement therapy (ERT) for the infantile form of Pompe disease: comparing a high-income country's approach (England) to that of a middle-income one (Colombia)." Rev Salud Publica (Bogota) **14**(1): 143-155.

Center for Drug Evaluation and Research. "BLA integrated review 761194 Nexviazyme® (Avalglucosidase Alfa-Ngpt)." 2023, from www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761194Orig1s000IntegratedR.pdf

Center for Drug Evaluation and Research. (2020). "BLA integrated review 761194 Nexviazyme® (Avalglucosidase Alfa-Ngpt)." 2023, from www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761194Orig1s000IntegratedR.pdf

Chan, J., A. K. Desai, Z. B. Kazi, K. Corey, S. Austin, L. D. Hobson-Webb, L. E. Case, H. N. Jones and P. S. Kishnani (2017). "The emerging phenotype of late-onset Pompe disease: A systematic literature review." Mol Genet Metab **120**(3): 163–172.

Chandler, J., M. Cumpston and T. Li (2019). Cochrane Handbook for Systematic Reviews of Interventions.

Chen, S., J. Wang, J. Zhu, R. Y. Chung and D. Dong (2021). "Quality of life and its contributors among adults with late-onset Pompe disease in China." Orphanet J Rare Dis **16**(1): 199.

Chien, Y. H., J. L. Goldstein, W. L. Hwu, P. B. Smith, N. C. Lee, S. C. Chiang, A. A. Tolun, H. Zhang, A. E. Vaisnins, D. S. Millington, P. S. Kishnani and S. P. Young (2015). "Baseline urinary glucose tetrasaccharide concentrations in patients with infantile- and late-onset Pompe disease identified by newborn screening." JIMD Rep **19**: 67–73.

Chu, Y. P., B. Sheng, K. K. Lau, H. F. Chan, G. Y. Kam, H. H. Lee and C. M. Mak (2016). "Clinical manifestation of late onset Pompe disease patients in Hong Kong." Neuromuscul Disord **26**(12): 873–879.

Cupler, E. J., K. I. Berger, R. T. Leshner, G. I. Wolfe, J. J. Han, R. J. Barohn and J. T. Kissel (2012a). "Consensus treatment recommendations for late-onset Pompe disease." Muscle Nerve **45**(3): 319–333.

Cupler, E. J., K. I. Berger, R. T. Leshner, G. I. Wolfe, J. J. Han, R. J. Barohn, J. T. Kissel and A. C. C. o. L.-o. P. Disease (2012b). "Consensus treatment recommendations for late-onset Pompe disease." Muscle & nerve **45**(3): 319-333.

Dakin, H., L. Abel, R. Burns and Y. Yang (2018). "Review and critical appraisal of studies mapping from quality of life or clinical measures to EQ-5D: an online database and application of the MAPS statement." Health and Quality of Life Outcomes **16**(1): 1-9.

Diaz-Manera, J., P. S. Kishnani, H. Kushlaf, S. Ladha, T. Mozaffar, V. Straub, A. Toscano, A. T. van der Ploeg, K. I. Berger, P. R. Clemens, Y. H. Chien, J. W. Day, S. Illarioshkin, M. Roberts, S. Attarian, J. L. Borges, F. Bouhour, Y. C. Choi, S. Erdem-Ozdamar, O. Goker-Alpan, A. Kostera-Pruszczyk, K. A. Haack, C. Hug, O. Huynh-Ba, J. Johnson, N. Thibault, T. Zhou, M. M. Dimachkie and B. Schoser (2021). "Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised, multicentre trial." Lancet Neurol **20**(12): 1012-1026.

Dimachkie, M. M., R. J. Barohn, B. Byrne, O. Goker-Alpan, P. S. Kishnani, S. Ladha, P. Laforêt, K. E. Mengel, L. D. Peña and S. Sacconi (2022a). "Long-term Safety and Efficacy of Avalglucosidase Alfa in Patients With Late-Onset Pompe Disease." Neurology.

Dimachkie, M. M., R. J. Barohn, B. Byrne, O. Goker-Alpan, P. S. Kishnani, S. Ladha, P. Laforêt, K. E. Mengel, L. D. M. Peña, S. Sacconi, V. Straub, J. Trivedi, P. Van Damme, A. T. van der Ploeg, J. Vissing, P. Young, K. A. Haack, M. Foster, J. M. Gilbert, P. Miossec, O. Vitse, T. Zhou and B. Schoser (2022b). "Long-term Safety and Efficacy of Avalglucosidase Alfa in Patients With Late-Onset Pompe Disease." Neurology **99**(5): e536-548.

Do, H. V., R. Khanna and R. Gotschall (2019). "Challenges in treating Pompe disease: an industry perspective." Ann Transl Med **7**(13): 291.

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). Methods for the Economic Evaluation of Health Care Programmes. (4th ed.), Oxford University Press.

du Bois, R. M., D. Weycker, C. Albera, W. Z. Bradford, U. Costabel, A. Kartashov, T. E. King, Jr., L. Lancaster, P. W. Noble, S. A. Sahn, M. Thomeer, D. Valeyre and A. U. Wells (2011). "Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference." Am J Respir Crit Care Med **184**(12): 1382–1389.

Duke University Hospital Biochemical Genetics Laboratory. (2020). "Information Sheet, Hex4, 2020. Accessed from https://pediatrics.duke.edu/sites/pediatrics.duke.edu/files/field/attachments/urine_Hex4_test_%20information.pdf Accessed date 18 August 2021."

Dunaway, S., J. Montes, C. E. Garber, B. Carr, S. S. Kramer, S. Kamil-Rosenberg, N. Strauss, D. Sproule and D. C. De Vivo (2014). "Performance of the timed "up & go" test in spinal muscular atrophy." Muscle Nerve **50**(2): 273–277.

Dunaway Young, S., J. Montes, S. S. Kramer, J. Marra, R. Salazar, R. Cruz, C. A. Chiriboga, C. E. Garber and D. C. De Vivo (2016). "Six-minute walk test is reliable and valid in spinal muscular atrophy." Muscle Nerve **54**(5): 836-842.

Echaniz-Laguna, A., R. Y. Carlier, K. Laloui, P. Carlier, E. Salort-Campana, J. Pouget and P. Laforet (2015). "Should patients with asymptomatic pompe disease be treated? A nationwide study in France." Muscle Nerve **51**(6): 884–889.

European Commission (2021). "Community register of orphan medicinal products. Accessed on 26_07_2021 from https://ec.europa.eu/health/documents/community-register/html/reg_od_act.htm?sort=a.".

European Medicines Agency (2020). Myozyme alglucosidase alfa

European Medicines Agency (2021a). "Committee for Medicinal Products for Human Use (CHMP) summary of opinion (Nexviadyme). Accessed January 2022 from https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-nexviadyme_en.pdf."

European Medicines Agency (2021b). "Orphan designation overview. Accessed on 26_07_2021 from https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview.".

European Medicines Agency (2022). "Committee for Medicinal Products for Human Use (CHMP) summary of opinion (Nexviadyme). Accessed January 2022 from https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-nexviadyme_en.pdf."

European Medicines Agency. (2023). "Pombiliti (cipaglucosidase alfa) EMA/950090/2022." from https://www.ema.europa.eu/en/documents/overview/pombiliti-epar-medicine-overview_en.pdf.

EuroQol. (2023). "EQ-5D." from https://euroqol.org/.

Eurostat (2021). "Mortality and life expectancy statistics. Accessed on 26_07_2021 from https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Mortality_and_life_expectancy_statistics.".

FDA (2019). "US Food and Drug Administration. Patient-focused drug development guidance public workshop. Incorportating clinical outcome assessments into endpoints for regulatory decision-making. Workshop date: 6 December 2019. Available from: https://www.fda.gov/media/132505/download. (Accessed 18 August 2022).".

Finansministeriet (2021). Dokumentationsnotat – den samfundsøkonomiske diskonteringsrente. Finansministeriet. https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf.

Fu, H., Mozaffar, Castelli, Fox, Keyzor, Raza, Sitaraman, Shohet (2022). Indirect treatment comparison of three enzyme replacement treatments for late-onset Pompe disease: a network meta-analysis with patient-level and aggregate data. World Muscle Society. Halifax, Canada.

Güngör, D., J. M. de Vries, W. C. Hop, A. J. Reuser, P. A. van Doorn, A. T. van der Ploeg and M. L. Hagemans (2011). "Survival and associated factors in 268 adults with Pompe disease prior to treatment with enzyme replacement therapy." Orphanet J Rare Dis **6**: 34.

Güngör, D., M. E. Kruijshaar, I. Plug, R. B. D'Agostino, M. L. Hagemans, P. A. van Doorn, A. J. Reuser and A. T. van der Ploeg (2013). "Impact of enzyme replacement therapy on survival in adults with Pompe disease: results from a prospective international observational study." Orphanet J Rare Dis **8**: 49.

Gutschmidt, K., O. Musumeci, J. Díaz-Manera, Y.-H. Chien, K. C. Knop, S. Wenninger, F. Montagnese, A. Pugliese, G. Tavilla, J. Alonso-Pérez, P. W.-L. Hwu, A. Toscano and B. Schoser (2021). "STIG study: real-world data of long-term outcomes of adults with Pompe disease under enzyme replacement therapy with alglucosidase alfa." J. Neurol **268:2482–92; 32–31:9798**: 2482–2492.

Hagemans, M. L., W. J. Hop, P. A. Van Doorn, A. J. Reuser and A. T. Van der Ploeg (2006). "Course of disability and respiratory function in untreated late-onset Pompe disease." Neurology **66**(4): 581–583.

Hagemans, M. L., A. C. Janssens, L. P. Winkel, K. A. Sieradzan, A. J. Reuser, P. A. Van Doorn and A. T. Van der Ploeg (2004). "Late-onset Pompe disease primarily affects quality of life in physical health domains." Neurology **63**(9): 1688–1692.

Hagemans, M. L., P. Laforêt, W. J. Hop, I. S. Merkies, P. A. Van Doorn, A. J. Reuser and A. T. Van der Ploeg (2007a). "Impact of late-onset Pompe disease on participation in daily life activities: evaluation of the Rotterdam Handicap Scale." Neuromuscul Disord **17**(7): 537–543.

Hagemans, M. L., S. P. van Schie, A. C. Janssens, P. A. van Doorn, A. J. Reuser and A. T. van der Ploeg (2007b). "Fatigue: an important feature of late-onset Pompe disease." J Neurol **254**(7): 941-945.

Hahn, A., S. Praetorius, N. Karabul, J. Dießel, D. Schmidt, R. Motz, C. Haase, M. Baethmann, J. B. Hennermann, M. Smitka, R. Santer, N. Muschol, A. Meyer, T. Marquardt, M. Huemer, C. Thiels, M. Rohrbach, G. Seyfullah and E. Mengel (2015). "Outcome of patients with classical infantile Pompe disease receiving enzyme replacement therapy in Germany." JIMD Rep **20**: 65–75.

Harfouche, M., P. S. Kishnani, E. Krusinska, J. Gault, S. Sitaraman, A. Sowinski, I. Katz, S. Austin, M. Goldstein and A. E. Mulberg (2020). "Use of the patient-reported outcomes measurement information system (PROMIS®) to assess late-onset Pompe disease severity." J Patient Rep Outcomes **4**(1): 83.

Harlaar, L., J. Y. Hogrel, B. Perniconi, M. E. Kruijshaar, D. Rizopoulos, N. Taouagh, A. Canal, E. Brusse, P. A. van Doorn, A. T. van der Ploeg, P. Laforêt and N. van der Beek (2019). "Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease." Neurology **93**(19): e1756–e1767.

Hensel, O., I. Schneider, M. Wieprecht, T. Kraya and S. Zierz (2018). "Decreased outlet angle of the superior cerebellar artery as indicator for dolichoectasia in late onset Pompe disease." Orphanet J Rare Dis **13**(1): 57.

Herbison, G. J., Z. Isaac, M. E. Cohen and J. F. Ditunno, Jr. (1996). "Strength post-spinal cord injury: myometer vs manual muscle test." Spinal Cord **34**(9): 543-548.

HM de Freitas, R. G., L Hubig, AK Sussex, S Raza, A MacCulloch, AJ Lloyd, A Sowinski (2022). "Improving the methods of vignette development for utility estimation: a case study in Pompe disease." Presented at the annual meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe, Vienna, Austria; 6–9 November 2022.

Hobson-Webb, L. D. and P. S. Kishnani (2012). "How common is misdiagnosis in late-onset Pompe disease?" Muscle Nerve **45**(2): 301–302.

Hubig, L., A.-K. Sussex, A. MacCulloch, D. Hughes, R. Graham, L. Morris, S. Raza, A. J. Lloyd, A. Sowinski and K. Gallop (2023). "Quality of Life with Late-Onset Pompe Disease: Qualitative Interviews and General Public Utility Estimation in the United Kingdom." Journal of Health Economics and Outcomes Research **10**(1): 41.

Hui, D. and E. Bruera (2016). "Reply to minimal clinically important difference and Edmonton Symptom Assessment Scale." Cancer **122**(1): 159-160.

Hundsberger, T., M. Rohrbach, L. Kern and K. M. Rösler (2013). "Swiss national guideline for reimbursement of enzyme replacement therapy in late-onset Pompe disease." J Neurol **260**(9): 2279–2285.

Iolascon, G., M. Vitacca, E. Carraro, C. Chisari, P. Fiore, S. Messina, T. Mongini, A. Moretti, V. A. Sansone, A. Toscano and G. Siciliano (2020). "Adapted physical activity and therapeutic exercise in late-onset Pompe disease (LOPD): a two-step rehabilitative approach." Neurol Sci **41**(4): 859–868.

Johnson, E. M., M. Roberts, T. Mozaffar, P. Young, A. Quartel and K. I. Berger (2016). "Pulmonary function tests (maximum inspiratory pressure, maximum expiratory pressure, vital capacity, forced vital capacity) predict ventilator use in late-onset Pompe disease." Neuromuscul Disord **26**(2): 136–145.

Johnson, F. e. a. (2017). "Poster presented at the 13th Annual WORLDSymposium; February 13–17, 2017; San Diego, CA, USA."

Jones, H. N., M. Kuchibhatla, K. D. Crisp, L. D. Hobson Webb, L. Case, M. T. Batten, J. A. Marcus, R. M. Kravitz and P. S. Kishnani (2019). "Respiratory muscle training (RMT) in late-onset Pompe disease (LOPD): A protocol for a sham-controlled clinical trial." Mol Genet Metab **127**(4): 346–354.

Kanters, T. A., M. L. Hagemans, N. A. van der Beek, F. F. Rutten, A. T. van der Ploeg and L. Hakkaart (2011). "Burden of illness of Pompe disease in patients only receiving supportive care." J Inherit Metab Dis **34**(5): 1045–1052.

Kanters, T. A., I. Hoogenboom-Plug, M. P. Rutten-Van Molken, W. K. Redekop, A. T. van der Ploeg and L. Hakkaart (2014). "Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in classic-infantile patients with Pompe disease." Orphanet J Rare Dis **9**: 75.

Kanters, T. A., W. K. Redekop, M. E. Kruijshaar, A. T. van der Ploeg, M. P. Rutten-van Mölken and L. Hakkaart (2015). "Comparison of EQ-5D and SF-6D utilities in Pompe disease." Qual Life Res **24**(4): 837-844.

Kanters, T. A., A. T. van der Ploeg, W. B. Brouwer and L. Hakkaart (2013). "The impact of informal care for patients with Pompe disease: an application of the CarerQol instrument." Mol Genet Metab **110**(3): 281-286.

Kanters, T. A., A. T. van der Ploeg, M. E. Kruijshaar, D. Rizopoulos, W. K. Redekop, M. Rutten-van Mölken and L. Hakkaart-van Roijen (2017). "Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in adult patients with Pompe disease." Orphanet J Rare Dis **12**(1): 179.

Khan, A. A., T. Boggs, M. Bowling, S. Austin, M. Stefanescu, L. Case and P. S. Kishnani (2020). "Whole-body magnetic resonance imaging in late-onset Pompe disease: Clinical utility and correlation with functional measures." J Inherit Metab Dis **43**(3): 549-557.

Kishnani (2022). "Kishnani PS, Berger KI, Dimachkie MM et al. LB-37. Avalglucosidase alfa improves health-related quality of life (HRQoL) in patients with late-onset Pompe disease (LOPD) vs. alglucosidase alfa: patient-reported outcome measures (PROMs) from the phase 3 COMET trial. Poster presented at the 18th Annual WORLDSymposium, 7-11 February 2022, San Diego, California, USA."

Kishnani (2023). "Priya S. Kishnani, Jordi Díaz-Manera, Hani Kushlaf, Shafeeq Ladha, Tahseen Mozaffar, Volker Straub, Antonio Toscano, Ans T. van der Ploeg, Paula R. Clemens, John W. Day, Sergey Illarioshkin, Mark Roberts, Shahram Attarian, Gerson Carvalho, Sevim Erdem-Özdamar, Ozlem Goker-Alpan, Anna Kostera-Pruszczyk, Kristina An Haack, Olivier Huynh-Ba, Swathi Tammireddy, Nathan Thibault, Tianyue Zhou, Mazen M. Dimachkie, Benedikt Schoser on behalf of the COMET Investigator Group. Efficacy and Safety of Avalglucosidase Alfa in Participants With Late-Onset Pompe Disease After 145 Weeks' Treatment During the COMET Trial. ePoster presented in Orlando, Florida, USA, February 22–26, 2023."

Kishnani, P. "The patient and clinician point of view: living with late-onset Pompe disease; poster presented at WORLDSymposium; February 5–9, 2018; San Diego, CA."

Kishnani, P., M. Tarnopolsky, M. Roberts, K. Sivakumar, M. Dasouki, M. M. Dimachkie, E. Finanger, O. Goker-Alpan, K. A. Guter, T. Mozaffar, M. A. Pervaiz, P. Laforet, T. Levine, M. Adera, R. Lazauskas, S. Sitaraman, R. Khanna, E. Benjamin, J. Feng, J. J. Flanagan, J. Barth, C. Barlow, D. J. Lockhart, K. J. Valenzano, P. Boudes, F. K. Johnson and B. Byrne (2017). "Duvoglustat HCl increases systemic and tissue exposure of active acid α-glucosidase in Pompe patients co-administered with alglucosidase α." Mol Ther **25**(5): 1199–1208.

Kishnani, P. S. and A. A. Beckemeyer (2014). "New therapeutic approaches for Pompe disease: enzyme replacement therapy and beyond." Pediatr Endocrinol Rev **12 Suppl 1**: 114–124.

Kishnani, P. S., A. A. Beckemeyer and N. J. Mendelsohn (2012). "The new era of Pompe disease: advances in the detection, understanding of the phenotypic spectrum, pathophysiology, and management." Am J Med Genet C Semin Med Genet **160c**(1): 1–7.

Kishnani, P. S., D. Corzo, N. D. Leslie, D. Gruskin, A. Van der Ploeg, J. P. Clancy, R. Parini, G. Morin, M. Beck, M. S. Bauer, M. Jokic, C. E. Tsai, B. W. Tsai, C. Morgan, T. O'Meara, S. Richards, E. C. Tsao and H. Mandel (2009). "Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease." Pediatr Res **66**(3): 329–335.

Kishnani, P. S. and R. R. Howell (2004). "Pompe disease in infants and children." J Pediatr **144**(5 Suppl): S35–43.

Kishnani, P. S., R. D. Steiner, D. Bali, K. Berger, B. J. Byrne, L. E. Case, J. F. Crowley, S. Downs, R. R. Howell, R. M. Kravitz, J. Mackey, D. Marsden, A. M. Martins, D. S. Millington, M. Nicolino, G. O'Grady, M. C. Patterson, D. M. Rapoport, A. Slonim, C. T. Spencer, C. J. Tifft and M. S. Watson (2006). "Pompe disease diagnosis and management guideline." Genet Med **8**(5): 267–288.

Koeberl, D. D., L. E. Case, A. Desai, E. C. Smith, C. Walters, S. O. Han, B. L. Thurberg, S. P. Young, D. Bali and P. S. Kishnani (2020). "Improved muscle function in a phase I/II clinical trial of albuterol in Pompe disease." Mol Genet Metab **129**(2): 67-72.

Koeberl, D. D., L. E. Case, E. C. Smith, C. Walters, S. O. Han, Y. Li, W. Chen, C. P. Hornik, K. M. Huffman, W. E. Kraus, B. L. Thurberg, D. L. Corcoran, D. Bali, N. Bursac and P. S. Kishnani (2018). "Correction of Biochemical Abnormalities and Improved Muscle Function in a Phase I/II Clinical Trial of Clenbuterol in Pompe Disease." Mol Ther **26**(9): 2304-2314.

Kronn, D. F., D. Day-Salvatore, W. L. Hwu, S. A. Jones, K. Nakamura, T. Okuyama, K. J. Swoboda and P. S. Kishnani (2017). "Management of confirmed newborn-screened patients with Pompe disease across the disease spectrum." Pediatrics **140**(Suppl 1): S24–S45.

Kuperus, E., M. E. Kruijshaar, S. C. A. Wens, J. M. de Vries, M. M. Favejee, J. C. van der Meijden, D. Rizopoulos, E. Brusse, P. A. van Doorn, A. T. van der Ploeg and N. van der Beek (2017). "Long-term benefit of enzyme replacement therapy in Pompe disease: A 5-year prospective study." Neurology **89**(23): 2365–2373.

Lachmann, R. and B. Schoser (2013). "The clinical relevance of outcomes used in late-onset Pompe disease: can we do better?" Orphanet J Rare Dis **8**: 160.

Lægehåndbogen. (2021). "[Pompe disease]." from https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/sjaeldne-sygdomme/sjaeldne-sygdomme/pompes-sygdom/.

Leahy, J., H. Thom, J. P. Jansen, E. Gray, A. O'Leary, A. White and C. Walsh (2019). "Incorporating single-arm evidence into a network meta-analysis using aggregate level matching: Assessing the impact." Stat Med **38**(14): 2505-2523.

Leslie and Bailey (2007). " Pompe Disease. 2007 Aug 31 [Updated 2017 May 11]. In: Adam MP, Ardinger HH, Pagon RA, *et al*., editors. GeneReviews® [Internet]. Seattle: University of Washington; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1261/."

Lim, J. A., L. Li and N. Raben (2014). "Pompe disease: from pathophysiology to therapy and back again." Front Aging Neurosci **6**: 177.

Lukacs, Z., P. Nieves Cobos, S. Wenninger, T. A. Willis, M. Guglieri, M. Roberts, R. Quinlivan, D. Hilton-Jones, T. Evangelista, S. Zierz, B. Schlotter-Weigel, M. C. Walter, P. Reilich, T. Klopstock, M. Deschauer, V. Straub, W. Müller-Felber and B. Schoser (2016). "Prevalence of Pompe disease in 3,076 patients with hyperCKemia and limb-girdle muscular weakness." Neurology **87**(3): 295–298.

McDonald, C. M., E. K. Henricson, R. T. Abresch, J. M. Florence, M. Eagle, E. Gappmaier, A. M. Glanzman, R. Spiegel, J. Barth, G. Elfring, A. Reha and S. Peltz (2013). "The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study." Muscle Nerve **48**(3): 343-356.

McIntosh, P., S. Austin, J. Sullivan, L. Bailey, C. Bailey, D. Viskochil and P. S. Kishnani (2017). "Three cases of multi-generational Pompe disease: Are current practices missing diagnostic and treatment opportunities?" Am J Med Genet A **173**(10): 2628–2634.

Medicinrådet. (2022). "Avalglucosidase alfa (Nexviadyme)." from https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/a-d/avalglucosidase-alfa-nexviadyme-pompes-sygdom.

Meena, N. K. and N. Raben (2020). "Pompe disease: new developments in an old lysosomal storage disorder." Biomolecules **10**(9): 1339.

Meznaric, M., K. Fumic and L. Leonardis (2019). "Selective screening of late-onset Pompe disease (LOPD) in patients with non-diagnostic muscle biopsies." J Clin Pathol **72**(7): 468–472.

Moher, D., A. Liberati, J. Tetzlaff, D. G. Altman and P. Group (2010). "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement." International journal of surgery (London, England) **8**(5): 336-341.

Moreland, R. J., X. Jin, X. K. Zhang, R. W. Decker, K. L. Albee, K. L. Lee, R. D. Cauthron, K. Brewer, T. Edmunds and W. M. Canfield (2005). "Lysosomal acid alpha-glucosidase consists of four different peptides processed from a single chain precursor." J Biol Chem **280**(8): 6780–6791.

Muir (2021). "Allan Muir, Kayuri Odedra, Neil Johnson, Lisa Bashorum, Anjala Patmore, Peter Slade, Jane Lewthwaite. Living with late-onset Pompe disease in the UK: interim results characterising the patient journey and burden on physical,

emotional and social quality of life. EP.201. Presented at the World Muscle Society 2021 Virtual Congress, 20–24 September.".

Muir, A. W., PN. (2019). "Disease burden and unmet needs: Results from a new survey in adult patients living with Pompe disease in the United Kingdom; Poster presented at International Glycogen Storage Disease Conference; November 14–16, 2019; Porto Alegre, Brazil."

Musumeci, O., G. la Marca, M. Spada, S. Mondello, C. Danesino, G. P. Comi, E. Pegoraro, G. Antonini, G. Marrosu, R. Liguori, L. Morandi, M. Moggio, R. Massa, S. Ravaglia, A. Di Muzio, M. Filosto, P. Tonin, G. Di Iorio, S. Servidei, G. Siciliano, C. Angelini, T. Mongini and A. Toscano (2016). "LOPED study: looking for an early diagnosis in a late-onset Pompe disease high-risk population." J Neurol Neurosurg Psychiatry **87**(1): 5–11.

National Institute for Health and Care Excellence. (2016). "Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene." from https://www.nice.org.uk/guidance/hst3.

National Institute for Health and Care Excellence. (2022). "Avalglucosidase alfa for treating Pompe disease [ID3737]." 2022, from https://www.nice.org.uk/guidance/indevelopment/gid-ta10876.

National Institute for Rare Disorders (2020). "Pompe Disease (Accessed from: https://rarediseases.org/rare-diseases/pompe-disease/ on 27 April 2021) ".

Nicolino, M., B. Byrne, J. E. Wraith, N. Leslie, H. Mandel, D. R. Freyer, G. L. Arnold, E. K. Pivnick, C. J. Ottinger, P. H. Robinson, J. C. Loo, M. Smitka, P. Jardine, L. Tatò, B. Chabrol, S. McCandless, S. Kimura, L. Mehta, D. Bali, A. Skrinar, C. Morgan, L. Rangachari, D. Corzo and P. S. Kishnani (2009). "Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease." Genet Med **11**(3): 210–219.

Nordin, S. (2023). "Abstract/Poster 257. 19th annual WORLD Symposium 2023. Orlando."

Papaioannou, D., J. Brazier and S. Paisley (2013). "Systematic searching and selection of health state utility values from the literature." Value in health **16**(4): 686-695.

Parenti, G., S. Fecarotta, G. la Marca, B. Rossi, S. Ascione, M. A. Donati, L. O. Morandi, S. Ravaglia, A. Pichiecchio, D. Ombrone, M. Sacchini, M. B. Pasanisi, P. De Filippi, C. Danesino, R. Della Casa, A. Romano, C. Mollica, M. Rosa, T. Agovino, E. Nusco, C. Porto and G. Andria (2014). "A chaperone enhances blood α-glucosidase activity in Pompe disease patients treated with enzyme replacement therapy." Mol Ther **22**(11): 2004-2012.

Park, K. S. (2021). "Carrier frequency and predicted genetic prevalence of Pompe disease based on a general population database." Mol Genet Metab Rep **27**: 100734.

Pérez-López, J., A. Selva-O'Callaghan, J. M. Grau-Junyent, L. Gallego-Galindo, M. J. Coll, S. García-Morillo, M. A. Torralba-Cabeza and M. Vilardell-Tarrés (2015). "Delayed diagnosis of late-onset Pompe disease in patients with myopathies of unknown origin and/or hyperCKemia." Mol Genet Metab **114**(4): 580–583.

Phillippo, D. M., S. Dias, A. Ades, M. Belger, A. Brnabic, A. Schacht, D. Saure, Z. Kadziola and N. J. Welton (2020). "Multilevel network meta-regression for population-adjusted treatment comparisons." Journal of the Royal Statistical Society. Series A,(Statistics in Society) **183**(3): 1189.

Phillips, D., I. C. Tomazos, S. Moseley, G. L'Italien, H. Gomes da Silva and S. Lerma Lara (2019). "Reliability and Validity of the 6-Minute Walk Test in Hypophosphatasia." JBMR Plus **3**(6): e10131.

Pompe Disease News (2018). "Living with Pompe disease. Available from: https://pompediseasenews.com/pompe-disease-adjustments-can-improve-patients-lives/. (Accessed 22 February 2021).".

Pompeforeningen i Danmark (2023). "https://pompeforeningen.dk/om-pompes-sygdom/, Accessed March 2023."

Quanjer, P. H., S. Stanojevic, T. J. Cole, X. Baur, G. L. Hall, B. H. Culver, P. L. Enright, J. L. Hankinson, M. S. Ip, J. Zheng, J. Stocks and E. R. S. G. L. F. Initiative (2012). "Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations." Eur Respir J **40**(6): 1324-1343.

Rampakakis, E., P. A. Ste-Marie, J. S. Sampalis, A. Karellis, Y. Shir and M. A. Fitzcharles (2015). "Real-life assessment of the validity of patient global impression of change in fibromyalgia." RMD Open **1**(1): e000146.

Raza, S., I. Keyzor, S. Shohet, A. Chandak, A. Cheng and N. Hummel (2022a). "Association of walking distance with quality of life and other patient-reported outcomes in Pompe disease. 2022. Poster presented at the 2022 International Society of Pharmacoeconomics and Outcomes Research Annual Meeting, 15–18 May 2022, Washington DC, USA. ."

Raza, S., I. Keyzor, S. Shohet, M. Zalewska, N. Hummel and M. Brougham (2022b). "POSA283 Differential Appraisal of Functional Outcome Measures by Health Technology Assessment (HTA) Agencies When Reviewing Therapies for Rare Muscular, Skeletal and Neurodegenerative Disorders." Value in Health **25**(1): S175.

Rose, M., J. B. Bjorner, B. Gandek, B. Bruce, J. F. Fries and J. E. Ware, Jr. (2014). "The PROMIS Physical Function item bank was calibrated to a standardized metric and shown to improve measurement efficiency." J Clin Epidemiol **67**(5): 516–526.

Sanofi (2021). "Sanofi announces results of CHMP re-examination of the New Active Substance status for avalglucosidase alfa, a potential new standard of care for the treatment of Pompe disease. Accessed January 2022 from: https://www.sanofi.com/en/media-room/press-releases/2021/2021-11-12-12-38-38-2333221 ".

Schoser, B. (2022). Long-term follow-up of cipaglucosidase alfa/miglustat in ambulatory patients with Pompe disease: an open-label phase I/II study (ATB200-02) (Poster #FP.17). 27th International Hybrid Annual Congress of the World Muscle Society, Halifax, Canada.

Schoser, B. (2023). Long-term efficacy and safety of cipaglucosidase alfa/miglustat in ambulatory patients with Pompe disease: A phase III open-label extension study (ATB200-07): (Poster #LB-59). 19th Annual WORLDSymposium™, Orlando, USA.

Schoser, B., A. Hahn, E. James, D. Gupta, M. Gitlin and S. Prasad (2019). "A systematic review of the health economics of Pompe disease." PharmacoEconomics - Open **3**(4): 479–493.

Schoser, B., M. Roberts, B. J. Byrne, S. Sitaraman, H. Jiang, P. Laforêt, A. Toscano, J. Castelli, J. Díaz-Manera, M. Goldman, A. T. van der Ploeg, D. Bratkovic, S. Kuchipudi, T. Mozaffar and P. S. Kishnani (2021a). "Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial." Lancet Neurol **20**(12): 1027-1037.

Schoser, B., M. Roberts, B. J. Byrne, S. Sitaraman, H. Jiang, P. Laforêt, A. Toscano, J. Castelli, J. Díaz-Manera, M. Goldman, A. T. van der Ploeg, D. Bratkovic, S. Kuchipudi, T. Mozaffar, P. S. Kishnani, A. Sebok, A. Pestronk, A. Dominovic-Kovacevic, A. Khan, B. Koritnik, C. Tard, C. Lindberg, C. Quinn, C. Eldridge, C. Bodkin, D. Reyes-Leiva, D. Hughes, E. Stefanescu, E. Salort-Campana, E. Butler, F. Bouhour, G. Kim, G. Konstantinos Papadimas, G. Parenti, H. Bartosik-Psujek, H. Kushlaf, H. Akihiro, H. Lau, H. Pedro, H. Andersen, H. Amartino, H. Shiraishi, H. Kobayashi, I. Tarnev, J. Vengoechea, J. Avelar, J.-H. Shin, J. Cauci, J. Alonso-Pérez, J. Janszky, J. Berthy, K. Cornelia, K. Gutschmidt, K. Claeys, M. Judit Molnar, M. Wencel, M. Tarnopolsky, M. Dimachkie, M. Tchan, M. Freimer, N. Longo, N. Vidal-Fernandez, O. Musumeci, O. Goker-Alpan, P. Deegan, P. R. Clemens, R. Roxburgh, R. Henderson, R. Hopkin, S. Sacconi, S. Fecarotta, S. Attarian, S. Wenninger, S. Dearmey, T. Hiwot, T. Burrow, T. Ruck, T. Sawada, V. Laszlo, W. Löscher and Y.-H. Chien (2021b). "Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial." The Lancet Neurology **20**(12): 1027-1037.

Schoser, B., M. Roberts, B. J. Byrne, S. Sitaraman, H. Jiang, P. Laforêt, A. Toscano, J. Castelli, J. Díaz-Manera, M. Goldman, A. T. van der Ploeg, D. Bratkovic, S. Kuchipudi, T. Mozaffar, P. S. Kishnani, A. Sebok, A. Pestronk, A. Dominovic-Kovacevic, A. Khan, B. Koritnik, C. Tard, C. Lindberg, C. Quinn, C. Eldridge, C. Bodkin, D. Reyes-Leiva, D. Hughes, E. Stefanescu, E. Salort-Campana, E. Butler, F. Bouhour, G. Kim, G. Konstantinos Papadimas, G. Parenti, H. Bartosik-Psujek, H. Kushlaf, H. Akihiro, H. Lau, H. Pedro, H. Andersen, H. Amartino, H. Shiraishi, H. Kobayashi, I. Tarnev, J. Vengoechea, J. Avelar, J.-H. Shin, J. Cauci, J. Alonso-Pérez, J. Janszky, J. Berthy, K. Cornelia, K. Gutschmidt, K. Claeys, M. Judit Molnar, M. Wencel, M. Tarnopolsky, M. Dimachkie, M. Tchan, M. Freimer, N. Longo, N. Vidal-Fernandez, O. Musumeci, O. Goker-Alpan, P. Deegan, P. R. Clemens, R. Roxburgh, R. Henderson, R. Hopkin, S. Sacconi, S. Fecarotta, S. Attarian, S. Wenninger, S. Dearmey, T. Hiwot, T. Burrow, T. Ruck, T. Sawada, V. Laszlo, W. Löscher and Y.-H. Chien (2021c). "Supplement: Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial." The Lancet Neurology **20**(12): 1027-1037.

Schrover, R., K. Evans, R. Giugliani, I. Noble and K. Bhattacharya (2017). "Minimal clinically important difference for the 6-min walk test: literature review and application to Morquio A syndrome." Orphanet J Rare Dis **12**(1): 78.

Scott, C. R., S. Elliott, N. Buroker, L. I. Thomas, J. Keutzer, M. Glass, M. H. Gelb and F. Turecek (2013). "Identification of infants at risk for developing Fabry, Pompe, or mucopolysaccharidosis-I from newborn blood spots by tandem mass spectrometry." J Pediatr **163**(2): 498–503.

Selvan, N., N. Mehta, S. Venkateswaran, N. Brignol, M. Graziano, M. O. Sheikh, Y. McAnany, F. Hung, M. Madrid, R. Krampetz, N. Siano, A. Mehta, J. Brudvig, R. Gotschall, J. M. Weimer and H. V. Do (2021). "Endolysosomal N-glycan processing is critical to attain the most active form of the enzyme acid alpha-glucosidase." J Biol Chem **296**: 100769.

Semplicini, C., M. De Antonio, N. Taouagh, A. Béhin, F. Bouhour, A. Echaniz-Laguna, A. Magot, A. Nadaj-Pakleza, D. Orlikowski, S. Sacconi, E. Salort-Campana, G. Solé, C. Tard, F. Zagnoli, J. Y. Hogrel, D. Hamroun and P. Laforêt (2020). "Long-term benefit of enzyme replacement therapy with alglucosidase alfa in adults with Pompe disease: Prospective analysis from the French Pompe Registry." J Inherit Metab Dis **43**(6): 1219–1231.

Semplicini, C., P. Letard, M. De Antonio, N. Taouagh, B. Perniconi, F. Bouhour, A. Echaniz-Laguna, D. Orlikowski, S. Sacconi, E. Salort-Campana, G. Solé, F. Zagnoli, D. Hamroun, R. Froissart, C. Caillaud and P. Laforêt (2018). "Late-onset Pompe disease in France: molecular features and epidemiology from a nationwide study." J Inherit Metab Dis **41**(6): 937–946.

Shohet, S., Keyzor, I. Kopiec, A., Zalewska, M., Brougham, M. (2021). "Associations between physical function measures and patient-reported outcomes in Pompe disease and other rare disorders impacting motor, respiratory and skeletal function. IPSOR poster Europe December 2021. Accessed from: https://www.ispor.org/docs/default-source/euro2021/shohetposc30associations-bw-functional-measurespompeispor-eu-2021final-poster-pdf.pdf?sfvrsn=e9e11658_0."

SIGN (Healthcare Improvement Scotland). (2021). "SIGN Filters." Retrieved 29th September 2022, from https://www.sign.ac.uk/what-we-do/methodology/search-filters/.

Simon, N. J., J. Richardson, A. Ahmad, A. Rose, E. Wittenberg, B. D'Cruz and L. A. Prosser (2019). "Health utilities and parental quality of life effects for three rare conditions tested in newborns." J Patient Rep Outcomes **3**(1): 4.

Spada, M., F. Porta, L. Vercelli, V. Pagliardini, L. Chiadò-Piat, P. Boffi, S. Pagliardini, G. Remiche, D. Ronchi, G. Comi and T. Mongini (2013). "Screening for later-onset Pompe's disease in patients with paucisymptomatic hyperCKemia." Mol Genet Metab **109**(2): 171–173.

Sterne, J. A., M. A. Hernán, B. C. Reeves, J. Savović, N. D. Berkman, M. Viswanathan, D. Henry, D. G. Altman, M. T. Ansari, I. Boutron, J. R. Carpenter, A. W. Chan, R. Churchill, J. J. Deeks, A. Hróbjartsson, J. Kirkham, P. Jüni, Y. K. Loke, T. D. Pigott, C. R. Ramsay, D. Regidor, H. R. Rothstein, L. Sandhu, P. L. Santaguida, H. J. Schünemann, B. Shea, I. Shrier, P. Tugwell, L. Turner, J. C. Valentine, H. Waddington, E. Waters, G. A. Wells, P. F. Whiting and J. P. Higgins (2016). "ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions." Bmj **355**: i4919.

Sterne, J. A. C., J. Savović, M. J. Page, R. G. Elbers, N. S. Blencowe, I. Boutron, C. J. Cates, H. Y. Cheng, M. S. Corbett, S. M. Eldridge, J. R. Emberson, M. A. Hernán, S. Hopewell, A. Hróbjartsson, D. R. Junqueira, P. Jüni, J. J. Kirkham, T. Lasserson, T. Li, A. McAleenan, B. C. Reeves, S. Shepperd, I. Shrier, L. A. Stewart, K. Tilling, I. R. White, P. F. Whiting and J. P. T. Higgins (2019). "RoB 2: a revised tool for assessing risk of bias in randomised trials." Bmj **366**: l4898.

Taglia, A., E. Picillo, P. D'Ambrosio, M. R. Cecio, E. Viggiano and L. Politano (2011). "Genetic counseling in Pompe disease." Acta Myol **30**(3): 179–181.

Tarnopolsky, M., H. Katzberg, B. J. Petrof, S. Sirrs, H. B. Sarnat, K. Myers, N. Dupré, D. Dodig, A. Genge, S. L. Venance, L. Korngut, J. Raiman and A. Khan (2016). "Pompe disease: diagnosis and management. evidence-based guidelines from a Canadian expert panel." Can J Neurol Sci **43**(4): 472–485.

Taverna, S., G. Cammarata, P. Colomba, S. Sciarrino, C. Zizzo, D. Francofonte, M. Zora, S. Scalia, C. Brando, A. L. Curto, E. M. Marsana, R. Olivieri, S. Vitale and G. Duro (2020). "Pompe disease: pathogenesis, molecular genetics and diagnosis." Aging (Albany NY) **12**(15): 15856–15874.

TGA (2021). "Orphan drug designation eligibility criteria. Accessed on 26_07_2021 from https://www.tga.gov.au/publication/orphan-drug-designation-eligibility-criteria.".

Thurberg, B. L., C. Lynch Maloney, C. Vaccaro, K. Afonso, A. C. Tsai, E. Bossen, P. S. Kishnani and M. O'Callaghan (2006). "Characterization of pre- and post-treatment pathology after enzyme replacement therapy for Pompe disease." Lab Invest **86**(12): 1208–1220.

Tihanyi, B. and L. Nyitray (2020). "Recent advances in CHO cell line development for recombinant protein production." Drug discovery today. Technologies **38**: 25-34.

Tong, P. Y. and S. Kornfeld (1989). "Ligand interactions of the cation-dependent mannose 6-phosphate receptor. Comparison with the cation-independent mannose 6-phosphate receptor." J Biol Chem **264**(14): 7970–7975.

Toscano, A. and B. Schoser (2013). "Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review." J Neurol **260**(4): 951–959.

University of York Centre for Reviews and Dissemination. (2009). "Systematic Reviews: CRD's guidance for undertaking reviews in health care. Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. [Last accessed: April 2022]."

US Food and Drug Administration (2010). "FDA Lumizyme prescribing information. Accessed on 10 November 2021 from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125291lbl.pdf."

US Food and Drug Administration (2020). "Lumizyme prescribing information. Accessed on 17 May 2021 from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125291s151lbl.pdf."

van den Hout, H. M., W. Hop, O. P. van Diggelen, J. A. Smeitink, G. P. Smit, B. T. Poll-The, H. D. Bakker, M. C. Loonen, J. B. de Klerk, A. J. Reuser and A. T. van der Ploeg (2003). "The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature." Pediatrics **112**(2): 332–340.

van der Beek, N. A., M. L. Hagemans, A. T. van der Ploeg, P. A. van Doorn and I. S. Merkies (2013). "The Rasch-built Pompe-specific activity (R-PAct) scale." Neuromuscul Disord **23**(3): 256–264.

Van der Ploeg, A. T., R. Barohn, L. Carlson, J. Charrow, P. R. Clemens, R. J. Hopkin, P. S. Kishnani, P. Laforêt, C. Morgan and S. Nations (2012). "Open-label extension study following the late-onset treatment study (LOTS) of alglucosidase alfa." Molecular genetics and metabolism **107**(3): 456-461.

van der Ploeg, A. T., P. R. Clemens, D. Corzo, D. M. Escolar, J. Florence, G. J. Groeneveld, S. Herson, P. S. Kishnani, P. Laforet, S. L. Lake, D. J. Lange, R. T. Leshner, J. E. Mayhew, C. Morgan, K. Nozaki, D. J. Park, A. Pestronk, B. Rosenbloom, A. Skrinar, C. I. van Capelle, N. A. van der Beek, M. Wasserstein and S. A. Zivkovic (2010). "A randomized study of alglucosidase alfa in late-onset Pompe's disease." N Engl J Med **362**(15): 1396–1406.

van der Ploeg, A. T., M. E. Kruijshaar, A. Toscano, P. Laforêt, C. Angelini, R. H. Lachmann, S. I. Pascual Pascual, M. Roberts, K. Rösler, T. Stulnig, P. A. van Doorn, P. Y. K. Van den Bergh, J. Vissing and B. Schoser (2017). "European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience." Eur J Neurol **24**(6): 768–e731.

van Kooten, H. A., L. Harlaar, N. A. M. E. van der Beek, P. A. van Doorn, A. T. van der Ploeg, E. Brusse, W. L. van der Pol, E. Brusse, I. A. M. Ditters, L. Harlaar, M. J. Hoogendijk-Boon, H. H. Huidekoper, E. J. O. Kompanje, A. Oskam, W. W. M. Pijnappel, B. J. Sibbles, J. J. A. van den Dorpel, N. A. M. E. van der Beek, J. M. P. van der Hout, H. van der Kuy, A. T. van der Ploeg, P. A. van Doorn, H. A. van Kooten, A. G. Vulto and M. A. E. M. Wagenmakers (2020). "Discontinuation of enzyme replacement therapy in adults with Pompe disease: Evaluating the European POmpe Consortium stop criteria." Neuromuscular Disorders **30**(1): 59–66.

Vielhaber, S., A. Brejova, G. Debska-Vielhaber, J. Kaufmann, H. Feistner, M. A. Schoenfeld and F. Awiszus (2011). "24-months results in two adults with Pompe disease on enzyme replacement therapy." Clin Neurol Neurosurg **113**(5): 350–357.

Wang, Y. (2019). "Trial design and statistical considerations in rare disease clinical trials. Presented at the Developing Therapies for Primary Mitochondrial Diseases: bridging the gap workshop on 6 September 2019 in Maryland USA. Available from: https://www.fda.gov/media/131882/download (Accessed 11 June 2021)."

Welton (2020). "Welton NJ et al. NICE Decision Support Unit, 2020.".

Winkel, L. P., M. L. Hagemans, P. A. van Doorn, M. C. Loonen, W. J. Hop, A. J. Reuser and A. T. van der Ploeg (2005). "The natural course of non-classic Pompe's disease; a review of 225 published cases." J Neurol **252**(8): 875–884.

Wisselaar, H. A., M. A. Kroos, M. M. Hermans, J. van Beeumen and A. J. Reuser (1993). "Structural and functional changes of lysosomal acid alpha-glucosidase during intracellular transport and maturation." J Biol Chem **268**(3): 2223–2231.

Wyatt, K., W. Henley, L. Anderson, R. Anderson, V. Nikolaou, K. Stein, L. Klinger, D. Hughes, S. Waldek, R. Lachmann, A. Mehta, A. Vellodi and S. Logan (2012). "The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: a longitudinal cohort study of people with lysosomal storage disorders." Health Technol Assess **16**(39): 1–543.

Xu, S., Y. Lun, M. Frascella, A. Garcia, R. Soska, A. Nair, A. S. Ponery, A. Schilling, J. Feng, S. Tuske, M. C. D. Valle, J. A. Martina, E. Ralston, R. Gotschall, K. J. Valenzano, R. Puertollano, H. V. Do, N. Raben and R. Khanna (2019). "Improved efficacy of a next-generation ERT in murine Pompe disease." JCI Insight **4**(5).

York Health Economics Consortium (2020a). Targeted Reviews of the Clinical, Economic, Resource Use and Utility Evidence for Pompe Disease.

York Health Economics Consortium (2020b). "Targeted reviews of the clinical, economic, resource use and utility evidence for Pompe disease."

Yuan, M., E. R. Andrinopoulou, M. E. Kruijshaar, A. Lika, L. Harlaar, A. T. van der Ploeg, D. Rizopoulos and N. van der Beek (2020). "Positive association between physical outcomes and patient-reported outcomes in late-onset Pompe disease: a cross sectional study." Orphanet J Rare Dis **15**(1): 232.

Appendix A – Literature search for efficacy and safety of intervention and comparators

A systematic literature was conducted to identify and synthesise published evidence on the clinical efficacy and safety of cipaglucosidase alfa/miglustat and its relevant comparators in treatment of adults with LOPD. The SLR is relevant for the comparison of cipaglucosidase alfa/miglustat and BSC. The comparison of cipaglucosidase alfa/miglustat with alglucosidase alfa is available through in-trial, direct comparison in PROPEL. As such, no ITC nor SLR are required. While the SLR did capture other LOPD treatments outside of BSC, these are not relevant comparators for this health technology assessment and have not been considered; the full SLR strategy is presented for reference, with only the relevant studies outlined.

13.1. Search strategy

The scope of the SLR was determined based on the PICO(+) (Population, Intervention, Comparator, Outcome) framework, as presented in (Table 43), which was the basis for developing the search strategy as well as the eligibility criteria for selecting the relevant studies.

The search was conducted in the medical bibliographic databases: Embase, Medline, and Cochrane Library via Ovid Platform. The search in the medical bibliographic databases was supplemented by a search for grey literature (trial registry, conferences, etc), as presented in Table 44.

The search strategy was adapted to the requirements of each database and other sources queried. Searches were restricted with regard to timeframe: limiting the search results to September 2022 for medical bibliographic databases and last 3 years for conference abstracts.

Table 43: PICO(+) framework for scope of SLR

Category	Inclusion	Exclusion
Population	▪ Late-onset Pompe disease – adult patients (≥ 18 years)	▪ Studies that do not include patients of interest in the SLR ▪ Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, or with only a minority of patients being of interest
Intervention	▪ Cipaglucosidase alfa/miglustat	▪ No Cipaglucosidase alfa/miglustat
Comparator	▪ Myozyme® (alglucosidase alfa; Lumizyme® in the US) ▪ Nexviazyme® (avalglucosidase alfa-ngpt) ▪ Nexviadyme® (Avalglucosidase alfa) ▪ Placebo/BSC	▪ No comparators of interest
Outcomes	▪ 6-Minute Walk Test/Distance ▪ Pulmonary Function – Forced vital capacity ▪ Motor outcome function measures, e.g.: ▪ Timed Up and Go ▪ Manual Muscle Testing ▪ Gait, Stairs, Gower, Chair scores, ▪ Walton and Gardner-Medwin Scale score ▪ others, if necessary	▪ No reported outcomes of interest ▪ Outcomes reported only in studies with a mixed population ▪ Outcomes reporting only actual dose with no possibility of calculating cumulative dose
Study Type	▪ Randomised controlled trials, non-randomised clinical trials	▪ Observational studies ▪ Economic analyses

	▪ Single arm studies, open-label studies, phase I/II studies ▪ Systematic literature reviews, meta-analyses*	▪ Narrative literature reviews, expert opinions, letters to the editor, editorials, or consensus reports ▪ Case reports and case series ▪ In vitro, animal, or foetal studies
Publication type	▪ Peer-reviewed article, conference abstract, conference paper, article in press, report	▪ Short survey, editorial, review
Language	▪ Article or abstract available in English	▪ Non-English language articles (no abstract available in English) will be excluded
Search timeframe	▪ No limit in publication years reported ▪ Conference abstract – the last 3 years (2020-2022)	not applicable
Bibliographic Databases	▪ Medline® ALL (via Ovid) ▪ Embase (via Ovid) ▪ Cochrane Library included Cochrane Central Register of Controlled Trials (CENTRAL) & Cochrane Database of Systematic Reviews (CDSR) (via Ovid) ▪ PROSPERO ▪ ISRCTN.com ▪ Database of abstracts of review of effects (DARE)	not applicable

Other Sources	▪ Clinical trial registries:
	  ▪ ClinicalTrials.gov
	  ▪ WHO International Clinical Trials Registry Platform (ICTRP)
	  ▪ EU Clinical Trials Register
	▪ Conferences:
	  ▪ WORLD Symposium (We're Organizing Research on Lysosomal Diseases)
	  ▪ World Muscle Society
	  ▪ Muscular Dystrophy Association
	  ▪ European Study Group on Lysosomal Diseases
	  ▪ SSIEM (Society for the study of inborn errors of metabolism)
	  ▪ International Congress on Neuromuscular Diseases
	  ▪ American College of Medical Geneticists
	  ▪ European Academy of Neurology
	  ▪ American Academy of Neurology
	▪ Grey Literature:
	  ▪ Google Scholar
	  ▪ Center for Drug Evaluation and Research
		not applicable

*Systematic literature reviews were included only for reference checking

Table 44: Data sources and date of searches

Database/ Date of search	Sources

BIBLIOGRAPHIC DATABASES SEARCH	
Bibliographic Databases Date of search: September 15, 2022	▪ **MEDLINE®** ▪ **Embase** ▪ **Cochrane library** ▪ Cochrane Central Register of Controlled Trials ▪ Cochrane Database of Systematic Reviews
Bibliographic Databases Date of search: September 14, 2022	▪ PROSPERO ▪ ISRCTN.com ▪ Database of Abstracts of Reviews of Effect (DARE)
GREY LITERATURE	
Clinical trial registries	
Clinical Trials Registers Date of search: September 13, 2022	▪ clinicaltrials.gov
WHO ICTRP Date of search: September 13, 2022	▪ trialsearch.who.int
EU Clinical Trials Register Date of search: September 13, 2022	▪ clinicaltrialsregister.eu
Conferences	
WORLDSymposium™ - 2022 POSTER, SESSION ABSTRACTS Date of search: September 08, 2022	▪ https://worldsymposia.org/wp-content/uploads/worldsymposium2021-poster-list.pdf
WORLDSymposium™ ePOSTER SESSION ABSTRACTS Date of search: September 08, 2022	▪ https://worldsymposia.org/wp-content/uploads/worldsymposium2021-poster-list.pdf
WORLDSymposium™ 2020 POSTER SESSION ABSTRACTS Date of search: September 08, 2022	▪ https://worldsymposia.org/wp-content/uploads/worldsymposium2020-poster-list.pdf
Word Muscle Society (WMS), 11-15 October 2022 Date of search: September 08, 2022	▪ https://www.wms2022.com/file/0d0212c3-a7a9-4bfd-a8d8-61071fe7ed83/WMS2022%20Summary%20Programme%20(10).pdf
Word Muscle Society (WMS), 2021, Virtual Congress, 20-24 September Date of search: September 08, 2022	▪ https://www.wms2021.com/file/38a7d9c9-38f5-4777-8a78-e0473e4dca03/WMS2021%20Full%20Programme%20FINAL%204.pdf
Word Muscle Society, 25: 30th September-2nd October 2000 Date of search: September 08, 2022	▪ https://archive.worldmusclesociety.org/www.wms2020.com/wp-content/uploads/2020/WMS%202020%20Preliminary%20Full%20Programme%20Final%20V16.pdf
Muscular Dystrophy Association Date of search: September 08, 2022	▪ https://www.mdaconference.org/abstracts/2022-abstract-library/
Muscular Dystrophy Association Date of search: September 08, 2022	▪ https://www.mdaconference.org/abstracts/2021-abstract-library/
Muscular Dystrophy Association – Virtual Conference Hub Date of search: September 08, 2022	▪ https://www.mda.org/conferences/virtual-conference-hub/agenda
European Study Group on Lysosomal Diseases Date of search: September 08, 2022	▪ https://esgld.org/wp-content/uploads/2022/09/24th-ESGLD-Workshop-and-Graduate-Course.pdf
European Study Group on Lysosomal Diseases – Virtual Summer Meeting 28th to 30th June 2021 Date of search: September 08, 2022	▪ https://esgld.org/esgld-2021/
European Study Group on Lysosomal Diseases Date of search: September 08, 2022	▪ not identified
Society for the study of inborn errors of metabolism Date of search: September 14, 2022	▪ https://ssiem2022.org/programme/

Society for the study of inborn errors of metabolism, 2021 Online Virtual Symposium Date of search: September 14, 2022	▪ https://ssiemvirtual.org/wp-content/uploads/2021/09/SSIEM-virtual-Programme.pdf
Society for the study of inborn errors of metabolism, 2020 Virtual Symposium Date of search: September 14, 2022	▪ https://www.spdm.org.pt/media/2623/ssiem-virtual-day-2020.pdf
International Congress on Neuromuscular Diseases Date of search: September 14, 2022	▪ https://icnmd.org/wp-content/uploads/2022/07/ICNMD2022_programbook_A5_digital.pdf
International Congress on Neuromuscular Diseases Date of search: September 14, 2022	▪ https://content.iospress.com/download/journal-of-neuromuscular-diseases/jnd219006?id=journal-of-neuromuscular-diseases%2Fjnd219006
International Congress on Neuromuscular Diseases Date of search: September 14, 2022	▪ https://content.iospress.com/articles/journal-of-neuromuscular-diseases/jnd209002
American college of medical geneticists* Date of search: September 14, 2022	▪ https://www.acmgeducation.net/Public/Catalog/Main.aspx?Criteria=3&Option=238
European Academy of Neurology, 8th Congress Date of search: September 14, 2022	▪ https://www.ean.org/congress2022/abstracts/important-information/ean-2022-book-of-abstracts
European Academy of Neurology, 7th Congress Date of search: September 14, 2022	▪ https://www.ean.org/fileadmin/user_upload/ean/congress-2021/EAN2021AbstractBook.pdf
European Academy of Neurology, 6th Congress Date of search: September 14, 2022	▪ https://www.ean.org/fileadmin/user_upload/ean/congress-2020/Present/Abstracts/00_EAN_Journal_2020_Book.pdf
American Academy of Neurology Date of search: September 14, 2022	▪ https://issuu.com/americanacademyofneurology/docs/aan_2022_abstracts_book_final_web ▪ https://issuu.com/americanacademyofneurology/docs/aan_2021_science_web ▪ https://issuu.com/americanacademyofneurology/docs/aan_science2020_book
Further Grey Literature	
Center for Drug Evaluation and Research Date of search: September 07, 2022	▪ https://www.fda.gov/about-fda/fda-organization/center-drug-evaluation-and-research-cder
Google Scholar Date of search: September 07, 2022	▪ https://scholar.google.com/

*The American College of Medical Geneticists (ACMG) sponsors an Annual Clinical Genetics Meeting and other events offering educational content in clinical genetics with the purpose of serving its members, other healthcare professionals and the public

Bibliographic searches

The Search strategy for hits for the bibliographical searches are presented in Table 45 to Table 51.

Table 45: Medline (incl. Medline in Process, Pubmed Not Medline, In Data Review, Publisher)

Database	Ovid MEDLINE(R) ALL 1946 to 2022 September 13	
#	Search Terms	Hits
1	Glycogen Storage Disease Type II/	1881
2	(Pompe disease or Pompe's disease or late-onset Pompe disease or LOPD or late-onset PD).af	2266
3	(glycogen-storage disease type II or glycogen storage disease type II or glycogen storage disease type 2 or glycogen storage disease II or glycogen storage disease 2 or glycogen storage disorder* or type II glycogenosis or type 2 glycogenosis or glycogenosis type II or glycogenosis type 2 or acid maltase deficienc* or acid alpha-glucosidase deficienc* or alpha glucosidase deficienc* or deficienc* of acid maltase or deficienc* of alpha-glucosidase or deficienc* of acid alpha-glucosidase or alpha-1,4-glucosidase deficienc* or alpha 1,4 glucosidase deficienc* or deficient activity of acid alpha-glucosidase or deficient activity of acid maltase or GAA deficienc* or deficienc* of GAA).af	2387

4	(GSDII or GSD II or GSD2 or GSD 2).af	226
5	(McKusick 23230 or McKusick 23230).af	1
6	(iopd or iopds or lopd or lopds or io-pd or io-pds or lo-pd or lo-pds).ti,ab,kf.	377
7	1 or 2 or 3 or 4 or 5 or 6	3197
8	Randomized Controlled Trials as Topic/ or Randomized Controlled Trial/ or Random Allocation/ or randomized controlled trial.pt. or (allocat$ adj2 random$).ti,ab,kf. Or (randomi?ed adj2 trial$).ti,ab,kf. Or RCT.ti,ab,kf. Or Double-Blind Method/ or Single-Blind Method/ or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kf. Or Placebos/ or placebo$.ti,ab,kf. Or exp Clinical Trials as topic/ or Clinical Trial/ or Clinical Trial, Phase I/ or Clinical Trial, Phase II/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Controlled Clinical Trial/ or Adaptive Clinical Trial/ or clinical trial.pt. or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv).pt. or (controlled clinical trial or multicenter study).pt. or (clinical adj trial$).ti,ab,kf.	1961993
9	((best adj2 support$) or (support$ adj3 care$) or (support$ adj3 caring) or (supportive adj3 treatment$)).mp.	69807
10	bsc.ti,ab.	2839
11	(single arm adj3 (trial$ or stud$)).ti,ab,kf. Or (open label adj (trial$ or stud$)).ti,ab,kf. Or (non blinded adj (trial$ or stud$)).ti,ab,kf.	20849
12	8 or 9 or 10 or 11	2029238
13	7 and 12	220
14	limit 7 to ”systematic review”	18
15	limit 7 to “meta analysis”	11
16	14 or 15	25
17	13 or 16	242
18	limit 17 to dt=19460101-20220531	239

Table 46: Embase

Database	Embase 1974 to 2022 September 14	
#	Search Terms	Hits
1	Glycogen Storage Disease Type II/	2977
2	(Pompe disease or Pompe’s disease or late-onset Pompe disease or LOPD or late-onset PD).af	4089
3	(glycogen-storage disease type II or glycogen storage disease type II or glycogen storage disease type 2 or glycogen storage disease II or glycogen storage disease 2 or glycogen storage disorder* or type II glycogenosis or type 2 glycogenosis or glycogenosis type II or glycogenosis type 2 or acid maltase deficienc* or acid alpha-glucosidase deficienc* or alpha glucosidase deficienc* or deficienc* of acid maltase or deficienc* of alpha-glucosidase or deficienc* of acid alpha-glucosidase or alpha-1,4-glucosidase deficienc* or alpha 1,4 glucosidase deficienc* or deficient activity of acid alpha-glucosidase or deficient activity of acid maltase or GAA deficienc* or deficienc* of GAA).af	5276
4	(GSDII or GSD II or GSD2 or GSD 2).af	339
5	(McKusick 23230 or McKusick 23230).af	1
6	(iopd or iopds or lopd or lopds or io-pd or io-pds or lo-pd or lo-pds).ti,ab,kf.	768
7	1 or 2 or 3 or 4 or 5 or 6	5974
8	Randomized Controlled Trials as Topic/ or Randomized Controlled Trial/ or Random Allocation/ or randomized controlled trial.pt. or (allocat$ adj2 random$).ti,ab,kf. Or (randomi?ed adj2 trial$).ti,ab,kf. Or RCT.ti,ab,kf. Or Double-Blind Method/ or Single-Blind Method/ or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kf. Or Placebos/ or placebo$.ti,ab,kf. Or exp Clinical Trials as topic/ or Clinical Trial/ or Clinical Trial, Phase I/ or Clinical Trial, Phase II/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Controlled Clinical Trial/ or Adaptive Clinical Trial/ or clinical trial.pt. or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv).pt. or (controlled clinical trial or multicenter study).pt. or (clinical adj trial$).ti,ab,kf.	2559322
9	((best adj2 support$) or (support$ adj3 care$) or (support$ adj3 caring) or (supportive adj3 treatment$)).mp.	98849

10	bsc.ti,ab.	5129
11	(single arm adj3 (trial$ or stud$)).ti,ab,kf. Or (open label adj (trial$ or stud$)).ti,ab,kf. Or (non blinded adj (trial$ or stud$)).ti,ab,kf.	39321
12	8 or 9 or 10 or 11	2661129
13	7 and 12	592
14	limit 7 to ”systematic review”	71
15	limit 7 to “meta analysis”	16
16	14 or 15	79
17	13 or 16	620
18	limit 17 to dd=19740101-20220531	386
19	limit 17 to rd=19740101-20220531	251
20	18 or 19	637

Table 47: Cochrane Central Register of Controlled Trials

Database	EBM Reviews – Cochrane Central Register of Controlled Trials, August 2022	
#	Search Terms	Hits
1	Glycogen Storage Disease Type II.af	41
2	(Pompe disease or Pompe’s disease or late-onset Pompe disease or LOPD or late-onset PD).af	126
3	(glycogen-storage disease type II or glycogen storage disease type II or glycogen storage disease type 2 or glycogen storage disease II or glycogen storage disease 2 or glycogen storage disorder* or type II glycogenosis or type 2 glycogenosis or glycogenosis type II or glycogenosis type 2 or acid maltase deficienc* or acid alpha-glucosidase deficienc* or alpha glucosidase deficienc* or deficienc* of acid maltase or deficienc* of alpha-glucosidase or deficienc* of acid alpha-glucosidase or alpha-1,4-glucosidase deficienc* or alpha 1,4 glucosidase deficienc* or deficient activity of acid alpha-glucosidase or deficient activity of acid maltase or GAA deficienc* or deficienc* of GAA).af	111
4	(GSDII or GSD II or GSD2 or GSD 2).af	8
5	(McKusick 23230 or McKusick 23230).af	0
6	(iopd or iopds or lopd or lopds or io-pd or io-pds or lo-pd or lo-pds).ti,ab,kw.	47
7	1 or 2 or 3 or 4 or 5 or 6	139
8	Randomized Controlled Trials as Topic/ or Randomized Controlled Trial/ or Random Allocation/ or randomized controlled trial.pt. or (allocat$ adj2 random$).ti,ab,kf. Or (randomi?ed adj2 trial$).ti,ab,kf. Or RCT.ti,ab,kf. Or Double-Blind Method/ or Single-Blind Method/ or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kf. Or Placebos/ or placebo$.ti,ab,kf. Or exp Clinical Trials as topic/ or Clinical Trial/ or Clinical Trial, Phase I/ or Clinical Trial, Phase II/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Controlled Clinical Trial/ or clinical trial.pt. or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv).pt. or (controlled clinical trial or multicenter study).pt. or (clinical adj trial$).ti,ab,kf.	1180176
9	((best adj2 support$) or (support$ adj3 care) or (support$ adj3 caring) or (supportive adj3 treatment$)).mp.	8902
10	BSC.tw.	907
11	(single arm adj3 (trial$ or stud$)).ti,ab,kf. Or (open label adj (trial$ or stud$)).ti,ab,kf. Or (non blinded adj (trial$ or stud$)).ti,ab,kf.	14612
12	8 or 9 or 10 or 11	1189355
13	7 and 12	78
14	limit 13 to last 32 years	77

Table 48: Cochrane Database of Systematic Reviews

Database	EBM Reviews – Cochrane Database of Systematic Reviews <2005 to September 14, 2022>	
#	Search Terms	Hits

1	Glycogen Storage Disease Type II.af	2
2	(Pompe disease or Pompe's disease or late-onset Pompe disease or LOPD or late-onset PD).af	8
3	(glycogen-storage disease type II or glycogen storage disease type II or glycogen storage disease type 2 or glycogen storage disease II or glycogen storage disease 2 or glycogen storage disorder* or type II glycogenosis or type 2 glycogenosis or glycogenosis type II or glycogenosis type 2 or acid maltase deficienc* or acid alpha-glucosidase deficienc* or alpha glucosidase deficienc* or deficienc* of acid maltase or deficienc* of alpha-glucosidase or deficienc* of acid alpha-glucosidase or alpha-1,4-glucosidase deficienc* or alpha 1,4 glucosidase deficienc* or deficient activity of acid alpha-glucosidase or deficient activity of acid maltase or GAA deficienc* or deficienc* of GAA).af	4
4	(GSDII or GSD II or GSD2 or GSD 2).af	0
5	(McKusick 23230 or McKusick 23230).af	0
6	(iopd or iopds or lopd or lopds or io-pd or io-pds or lo-pd or lo-pds).ti,ab,kw.	1
7	1 or 2 or 3 or 4 or 5 or 6	9
8	limit 7 to last 18 years	7

Table 49: Search in PROSPERO

Study Registry	PROSPERO
Source URL	https://www.crd.york.ac.uk/prospero/
Date of Search	September 14, 2022
Search Strategy	Pompe disease
No. Of Studies (with and without results)	10 records (ongoing and completed published/not published)
No. Of Studies (only studies with results)	3 records (presenting results): • Reena Sharma, Derralynn Hughes, Uma Ramaswami, Duncan Cole, Mark Roberts, Christian Hendriksz, Karolina Stepien, Ashma Krishan, Nikki Jahnke. Enzyme replacement therapy for late-onset Pompe disease [Cochrane protocol]. PROSPERO 2018 CRD42018096326 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018096326 • Alícia Dornelles, Ida Vanessa Doederlein Schwartz, Guilherme I. P. S. Gertsenchtein, Ana Paula Pedroso Junges, Haliton Oliveira Junior, Barbara Krug, Candice Gonçalves. Efficacy and safety of enzyme replacement therapy with alpha-alglucosidase for the treatment of patients with adult Pompe disease. PROSPERO 2019 CRD42019135102 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019135102 • Sarah Berli, Giovanna Brandi. Long-term effects in main functional assessment outcomes in patients with late-onset Pompe disease undergoing enzyme replacement therapy. PROSPERO 2020 CRD42020182462 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020182462

Table 50: Search in ISRCTN.com

Study Registry	ISRCTN.com
Source URL	https://www.isrctn.com/
Date of Search	September 14, 2022
Search Strategy	Pompe disease
No. Of Studies (with and without results)	3 results (with or without results)
No. Of Studies (only studies with results)	2 studies (presenting results): • ISRCTN53453484 : Effects of exercise on Pompe disease • ISRCTN72578000 : Protocolised follow-up of Pompe patients receiving enzyme replacement therapy on a compassionate use basis

Table 51: Search in DARE – Database of abstracts of review of effects

Study Registry	DARE
Source URL	https://www.crd.york.ac.uk/CRDWeb/
Date of Search	September 14, 2022
Search Strategy in Field "Any field"	Pompe disease
No. Of Studies (with and without results)	2 results (with or without results)
No. Of Studies (only studies with results)	1 result (presenting results): • Toscano A, Schoser B. Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review. Journal of Neurology 2013; 260(4): 951-959

Grey literature searches

The Search strategy for hits for the grey literature searches are presented in Table 52 to Table 54.

Table 52: Search in Clinical Trials.gov

Study Registry	ClinicalTrials.gov
Source URL	http://www.clinicaltrials.gov
Date of Search	September 13, 2022
Search Strategy in Field "Other Terms"	glycogen storage disease type II OR glycogen storage disease type II late onset OR glycogen storage disorder type II OR GSD II OR Pompe Disease OR Pompe Disease (late-onset) OR acid maltase deficiency OR acid alpha-glucosidase deficiency
No. Of Studies (with and without results)	145 studies (with or without results)
No. Of Studies (only studies with results)	22 studies (presenting results)

Table 53: Search on WHO International Clinical Trials Registry Platform (WHO ICTRP)

Study Registry	WHO International Clinical Trials Registry Platform (ICTRP)
URL	https://trialsearch.who.int/
Date of Search	September 13, 2022
Final Search Strategy	glycogen storage disease type II OR glycogen storage disease type II late onset OR glycogen storage disorder type II OR GSD II OR Pompe Disease OR Pompe Disease (late-onset) OR acid maltase deficiency OR acid alpha-glucosidase deficiency
No. Of Studies (with and without results)	247 records/166 trials
No. Of Studies (only studies with results)	36 records (presenting results)/23 trials

Table 54: Search in EU Clinical Trials Register

Study Registry	EU Clinical Trials Register
Source URL	https://www.clinicaltrialsregister.eu/
Date of Search	September 13, 2022

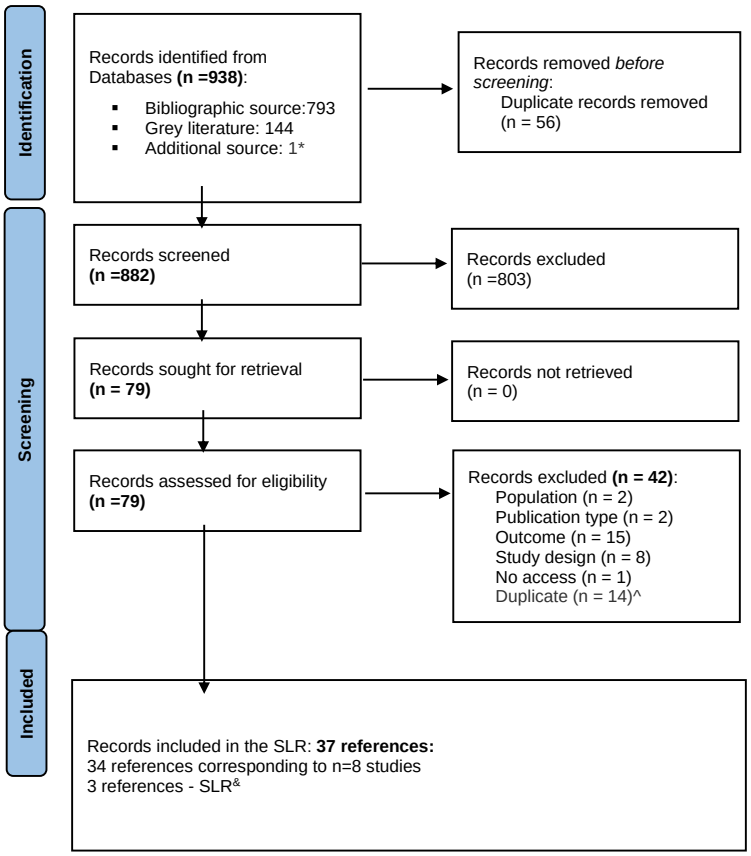
Search Strategy in Field "Other Terms"	"glycogen storage disease type II" OR "glycogen storage disease type II late onset" OR "glycogen storage disorder type II" OR "GSD II" OR "Pompe Disease" OR "Pompe Disease late-onset" OR "acid maltase deficiency" OR "acid alpha-glucosidase deficiency"
Select Date Range:	to 2022-05-31
No. Of Studies (with and without results)	36 studies (with or without results)
No. Of Studies (only studies with results)	24 studies (presenting results)

13.2. Systematic selection of studies

Bibliographic medical database searches yielded 938 records; an additional 144 records were retrieved from searches of the grey literature. After the exclusion of duplicates, 882 abstracts were screened by title/abstract for potential eligibility. After the abstract screening 803 papers were excluded, leaving 78 full-texts articles for further selection and one supplementary document which was provided by the Company. Therefore, a total of 79 full-text articles were obtained and scrutinised against the selection criteria. Finally, 34 references corresponding to 8 studies met the inclusion criteria.

Literature screening results are presented in the PRISMA flowchart below (Figure 28).

Figure 28: PRISMA 2020 flow diagram for cipaglucosidase alfa/miglustat SLR



^ Identified based on grey literature search in comparison to bibliographic search

* Data provided by the Company – Dimachkie MM, Barohn RJ, Byrne B, et al. Long-term Safety and Efficacy of Avalglucosidase Alfa in Patients with Late-Onset Pompe Disease [published online ahead of print, 2022 May 26]. Neurology. 2022;99(5):e536-e548

& Included for references verification only

As the SLR contained treatments that are not required for the ITC of cipaglucosidase alfa/miglustat against BSC in patients with LOPD, not all studies that the SLR captured are considering during this health technology assessment. Of the 8 studies captured by the SLR, 3 clinical trials were used for the ITC: PROPEL (cipaglucosidase alfa/miglustat versus alglucosidase alfa), and LOTS and LOTS OLE (alglucosidase alfa versus placebo). As no clinical study was found to include BSC, the placebo arm from LOTS was used as a proxy for BSC. Relevant for the comparison of cipaglucosidase alfa/miglustat to BSC, the LOTS OLE trial was needed to match the alglucosidase alfa to the placebo arm of LOTS. Table 55 presents the studies that were included.

Table 55: Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Intervention and comparator, n	Relevant Outcome and follow-up period
PROPEL NCT03729362	Study the efficacy and safety of intravenous cipaglucosidase alfa/ miglustat in adult subjects with LOPD compared with alglucosidase alfa/ placebo	Phase III, randomised, double-blind, multicentre, active-controlled trial	Adult patients with LOPD ERT experienced and naïve patients	Cipaglucosidase alfa/ miglustat and alglucosidase alfa N=123	6MWD FVC Follow-up: 52 weeks
LOTS NCT00158600	Evaluate the safety, efficacy, and pharmacokinetics of alglucosidase alfa treatment in patients with late-onset Pompe disease	Phase III, randomised, masked, multicentre, active-controlled trial	LOPD patients (8 years or older) Naïve patients	Alglucosidase alfa and placebo N=90	6MWD FVC Follow-up: 104 weeks
LOTS OLE NCT00455195	Extension study to assess the long-term safety and efficacy of alglucosidase alfa treatment in patients with Late-Onset Pompe Disease who were previously treated under the placebo-controlled, double-blind study LOTS (NCT00158600)	Open-label extension study	LOPD patients (8 years or older) Naïve and ERT-experienced patients	Alglucosidase alfa and placebo N=81	6MWD FVC Follow-up: 104 weeks for experienced 26 weeks for naïve

Abbreviations: 6MWD, 6-minute walk distance; ERT, enzyme replacement therapy; FVC, forced vital capacity; LOPD, late onset Pompe disease

13.3. Quality assessment

The critical appraisal of all included RCTs was done using RoB2 tool *("RoB2 a revised tool for assessing risk of bias in randomized trials")*(Sterne 2019). The quality of each interventional non-RCT studies was performed using ROBINS-I *("Risk Of Bias In Non-randomized Studies – of Interventions")* tool (Sterne 2016).

Critical appraisal was limited to full-text publications (conference abstracts/posters and reviews were assessed). When multiple publications/abstracts for one study were available the main publication was primarily used unless linked publications could provide missing data.

13.4. Unpublished data

The unpublished data used in this submission are all sourced from the PROPEL study clinical trials.

Appendix B – Main characteristics of included studies

14.1. PROPEL – phase 3 randomised, double-blind, active-controlled trial

PROPEL is a pivotal phase 3, randomised, double-blind, active-controlled trial (NCT03729362) designed to assess the efficacy and safety of cipaglucosidase alfa/miglustat in adult patients with LOPD compared with alglucosidase alfa/placebo. Eligible patients were those aged 18 years and older, weighing more than 40 kg, and either ERT-experienced, defined as currently receiving ERT (alglucosidase alfa) for at least 24 months, or ERT-naïve, defined as never having received ERT. PROPEL provided the clinical evidence base for the ongoing regulatory approval of cipaglucosidase alfa/miglustat in Pompe disease, and is anticipated to support subsequent country-specific reimbursement; thus, PROPEL forms the basis of this dossier. An overview of the study design and efficacy outcomes are further presented below.

Table 56: PROPEL trial overview

Trial name: A study comparing cipaglucosidase alfa/miglustat with alglucosidase/placebo in adult subjects with LOPD	**NCT number: NCT03729362**
Objective	To assess the efficacy and safety of cipaglucosidase alfa/miglustat in adult patients with LOPD compared with alglucosidase alfa/placebo
Publications – title, author, journal, year	Schoser B, Roberts M, Byrne BJ, Sitaraman S, Jiang H, Laforêt P, Toscano A, Castelli J, Díaz-Manera J, Goldman M, van der Ploeg AT, Bratkovic D, Kuchipudi S, Mozaffar T, Kishnani PS; PROPEL Study Group. Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial. Lancet Neurol. 2021 Dec;20(12):1027-1037. Doi: 10.1016/S1474-4422(21)00331-8.
Study type and design	Phase 3, randomised, double-blind, multicentre, active-controlled trial
Sample size (n)	123 patients were randomised 2:1 to cipaglucosidase alfa/miglustat or placebo plus alglucosidase alfa. Of these patients: • 85 received cipaglucosidase alfa/miglustat: 65 in the cipaglucosidase alfa/miglustat arm were ERT-experienced, defined as currently receiving ERT (alglucosidase alfa) for at least 24 months, and 20 were ERT-naïve • 38 received alglucosidase alfa/placebo: 30 in the active control arm were ERT-experienced, and 8 were ERT-naïve
Main inclusion and exclusion criteria	Inclusion Criteria: 1. Subject must provide signed informed consent prior to any study-related procedures being performed. 2. Male and female subjects are ≥ 18 years old and weigh ≥ 40 kg at screening. 3. Female subjects of childbearing potential and male subjects must agree to use medically accepted methods of contraception during the study and for 90 days after the last dose of study drug.

4. Subject must have a diagnosis of LOPD based on documentation of one of the following:
    a. deficiency of GAA enzyme
    b. GAA genotyping
5. Subject is classified as one of the following with respect to ERT status:
    a. ERT-experienced, defined as currently receiving standard of care ERT (alglucosidase alfa) at the recommended dose and regimen (ie, 20 mg/kg dose every 2 weeks) for ≥ 24 months
    b. ERT-naïve, defined as never having received investigational or commercially available ERT
6. Subject has a sitting FVC ≥ 30% of the predicted value for healthy adults (National Health and Nutrition Examination Survey III) at screening.
7. Subject performs two 6MWTs at screening that are valid, as determined by the clinical evaluator, and that meet all of the following criteria:
    a. both screening values of 6MWD are ≥ 75 meters
    b. both screening values of 6MWD are ≤ 90% of the predicted value for healthy adults
    c. the lower value of 6MWD is within 20% of the higher value of 6MWD

Exclusion Criteria

1. Subject has received any investigational therapy or pharmacological treatment for Pompe disease, other than alglucosidase alfa, within 30 days or 5 half-lives of the therapy or treatment, whichever is longer, before Day 1 or is anticipated to do so during the study.
2. Subject has received gene therapy for Pompe disease
3. Subject is taking any of the following prohibited medications within 30 days before Day 1:
    - miglitol (eg, Glyset)
    - miglustat (eg, Zavesca)
    - acarbose (eg, Precose or Glucobay)
    - voglibose (eg, Volix, Vocarb, or Volibo)

    Note: None of these medications have a half-life that, when multiplied by 5, is longer than 30 days.
4. Subject requires the use of invasive or noninvasive ventilation support for > 6 hours per day while awake.
5. Subject has a hypersensitivity to any of the excipients in ATB200, alglucosidase alfa, or AT2221.
6. Subject has a medical condition or any other extenuating circumstance that may, in the opinion of the investigator or medical monitor, pose an undue safety risk to the subject or may compromise his/her ability to comply with or adversely impact protocol requirements. This includes clinical depression (as diagnosed by a psychiatrist or other mental health professional) with uncontrolled or poorly controlled symptoms.
7. Subject, if female, is pregnant or breastfeeding at screening.
8. Subject, whether male or female, is planning to conceive a child during the study.
9. Subject does not have documentation of diagnosis of Pompe disease and refuses to undergo genetic testing.

Intervention	• IV cipaglucosidase alfa 20 mg/kg Q2W • Oral miglustat 260 mg or 195 mg for patients who weighed at least 50 kg or between 40 and 50 kg, respectively, 1 hour prior to cipaglucosidase
Comparator(s)	• IV alglucosidase alfa 20 mg/kg Q2W • Oral placebo 1 hour prior to alglucosidase alfa
Follow-up time	52 weeks
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary Outcome Measures : 1. 6-Minute Walk Test [Time Frame: 12 months] Change in 6MWD from baseline to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo **Other endpoints:** Secondary Outcome Measures : 1. Pulmonary Function – Forced vital capacity (FVC) [Time Frame: 12 months] Change from baseline in FVC (sitting and supine) to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo 2. Manual Muscle Strength [Time Frame: 12 months] Change in manual muscle strength from baseline to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo 3. Quantitative Muscle Strength [Time Frame: 12 months] Change in Quantitative muscle strength from baseline to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo 4. PROMIS instruments questionnaires [Time Frame: 12 months] Change from baseline in scores of PROMIS instruments for physical function, fatigue, dyspnea, and upper extremity questionnaire to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo. The PROMIS instruments for physical function (20 items), d upper extremity (7 items) measure signs and symptoms using general questions without a temporal reference. The PROMIS instruments for fatigue (8 items) and dyspnea severity (10 items) measure signs and symptoms over the past 7 days. A 5-point scale is used for each instrument (though responses may vary within or among instruments), and a total score is generated for each instrument.

5. Motor Function – Gait, Stairs, Gower, Chair (GSGC) test [Time Frame: 12 months]

   Change from baseline in GSGC score to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo. The GSGC consists of a 10-meter walk for evaluation of gait, a 4-stair climb, Gower's maneuver, and arising from a chair. Results of the GSGC include the time required to complete the individual tests, individual scores for each of the tests (1 to 7 points for each of gait, 4-stair climb, and Gower's maneuver and 1 to 6 points for arising from a chair), and a total score. The total score ranges from a minimum of 4 points (normal performance) to a maximum of 27 points (worst score).

6. Motor Function – Timed Up and Go (TUG) [Time Frame: 12 months]

   Change from baseline in TUG to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo. The TUG test measures the time it takes for the subject to rise from a chair, walk 3 meters, turn around, walk back to the chair, and sit down will be recorded.

7. The Rasch-built Pompe-specific activity (R-Pact) questionnaires [Time Frame: 12 months]

   Change from baseline in scores of R-Pact scale questionnaire to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo. The R-Pact scale is an 18-item questionnaire to measure limitations in activities and restriction in social participation. Possible responses to questions are as follows: unable to perform, able to perform, but with difficulty, and able to perform without difficulty. A raw score ranging from 0 to 36 points is generated. The low score indicates the highest level of disability.

8. EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) questionnaires [Time Frame: 12 months]

   Change from baseline in scores of EQ-5D-5L questionnaire to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo. The EQ-5D-5L comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. Subjects are asked to indicate their health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. The subject's self rated health is also recorded on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'.

9. Subject's Global Impression of Change questionnaires [Time Frame: 12 months]

   Change from baseline in scores of Subject's Global Impression of Change (SGIC) questionnaire to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo. The Subject's Global Impression of Change is designed to record the subjects' impression of their functional status since starting study drug using a 7-point scale ranging from "very much worse" to "very much improved".

10. Physician Overall Clinical Impression [Time Frame: 12 months]

Change in the Physician's Global Impression of Change (PGIC) evaluation to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo

11. Pulmonary Function – Slow Vital Capacity (SVC) [Time Frame: 12 months]

    Change from baseline in SVC (sitting and supine) to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo

12. Pulmonary Function – Maximum Inspiratory Pressure (MIP) [Time Frame: 12 months]

    Change from baseline in MIP to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo

13. Pulmonary Function – Maximum Expiratory Pressure [Time Frame: 12 months]

    Change from baseline in MEP to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo

14. Pulmonary Function – Sniff Nasal Inspiratory Pressure (SNIP) [Time Frame: 12 months]

    Change from baseline in SNIP to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo

15. Number of participants with TEAEs and SARs [Time Frame: 12 months]

    Evaluation of Treatment Emergent Adverse Events (TEAEs) begins after written informed consent is provided, including study related events that occur as a direct result of a study procedure to assess the safety, tolerability of cipaglucosidase alfa/miglustat co administration compared with alglucosidase alfa/placebo

16. Immunogenicity [Time Frame: 12 months]

    Measurement of anti-rhGAA Abs (total, cross-reactive, and neutralizing) to assess the Immunogenicity of cipaglucosidase alfa/miglustat co administration compared with alglucosidase alfa/placebo

17. Biomarkers/Pharmacodynamics of muscle injury and disease substrate [Time Frame: 12 months]

    Change from baseline in Creatine Kinase and Urinary Hexose Tetrasaccharide

18. popPK: Cmax [Time Frame: 12 months]

    Maximum observed plasma concentration

19. popPK: Tmax [Time Frame: 12 months]

    time to reach Tmax

20. popPK: AUC0-inf [Time Frame: 12 months]

Area under the curve from time 0 extrapolated to infinite time

21. popPK: t1/2 [Time Frame: 12 months]

    terminal elimination half-live

22. popPK: CLT [Time Frame: 12 months]

    Total Body Clearance

Method of analysis	The endpoint statistical analysis is described in Appendix K- PROPEL Endpoints and statistical analysis

Subgroup analyses	**Characteristics of included population**
	ITT
	• All randomised patients who received at least one dose of study drug. This population was analysed according to the planned treatment groups and two analysis approaches were used:
	  ○ ITT-OBS: used all available, observed data without imputation for missing post-baseline data
	  ○ ITT-LOCF: used LOCF method to replace missing data. Additional details provided in 'Method of analysis' below
	• Safety Population
	  ○ All patients who received at least one dose of study drug. This population was used in the assessment and reporting of safety data, and patients were analysed according to the actual treatment received.
	Method of analysis
	The ITT-LOCF is the ITT population with missing data replaced with the last available value from post-baseline results. That is, the LOCF replaces missing data at Weeks 26, 38, and 52 with the last available endpoint value. Where applicable, the observed baseline result will be used to replace a missing post-baseline result at the Week 12 visit. Imputed baseline value cannot be used to replace missing Week 12 result. The missing value at Week 52 is replaced with the last available value from the subject in the study. This can be the value from the early termination (ET)/end of study (EOS) visit if available. If not available, the last available value from prior post-baseline visits (Week 38, Week 26, or Week 12, whichever is available) will be used to replace the missing value at Week 52.
	Sample Size and Power Considerations
	The primary endpoint for this study is the change from baseline to Week 52 in the 6MWD. Using a 2-group t-test with a 1-sided significance level of 0.025 and a 2:1 randomization ratio, a total of 99 subjects (66 subjects in the ATB200/AT2221 group and 33 subjects in the alglucosidase alfa/placebo group) would yield approximately 90% power to detect a clinically meaningful standardised effect size of 0.7 between the 2 groups in a superiority test for the primary endpoint. This calculation was performed using nQuery 8©. Assuming a 10% dropout rate (after randomization), a total of approximately 110 subjects were planned to be randomised to ensure 99 evaluable patients.
	Safety Endpoints
	The safety profile of ATB200/AT2221 will be characterised using incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events (AEs) leading to discontinuation of study drug, frequency and severity of immediate and late infusion-associated reactions (IARs), and any abnormalities noted in other safety

assessments. The impact of immunogenicity to ATB200 and alglucosidase alfa on safety and efficacy will also be described. The immunogenicity analyses will also be performed by ERT status subgroups (ERT-naïve and ERT-experienced).

Analysis of efficacy

General Considerations

The Statistical Analysis System (SAS©) software version 9.4 (or the latest version at the time of the analysis) and R software will be used for all statistical procedures and analyses. In general, where basic summary statistics are needed, continuous variables will be summarised using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum); categorical variables will be summarised using number and percentage. For basic summaries involving the change from baseline, a 95% confidence interval (CI) for the mean difference will also be provided.

All inferential statistical tests for the primary and key secondary efficacy endpoints will be 1-sided and will be performed at the alpha level of 0.025, unless otherwise specified.

Other relevant information	-

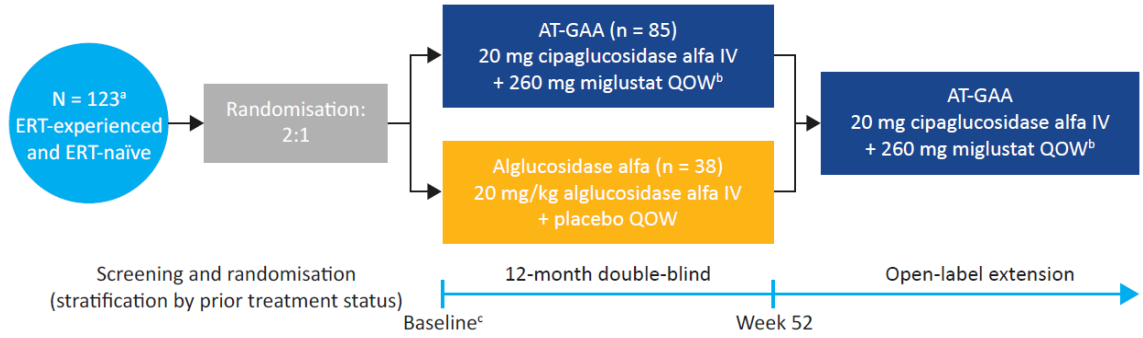
14.2. PROPEL study design

14.2.1. Design, interventions and dosing

Patients were randomised 2:1 in a double-blind manner to receive either cipaglucosidase alfa/miglustat (cipaglucosidase alfa 20 mg IV plus oral miglustat 260 mg [195 mg for patients weighing 40–49 kg] once every other week) or active treatment (alglucosidase alfa 20 mg/kg plus placebo once every other week) for 52 weeks. Stratification factors at randomisation were ERT status (ERT-experienced vs ERT-naïve) and baseline 6MWD (75 to < 150 m vs 150 to < 400 m vs ≥ 400 m).

Most patients remained enrolled in the study (95%) and subsequently enrolled in the cipaglucosidase alfa/miglustat extension study (NCT04138277).

Figure 29: PROPEL study design



[a]Two patients were randomised but not dosed.
[b]A dose of 195 mg was used in patients weighing 40 to < 50 kg.
[c]Baseline values were measured during screening (up to 30 days before dosing). For 6MWD and FVC the baseline value is the average of the last two measurements obtained on or prior to first dose date.
Abbreviations: 6MWD, 6-minute walk distance; ERT, enzyme replacement therapy; FVC, forced vital capacity; IV, intravenous; QOW, every other week.

14.2.2. Patient recruitment

PROPEL enrolled adult patients (aged 18 years and older) with a confirmed diagnosis of LOPD and either:

- *ERT-experienced:* defined as currently receiving ERT (alglucosidase alfa) for at least 24 months
- *ERT-naïve:* defined as never having received ERT

Key eligibility criteria are summarised in Table 57.

Table 57: Key eligibility criteria for PROPEL

Key inclusion criteria	Key exclusion criteria
Male and female patients aged ≥ 18 years weighing ≥ 40 kg at screening and a diagnosis of LOPD confirmed by one of the following: • Deficiency in GAA • GAA genotyping	Receipt of investigational therapy or pharmacological treatment or prohibited treatment[a] (other than alglucosidase alfa) for Pompe disease within 30 days or five half-lives of the therapy before day 1, or would be anticipated to do so during the study
ERT status: *ERT-experienced* – defined as currently receiving ERT (alglucosidase alfa) at the recommended dose and regimen (i.e. 20 mg/kg dose Q2W) for ≥ 24 months[b] *ERT-naïve* – defined as never having received investigational or commercially available ERT	Receipt of gene therapy for Pompe disease Requirement for invasive or non-invasive ventilation support > 6 hours per day while awake Unwilling to undergo genetic testing If patient had a hypersensitivity to any of the excipients in cipaglucosidase alfa, alglucosidase alfa, or miglustat If patient was pregnant or breast feeding at screening
A sitting FVC ≥ 30% of the predicted value for healthy adults[c] at screening	
Two 6MWTs at screening that were valid, as determined by the clinical evaluator and that met the following criteria: • both 6MWD were ≥ 75 m • both 6MWD were ≤ 90% of the predicted value for healthy adults • the lower value of 6MWD was within 20% of the higher value of 6MWD	

[a]These include miglitol (e.g. Glyset®), miglustat (e.g. Zavesca®), acarbose (e.g. Precose® or Glucobay®) and voglibose (e.g. Volix®, Vocarb® or Volibo®). Note that none of these medications have a half-life that, when multiplied by 5, is longer than 30 days.
[b]In Australia, this is defined as currently receiving ERT (alglucosidase alfa) at the recommended dose and regimen, at a dose of 20 mg/kg based on lean or ideal body weight every 2 weeks.
[c]As defined by the US National Health and Nutrition Examination Survey III.
Abbrevations: 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; GAA, α-1,4-glucosidase; ERT, enzyme replacement therapy; FVC, forced vital capacity; LOPD, late-onset Pompe disease; Q2W, every 2 weeks.

14.2.3. Dosing

Cipaglucosidase alfa was given IV at 20 mg/kg body weight and miglustat was given orally at a dose of 260 mg or 195 mg depending on body weight (≥ 50 kg or 40 to < 50 kg respectively), both once every other week for 52 weeks. The selection of doses of cipaglucosidase alfa and miglustat was based on data from the phase ½ ATB200-02 trial and data from an *in vitro* study that investigated the stabilisation of cipaglucosidase alfa by miglustat. Dosing information for cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo is summarised in Table 58.

Table 58: Dosing information for the investigational product and comparators

Study treatment	Component pharmaceutical form	Posology and mode of administration
Investigational product **Cipaglucosidase alfa/miglustat**	**Cipaglucosidase alfa** 15 mg/mL powder for concentrate for solution infused	20 mg/kg of body weight given every 2 weeks as a 4-hour IV infusion
	Miglustat[a] 65 mg hard capsules	*Patients weighing ≥ 40 kg and < 50 kg:* 195 mg (3 X 65 mg oral capsules) 1 hour prior to cipaglucosidase alfa *Patients weighing ≥ 50 kg:* 260 mg (4 x 65 mg oral capsules) 1 hour prior to cipaglucosidase alfa
Active control **Alglucosidase alfa/placebo**	**Alglucosidase alfa(European Medicines Agency)** 5 mg/mL powder for concentrate for solution infused	20 mg/kg of body weight administered every 2 weeks as a 4-hour IV infusion
	Placebo[a] Matched to represent miglustat 65 mg hard capsules	*Patients weighing ≥ 40 kg and < 50 kg:* Placebo (three oral capsules) 1 hour prior to alglucosidase alfa *Patients weighing ≥ 50 kg:* Placebo (four oral capsules) 1 hour prior to alglucosidase alfa

[a]Patients were required to fast for at least 2 hours before and 2 hours after administration of miglustat or placebo.
Abbrevations: IV, intravenous.

14.2.4. Sample size

Change from baseline 6MWD at week 52 was the primary endpoint in PROPEL. Based on a two-group t-test with a one-sided significance level of 0.025 and a 2:1 randomisation ratio, enrolment of 99 patients (66 in the cipaglucosidase alfa/miglustat arm and 33 in the alglucosidase alfa/placebo arm) would yield approximately 90% power to detect a clinically meaningful standardised effect size of 0.7 between the investigational and control groups in a superiority test for the primary endpoint. Assuming a 10% dropout rate after randomisation, the enrolment of 110 patients was planned to ensure data from 99 evaluable patients was available.

14.2.5. Patient disposition

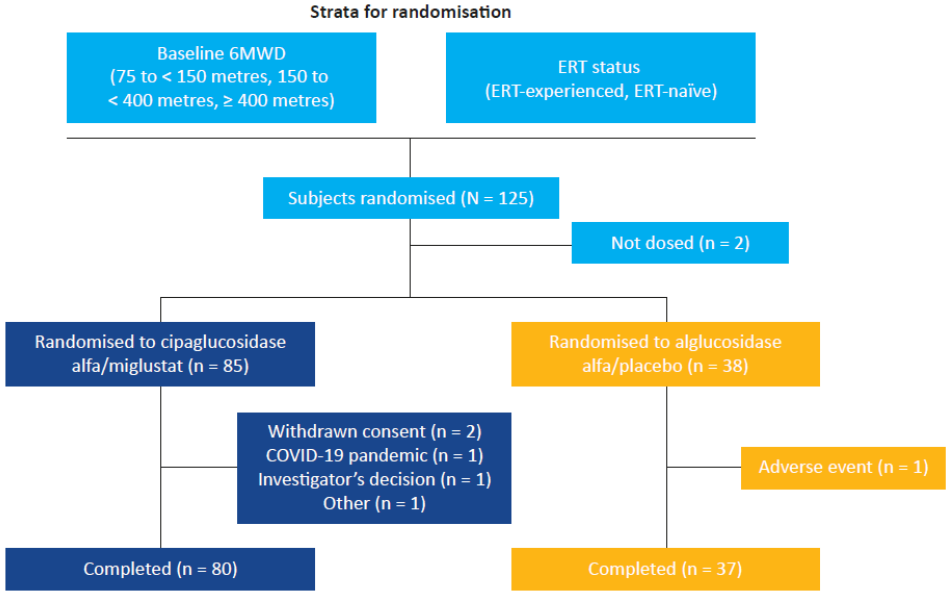
In total, 123 patients were enrolled across 62 sites in 24 countries (Figure 30). Patients were randomised 2:1 to receive treatment with cipaglucosidase alfa/miglustat, or alglucosidase alfa/placebo. Of these patients:

- *85 received cipaglucosidase alfa/miglustat: 65 in the cipaglucosidase alfa/miglustat arm were ERT-experienced, defined as currently receiving ERT (alglucosidase alfa) for at least 24 months, and 20 were ERT-naïve*
- *38 received alglucosidase alfa/placebo: 30 in the active control arm were ERT-experienced, and 8 were ERT-naïve*

Most patients (95%) completed the study; five patients in the cipaglucosidase alfa/miglustat arm and one in the alglucosidase alfa/placebo arm discontinued study treatment (Figure 30). Of the five patients who discontinued cipaglucosidase alfa/miglustat treatment, three discontinued owing to Aes (IAR, two patients; COVID-19-related pneumonia, one patient; Section 7.1.2.7), one owing to the COVID-19 pandemic and one withdrew consent because they did not want to travel to the site. A single patient in the alglucosidase alfa/placebo arm

discontinued study treatment owing to an AE (stroke, unrelated to study drug; Section 7.1.2.7). The full patient disposition is given in Figure 30.

Figure 30: Patient disposition (ITT population including patient 4005-2511)



Abbreviations: 6MWD, 6-minute walk distance; COVID-19, coronavirus disease 2019 that is caused by the SARS-CoV-2 virus; ERT, enzyme replacement therapy; ITT, intention-to-treat.

14.2.6. Exclusion of Patient 4005-2511

A review of all patients' post-baseline assessments of 6MWD revealed that Patient 4005-2511 had clinically implausible improvements in 6MWD between baseline and Week 52. Previous history for this patient showed a percent predicted FVC on 4 December 2018 of 93% and a 6MWD result on 15 April 2019 of 585 meters. His study Screening Visits on 5 and 6 August 2019 showed a 6MWD average of 320 meters and a percent predicted FVC of 83.5%, decreases of 265 meters and 10% from his preceding walk and pulmonary function testing, respectively. After data base lock, the subject revealed to the principal investigator that he deliberately underperformed on the 6MWT and pulmonary function test (PFT) to ensure that he would meet inclusion criteria and gain entry into the study. Subsequent assessments were performed with a full effort according to the subject. His underperformance at time of study start puts his clinically implausible results during the treatment period into context. Data from Patient 4005-2511 contributed approximately 56% of the mean change from baseline at 52 weeks in 6MWD in the alglucosidase alfa/placebo group and inflated the variance in the alglucosidase alfa/placebo arm to approximately six times that of the cipaglucosidase alfa/miglustat arm.

A pre-specified outlier exclusion analysis of 6MWD in the ITT population that excluded outliers with externally studentised residuals with a magnitude greater than 3 was performed. Patients receiving cipaglucosidase alfa/miglustat walked a mean distance of 14.0 m (95% CI, −2.72, 30.64) further than those in the alglucosidase alfa/placebo arm (two-sided p = 0.100), which is consistent with the distance reported for the overall population (i.e. ITT population excluding Patient 4005-2511; 14.21 [95% CI, −2.60, 31.02]; nominal two-sided p = [redacted]). All data presented exclude Patient 4005-2511.

[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

14.3. Supporting study ATB200-02

Study ATB200-02 is an ongoing phase 1/2, open-label, single-arm, fixed-sequence, ascending-dose, first-in-human trial (NCT02675465), which evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of cipaglucosidase alfa/miglustat in 29 adult patients with LOPD.

Patients were recruited from 16 clinical sites in five countries (Cohort 1, 11 patients; Cohort 2, 6 patients; Cohort 3, 6 patients; Cohort 4, 6 patients). Data from Study ATB200-02 may provide a further understanding of the long-term effect of cipaglucosidase alfa/miglustat in patients with Pompe disease (up to 48-month follow-up), and supplement the PROPEL open-label extension data. Of note, Study ATB200-02 also includes non-ambulatory patients (Cohort 2) who are wheelchair-bound or unable to walk.

ATB200-02 enrolled patients into four cohorts (1–4) based on ambulatory status and previous treatment with ERT. Cohort 1 comprised patients who had received cipaglucosidase (ATB200) alone for 6 weeks (stage 1) as part of the dose-escalation phase, with miglustat (ATB2221) added in stage 2 (12 weeks). Cohorts 2 to 4 were enrolled as part of phase 2 (stage 3); eligible patients, stratified by ERT status (ERT-switch vs ERT-naïve) and ambulatory ability (ambulatory vs non-ambulatory), continue to receive cipaglucosidase 20 mg/kg co-administered with miglustat 260 mg, with data currently available for up to 4 years.

14.3.1. Baseline characteristics

The table 41 below summarises the patient characteristics and disposition throughout the study. The baseline characteristics of the patients were representative of the Pompe disease population. Owing to the staggered timing of patient enrolment, the number of patients with data currently available decreased at later time points in this ongoing study.

Table 61: Baseline characteristics and patient disposition

	ERT experienced		ERT naïve
	Cohort 1 2–6 years prior ERT n = 11	Cohort 4 ≥ 7 years prior ERT n = 6	Cohort 3 n = 6
Baseline characteristics			
Median (range) age, years	49.4 (28–66)	40.8 (20–65)	49.3 (24–65)
Sex, M:F	9:2	2:4	1:5

Mean (SD) time on alglucosidase alfa, years	4.7 (1.4)	9.4 (1.2)	N/A[a]
Mean (SD) 6MWD, m	397.2 (96.8)	387.3 (161.3)	396.0 (75.2)
Mean (SD) sitting FVC, % predicted	52.6 (13.9)	65.3 (21.1)	55.8 (19.1)
Mean (SD) MMT lower extremity score	31.8 (1.9)	27.3 (3.7)	29.0 (1.7)
Patient disposition			
Ongoing in study, n (%)	9 (82)	6 (100)	6 (100)

[a] ERT–naïve patient had received 1 dose of alglucosidase alfa >6 months prior to study entry.

Abbrevations: ERT, enzyme replacement therapy; M:F, male:female; N/A, not applicable; SD, standard deviation.

14.4. Supporting study ATB200-07

ABT200-07 (NCT04138277) is an open-label extension to assess the long-term safety and tolerability (primary endpoint), and the efficacy (secondary endpoint), of cipaglucosidase alfa/miglustat in patients who participated in the phase 3 PROPEL study.

Patients who participated in the PROPEL study were scheduled to undergo an infusion approximately 2 weeks after their last visit for the PROPEL study, and every 2 weeks thereafter, ensuring the treatment regimen investigated in PROPEL was maintained. Study treatment will be continued until 31 December 2023 or until study termination, and after a 30-day safety follow-up. Patients discontinuing treatment for any reason will undergo immunogenicity testing for up to 12 months.

14.5. Key inclusion criteria for Study ATB200-02 and Study ATB200-07

Key inclusion criteria for Study ATB200-02 and Study ATB200-07 are included in Table 62.

Table 62: Study AT200-02 and Study ATB200-07: summary of inclusion criteria

Cohort	Inclusion criteria
ATB200-02	
Cohort 1: ambulatory ERT-switch	• Received ERT with alglucosidase alfa for 2–6 years prior to study initiation • Receiving alglucosidase alfa at a frequency of every other week before study start and had completed the last two infusions without a drug-related AE resulting in dose interruption • Able to walk 200–500 metres in the 6MWT • Upright FVC 30–80% of predicted normal value
Cohort 2: non-ambulatory ERT-switch	• Received ERT with alglucosidase alfa for ≥ 2 years prior to study initiation • Receiving alglucosidase alfa at a frequency of every other week before study start and had completed the last two infusions without a drug-related AE resulting in dose interruption • Wheelchair-bound and unable to walk unassisted
Cohort 3: ambulatory ERT-naïve	• Had not received ERT at any time, or any investigational therapy for Pompe disease within 30 days or five half-lives of the therapy, whichever was longer, before study start • Able to walk 200–500 m in the 6MWT • Upright FVC 30–80% of predicted normal value

Cohort 4: ambulatory ERT-switch	• Had been on ERT for ≥ 7 years • Receiving alglucosidase alfa at a frequency of every other week before study start and had completed the last two infusions without a drug-related AE resulting in dose interruption • Able to walk 75–600 metres in the 6MWT • Upright FVC 30–85% of predicted normal value
ATB200-07	
ATB200-07	• Subjects must have completed PROPEL. Note: Subjects who were forced to withdraw from PROPEL for a logistical reason not related to the efficacy or safety of cipaglucosidase alfa/miglustat (e.g. hospitalisation for a car accident, COVID-19 pandemic or emergency surgery) and which resulted in several consecutive missed doses may be eligible to participate in this study upon approval by the Amicus medical monitor. • Patients who participated in the PROPEL study were scheduled to undergo an infusion approximately 2 weeks after their last visit for the PROPEL study, and every 2 weeks thereafter, ensuring the treatment regimen investigated in PROPEL was maintained.

Abbrevations: 6MWT, 6-minute walk test; AE, adverse event; ERT, enzyme replacement therapy; FVC, forced vital capacity

14.6. LOTS study overview

Table 63: LOTS trial overview

Trial name: A Placebo-Controlled Study of Safety and Effectiveness of Myozyme (Alglucosidase Alfa) in Patients with Late-Onset Pompe Disease	**NCT number: NCT00158600**
Objective	To evaluate the safety, efficacy, and pharmacokinetics (PK) of alglucosidase alfa treatment in patients with late-onset Pompe disease as compared to placebo
Publications – title, author, journal, year	van der Ploeg AT, Clemens PR, Corzo D, Escolar DM, Florence J, Groeneveld GJ, Herson S, Kishnani PS, Laforet P, Lake SL, Lange DJ, Leshner RT, Mayhew JE, Morgan C, Nozaki K, Park DJ, Pestronk A, Rosenbloom B, Skrinar A, van Capelle CI, van der Beek NA, Wasserstein M, Zivkovic SA. A randomised study of alglucosidase alfa in late-onset Pompe's disease. N Engl J Med. 2010 Apr 15;362(15):1396-406. doi: 10.1056/NEJMoa0909859.
Study type and design	Randomised, Double-Blind, Placebo-Controlled Study
Sample size (n)	N=90
Main inclusion and exclusion criteria	Inclusion Criteria: • Diagnosis of Pompe disease based on deficient endogenous GAA activity in cultured skin fibroblasts of less than or equal to 40% of the normal mean of the testing laboratory and 2 confirmed GAA gene mutations; • 8 years of age or older at the time of enrollment • Able to ambulate 40 meters (approximately 130 feet) in 6 minutes on each test performed on two consecutive days (use of assistive devices such as a walker, cane, or crutches, is permitted) • FVC of greater than or equal to 30% and < 80% predicted in the upright position; • Postural drop in FVC (liters) of at least 10% from the upright to the supine position • Proximal muscle weakness in the lower limbs based on unilateral QMT of the knee extensors defined as < 80% of the predicted value based on age, gender and body size • Tolerate pulmonary function testing (PFT) and muscle testing in the supine position

	• Testable muscle in bilateral knee flexors and knee extensors, and testable muscle in bilateral elbow flexors and elbow extensors • Able to provide reproducible muscle and pulmonary function test results • A female patient of childbearing potential must have a negative pregnancy test (urine) at Baseline. Note: All female patients of childbearing potential and sexually mature males must use a medically accepted method of contraception throughout the study Exclusion Criteria: • Requires the use of invasive ventilatory support • Requires the use of noninvasive ventilatory support while awake and in an upright position • Received enzyme replacement therapy with GAA from any source • Used an investigational product within 30 days prior to study enrollment, or is currently enrolled in another study which involves clinical evaluations, unless prior approval is given by Genzyme • Major congenital anomaly, medical condition, serious intercurrent illness, or other extenuating circumstance that, in the opinion of the investigator, may significantly interfere with study compliance, including all prescribed evaluations and follow-up activities;
Intervention	• alglucosidase alfa: IV infusion of 20mg/kg; qow for 78 weeks
Comparator(s)	• Placebo: qow for 78 weeks
Follow-up time	78 weeks
Is the study used in the health economic model?	Yes, scenario analysis
Primary, secondary and exploratory endpoints	Primary Outcome Measures : 1. Summary of Patients Reporting Treatment-Emergent Adverse Events Overall safety summary of patients experiencing Adverse Events, Serious Adverse Events, treatment-related AEs, and Infusion Associated Reactions; Summary is based on Treatment-emergent AEs (TEAEs), defined as AEs that occurred following the initiation of study treatment 2. Mean Distance Walked as Measured by Six-minute Walk Test at Weeks 0 and 78, and Mean Change From Baseline The greater the distance, the greater the endurance. Mean values of distance walked in a six-minute walk test are offered for baseline, week 78 (or last available observation), and the mean change from baseline (at week 78 or last available post-baseline observation) 3. Percent of Predicted Forced Vital Capacity The volume of air that can forcibly be blown out after full inspiration in the upright position, measured in liters. Predicted forced vital capacity is based on a formula using sex, age and height of a person, and is an estimate of healthy lung capacity. 4. Recombinant Human Acid Alpha-Glucosidase Pharmacokinetic Parameters: Area Under the Curve Area under the plasma concentration versus time curve from time zero (pre-dose) to 16 hours after the end of infusion. Blood sample time points were

0 (before the start of the infusion), 1 and 2 hours after the start of infusion, end of the infusion, and then 0.25, 0.5, 1, 2, 3, 4, 8, 12,and 16 hours after the end of the infusion (with a 5-minute window for time-points after the start of infusion)

5. Recombinant Human Acid Alpha-Glucosidase Pharmacokinetic Parameters: Mean Maximum Plasma Concentration

   Maximum plasma concentration observed in blood samples taken at the following time points: 0 (before the start of the infusion), 1 and 2 hours after the start of infusion, end of the infusion, and then 0.25, 0.5, 1, 2, 3, 4, 8, 12,and 16 hours after the end of the infusion (with a 5-minute window for time-points after the start of infusion)

6. Recombinant Human Acid Alpha-Glucosidase Pharmacokinetic Parameters: Mean Time to Maximum Plasma Concentration

   Time to maximum plasma concentration observed in blood samples taken at the following time points: 0 (before the start of the infusion), 1 and 2 hours after the start of infusion, end of the infusion, and then 0.25, 0.5, 1, 2, 3, 4, 8, 12,and 16 hours after the end of the infusion (with a 5-minute window for time-points after the start of infusion)

Secondary Outcome Measures :

1. Percent Predicted Proximal Muscle Strength of the Lower Limbs as Measured by Quantitative Muscle Testing (QMT)

   QMT data were collected directly from sensors into laptop computers. Predicted normal values for QMT are based on a formula using sex, age and body mass index of a person, and is an estimate of healthy muscle force. Percent of predicted QMT = (observed value)/(predicted value) * 100%. The QMT Leg Score is the average of the bilateral means for percent predicted knee flexors and extensors. A value of 100% indicates 'normal' muscle strength.

2. Health-related Quality of Life Survey Values Related to Physical Components as Measured by the Medical Outcomes Study (MOS) Short Form-36 Health Survey

   Physical Component Scores (PCS) report the four domains of physical functioning, role-physical, bodily pain, and general health. Higher scores are associated with better quality of life. All questions are scored on a scale from 0 to 100, with 100 representing the highest level of functioning possible. The PCS scores are reported.

Method of analysis	The efficacy analysis was performed for the intention-to-treat population, defined as all patients randomly assigned to either alglucosidase alfa or placebo. A fixed-sequence testing procedure was used to account for multiple testing and to preserve the overall significance level of 5% for both coprimary end points. Formal testing for a treatment effect on FVC in the upright position was performed only after the significance of the treatment effect on the 6-minute walk test had been shown by means of a two-sided test. Prespecified testing of the assumptions for the linear mixed-effects model indicated that use of this model was not warranted; therefore, the primary efficacy analysis was an analysis of covariance (ANCOVA) for the change from baseline to week 78. The last-observation-carried-forward method was used for the ANCOVA model, with adjustment for randomization strata and baseline scores. Treatment effects were also estimated in predefined subgroups, and a post hoc sensitivity analysis with the use of mixed models for repeated measures and nonparametric tests was conducted to assess the robustness of the efficacy findings. Secondary

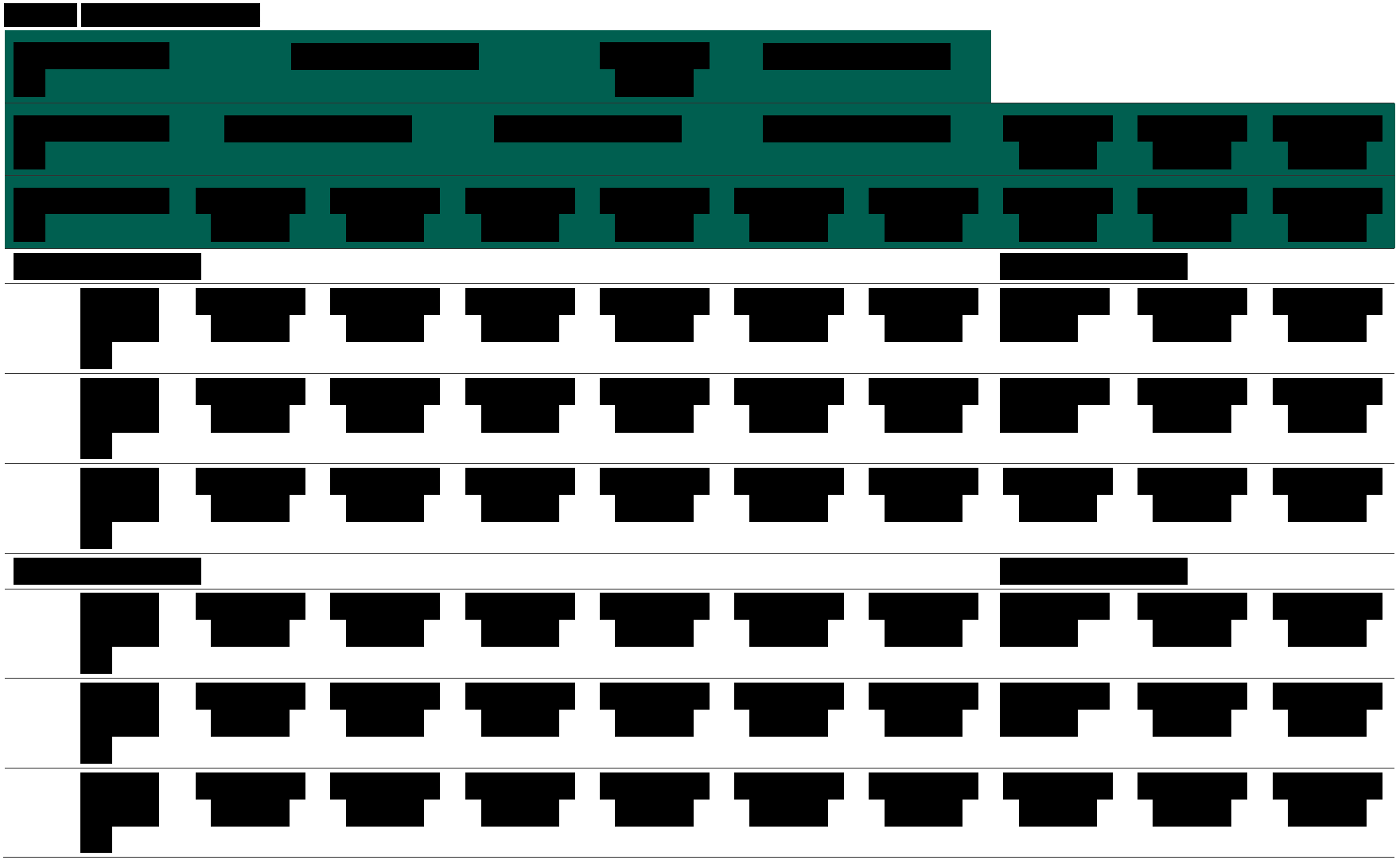
	and tertiary end points were analysed by means of ANCOVA. The reported P values are two-sided and were not adjusted for multiple testing.
Subgroup analyses	N/A
Other relevant information	-

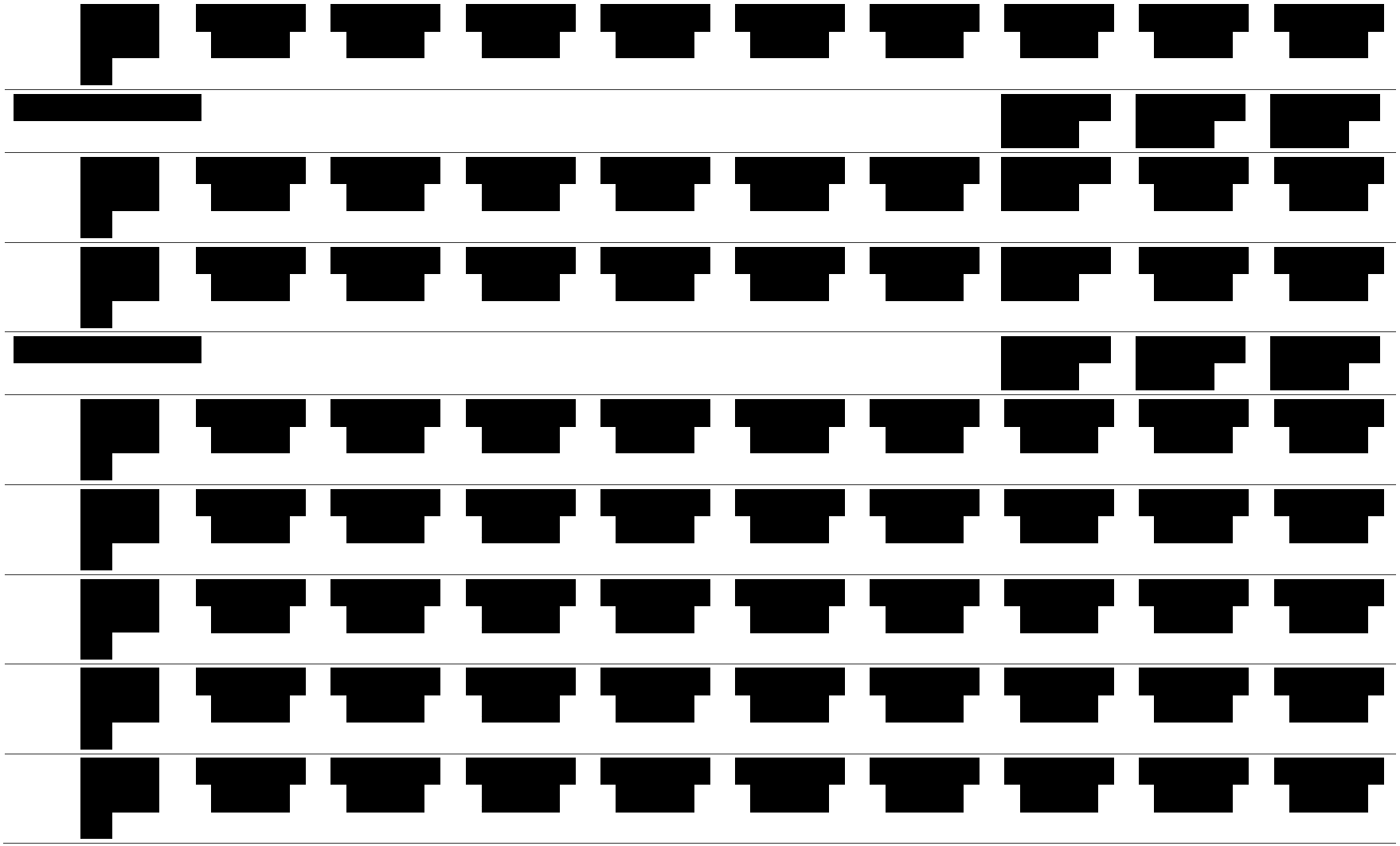
Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

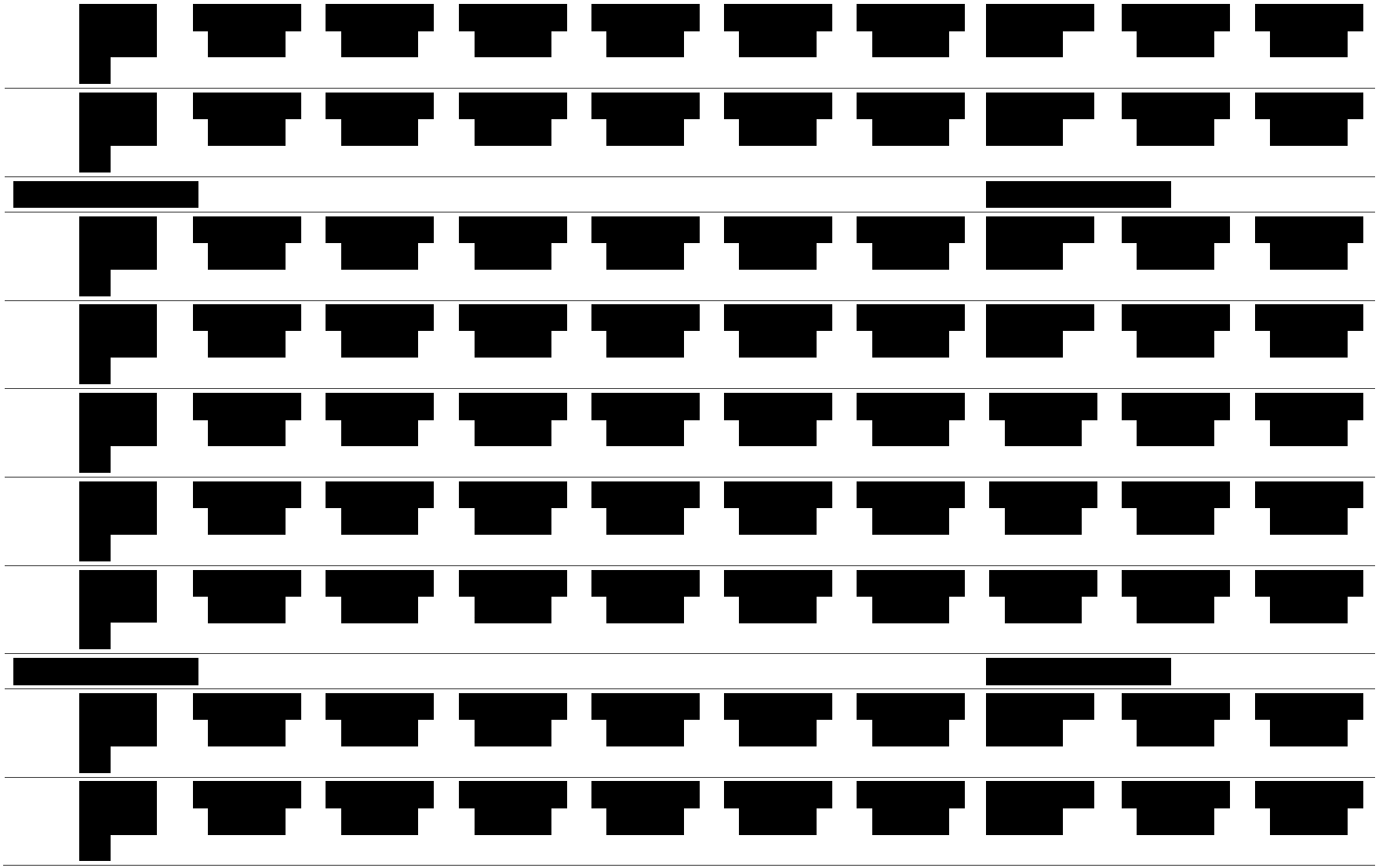
Baseline demographics for the ITT population, which included Patient 4005-2511, were generally well balanced between treatment arms ([redacted]). Baseline 6MWD, % predicted FVC and MMT and GSGC score were similar between treatment arms and are considered representative of the patient population with LOPD.

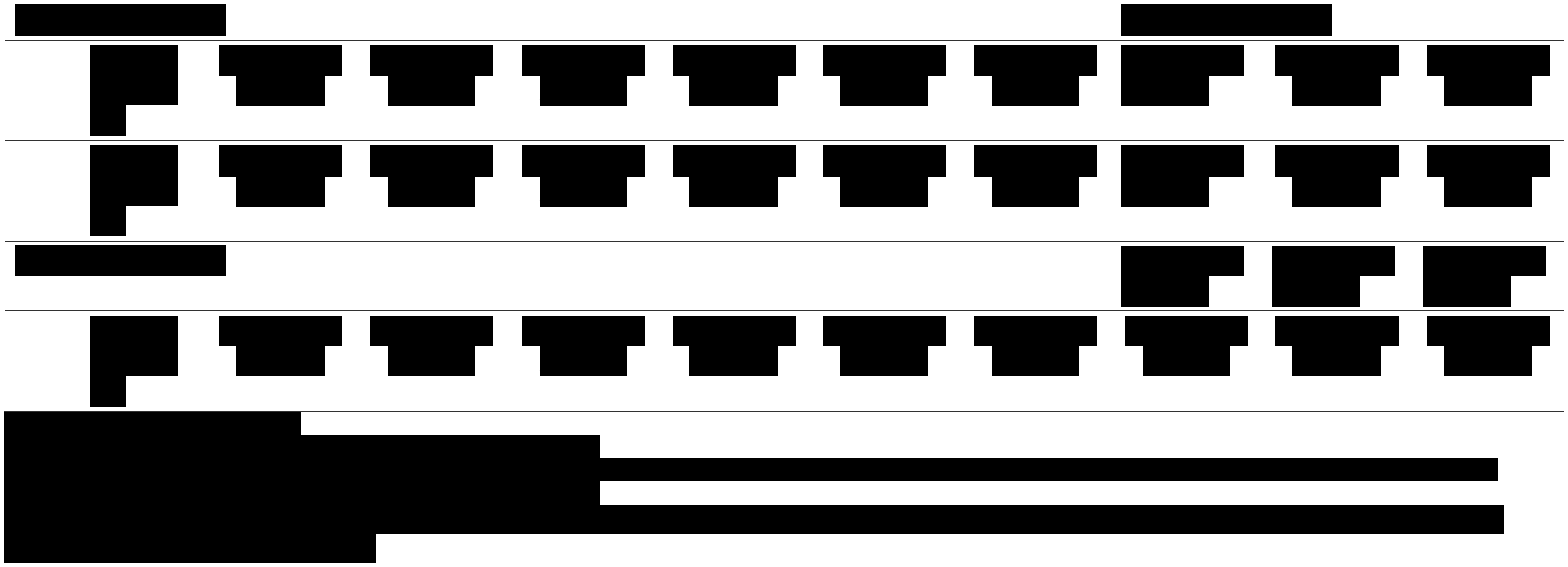
Most patients were **ERT-experienced**, with a mean treatment duration of 7.4 years (SD, 3.45): 7.5 years and 7.1 years in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively. Patient demographics and baseline characteristics in the **ERT-experienced population** were aligned with those described for the overall ITT population, with the exception of a lower mean baseline 6MWD, as expected ([redacted]).

Mean baseline 6MWD (397.8 m [SD, 115.6] vs 343.1 m [SD, 111.0]) and % predicted FVC (80.0 [SD, 18.97] vs 67.8 [SD, 19.6]) were higher in the **ERT-naïve population** than in the **ERT-experienced population**, and a smaller proportion of ERT-naïve patients had experienced a history of falls (10 [35.7%] vs 51 [53.7%]). Between treatment groups in the **ERT-naïve population**, there was a higher population of females (12 [60.0%] vs 2 [25.0%]) in the cipaglucosidase alfa/miglustat arm compared with the alglucosidase alfa/placebo arm, and mean baseline 6MWD was lower ([redacted]).









15.1. Comparability of patients across studies

In the phase 3 RCT PROPEL (Amicus Therapeutics; NCT03729362) in adult patients with LOPD, who either have previously received at least 24 months of alglucosidase alfa treatment (**ERT-experienced**) or who have not received previous treatment with alglucosidase alfa (**ERT-naïve**), compared with alglucosidase alfa/placebo (Section 7.1.2).

Best supportive care was assessed as best informed by the placebo arm in the LOTS trial. This patient group would function as a proxy for 'BSC', being reliant on other supportive measures in the absence of any available ERT at the time. This is in contrast to the 'ERT naïve' arms of more recent clinical trials, which likely included patients considered for pharmaceutical treatments early in their patient journey, and therefore not necessarily on 'BSC'. However, as discussed in section 5.2.3, Amicus would like to highlight that this scenario is purely theoretical and does not bear any clinical relevance in Denmark.

Thus, comparability of patient populations across PROPEL and LOTS bears little relevance for this analysis.

15.2. Comparability of the study populations with Danish patients eligible for treatment

According to feedback from clinical experts in Denmark (List of experts, section 11) the PROPEL patient baseline characteristics are transferrable to the Pompe patient population.

Appendix D – Efficacy and safety results per study

16.1. Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
6-Minute Walk Test	Change in 6MWD from baseline to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo	The reliability and validity of the 6-minute walk test (6MWT) has been assessed by evaluating correlation of 6MWT with other outcomes, e.g. MMT scores and FVC and has been confirmed in patients with similar diseases to Pompe disease including ambulatory spinal muscular atrophy,(Dunaway Young 2016) hypophosphatasia (Phillips 2019) and Duchenne muscular dystrophy (DMD) (McDonald 2013)	6MWD captures the influences of cardiac, pulmonary, circulatory and muscle systems on walking (Casanova 2011). See Appendix L – Clinical relevance of improvements in 6MWD and percent predicted FVC for more information
Change from baseline % predicted FVC at 52 weeks	Change from baseline in FVC (sitting and supine) to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo		FVC is an objective, reproducible measure of respiratory function that is a frequently assessed outcomes in LOPD, and is obtainable in most settings (Berger 2019). See Appendix L – Clinical relevance of improvements in 6MWD and percent predicted FVC for more information
Change from baseline MMT scores for lower extremities at 52 weeks	Change in manual muscle strength from baseline to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo		MMT is a widely used strength assessment where the ability of a muscle to act against gravity or resistance offered by the examiner (Herbison 1996). See Appendix L – Clinical relevance of improvements in 6MWD and percent predicted FVC for more information

Outcome measure	Definition	Validity	Clinical relevance
Change from baseline PROMIS–Physical Function score at 52 weeks **Change from baseline PROMIS–Fatigue score at 52 weeks**	Change from baseline in scores of PROMIS instruments for physical function, fatigue, dyspnea, and upper extremity questionnaire to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo. The PROMIS instruments for physical function (20 items), d upper extremity (7 items) measure signs and symptoms using general questions without a temporal reference. The PROMIS instruments for fatigue (8 items) and dyspnea severity (10 items) measure signs and symptoms over the past 7 days. A 5-point scale is used for each instrument (though responses may vary within or among instruments), and a total score is generated for each instrument.	The construct and validity of five Patient-Reported Outcomes Measurement Information System (PROMIS®) questionnaires were compared with clinically relevant outcome measures in 30 patients with LOPD, including 6MWD, FVC and MMT (Harfouche 2020). The findings of this comparison alongside reports from the Amicus Pompe Disease Patient Advocate Board suggested that clinical outcome measures assess concepts important to patient-reported experiences, and are meaningful to the patient (Harfouche 2020). However, further longitudinal studies including other PROMIS questionnaires, other measures of motor function and HRQoL, and a larger patient sample should be conducted (Harfouche 2020).	A measure of important aspects of daily function, PROMIS physical function scores are correlated with 6MWD and overall, upper and lower MMT scores (Harfouche 2020).
Change from baseline total GSGC at 52 weeks	Change from baseline in GSGC score to assess the efficacy of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo. The GSGC consists of a 10-meter walk for evaluation of gait, a 4-stair climb, Gower's maneuver, and arising from a chair. Results of the GSGC include the time required to complete the individual tests, individual scores for each of the tests (1 to 7 points for each of gait, 4-stair climb, and Gower's maneuver and 1 to 6 points for arising from a chair), and a total score. The total score ranges from a minimum of 4 points (normal performance) to a maximum of 27 points (worst score).		GSGC provides a broad view of overall function covering common functional activities including walking, standing up from a chair or floor, and climbing the stairs (Khan 2020). The Gait, Stairs, Chair, Gower (GSCG) score has recently been validated in 2012 as an alternative outcome measure for motor function in late-onset Pompe patients receiving ERT (Angelini 2012). The GSCG score is a composite test that evaluates the four main motor performances quantitatively and qualitatively and should be used in combination with both the Walton and Gardner-Medwin scale (WGM) and the 6-Minute Walk Test (6MWT) to identify individual response to ERT in late-

Outcome measure	Definition	Validity	Clinical relevance
			onset Pompe patients (Angelini 2012). The GSGC scoring is unique in that a lower score shows improvement

16.2. Results per study

Table A3a Results of [PROPEL (NCT 03729362)]

					Estimated absolute difference in effect (at week 52)			**Estimated relative difference in effect** (between baseline and week 52)			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N** (baseline)	**N** (52 weeks)	**Result (SD)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
LS mean change in baseline 6MWD at 52 weeks (overall population) (observed)	Cipaglucosidase alfa/miglustat	85	81	20.56 (42.27)	12.54	-4.016 – 29.096	0.136	14.21	−2.60, 31.02	[redacted]	Mixed-effect model for repeated measures (MMRM) difference in LS mean Nominal two-sided p value	PROPEL trial (Section 7.1.2) Absolute difference 95% CI and P calculated using: https://epitools.ausvet.com.au/twosamplettest
	Alglucosidase alfa/placebo	37	36	8.02 (40.56)								

Table A3a Results of [PROPEL (NCT 03729362)]												
Change from baseline in percent predicted sitting FVC at week 52 in the overall population	Cipaglucosidase alfa/miglustat	85	84	−0.93 (6.23)	3.02	0.732 – 5.308	0.01	2.66	(0.37, 4.95)	[redacted]	ANCOVA difference in LS mean Nominal two-sided p value	PROPEL trial (Section 7.1.2) Absolute difference 95% CI and P calculated using: https://epitools.ausvet.com.au/twosamplettest
	Alglucosidase alfa/placebo	37	37	−3.95 (4.89)								

Table A3a Results of [LOTS (NCT NCT00158600)]

		Result		Estimated absolute difference in effect (at week 78)		Estimated relative difference in effect (between baseline and week 78)			Description of methods used for estimation	References
Outcome	**Study arm**	**Baseline**	**Week 78**	**Difference**	**95% CI**	**Difference**	**95% CI**	***P* value**		
Distance walked on 6-min walk test – meters	Alglucosidase alfa group (n = 60)	332.2±126.7	357.9±141.3	25.13	(10.07 to 40.19)	28.12	(2.07 to 54.17)	0.03	The planned model for the primary efficacy analysis was a linear mixed-effects model with random intercepts and slopes. The estimated treatment effect was the absolute difference in the linear slopes of change between the alglucosidase alfa and placebo groups. An adaptive design was implemented (under a protocol amendment) in which the initial 52-week treatment period could be extended by 3 or 6 months on the basis of an interim estimate of the standard error of the treatment effect on the 6-minute walk test. Formal testing for a treatment effect on FVC in the upright position was performed only after the significance of the treatment effect on the 6-minute walk test had been shown by means of a two-sided test (van der Ploeg 2010)	(van der Ploeg 2010)
	Placebo group (N = 30)	317.9±132.3	313.1±144.7	−2.99	(−24.16 to 18.18)					
Forced vital capacity — % of predicted	Alglucosidase alfa group (n = 60)	55.4±14.4	56.7±16.3	1.20	(−0.16 to 2.57)	3.40	(1.03 to 5.77)	0.006		
	Placebo group (N = 30)	53.0±15.7	50.7±14.9	−2.20	(−4.12 to −0.28)					

Appendix E – Safety data for intervention and comparator

17.1. Intervention (PROPEL trial)

17.1.1. Exposure

Exposure to study drugs is summarised in Table 65. Median treatment duration was similar in both treatment arms (cipaglucosidase alfa/miglustat, 12.01 months vs alglucosidase alfa/placebo, 12.04 months). Most patients received study treatment for more than 12 months; a slightly lower proportion of patients in the cipaglucosidase alfa/miglustat arm had a treatment duration greater than 12 months than in the alglucosidase alfa/placebo arm (72.9% vs 86.8%).

Table 65: PROPEL study drug exposure (safety population)

	Number of patients, n (%)	
	Cipaglucosidase alfa/miglustat (n = 85)	Alglucosidase alfa/placebo (n = 38)
Mean number of administered doses (SD)	25.7 (3.79)	26.2 (1.99)
Median duration[a] of treatment, months (Q1, Q3)	12.01 (11.97, 12.07)	12.04 (12.01, 12.07)
Tri-monthly treatment duration,[a] n (%)		
≤ 3	1 (1.2)	0
> 3 to ≤ 6	1 (1.2)	0
> 6 to ≤ 9	2 (2.4)	1 (2.6)
> 9 to ≤ 12	19 (22.4)	4 (10.5)
> 12	62 (72.9)	33 (86.8)

[a]Duration of treatment (months) is defined as the difference between the date of the last and first doses plus 1 and divided by 30.4.
Abbrevations: Q1, first quartile; Q3, third quartile; SD, standard deviation.

17.1.2. Infusion-associated reactions

In total, 128 IARs were reported in 31 patients; incidence was similar between treatment arms (cipaglucosidase alfa/miglustat, 24.7% vs alglucosidase alfa/placebo, 26.3%; Table 66). All IARs were considered non-serious with the exception of one event of anaphylactic reaction in the cipaglucosidase alfa/miglustat arm. Two patients, both in the cipaglucosidase alfa/miglustat arm, discontinued study treatment owing to an IAR: one patient experienced a severe anaphylactic reaction and the other severe chills.

Table 66: PROPEL summary of the incidence of IARs (safety population)

	Number of patients, n (%)			
	Cipaglucosidase alfa/miglustat (n = 85)		Alglucosidase alfa/placebo (n = 38)	
Any IAR-TEAE	**21 (24.7)**		**10 (26.3)**	
Any IAR-TEAE leading to discontinuation of study drug	2 (2.4)		0	
Any IAR-TEAE potentially related to treatment	**Cipaglucosidase**	**Miglustat**	**Alglucosidase alfa**	**Placebo**
	20 (23.5)	10 (11.8)	9 (23.7)	5 (13.2)
Discontinuation of study drug owing to potentially drug-related IAR-TEAEs	2 (2.4)	0	0	
Any serious IAR-TEAEs	**1 (1.2)**		**0**	
Any serious IAR-TEAE leading to discontinuation of study drug	1 (1.2)		0	
Any serious IAR-TEAEs potentially related to treatment	**Cipaglucosidase**	**Miglustat**	**Alglucosidase alfa**	**Placebo**
	1 (1.2)	0	0	0
Discontinuation of study drug owing to potentially drug-related IAR-TEAEs	1 (1.2)	0	0	0
IAR-TEAEs leading to death	0		0	

Abbrevations: IAR, infusion-associated reaction; TEAE, treatment-emergent adverse event.

17.1.3. Immunogenicity

In the ERT-experienced population, the percentage of patients with positive specific anti-rhGAA-antibodies and detectable titres remained stable for those receiving cipaglucosidase alfa/miglustat (83.1% at baseline and 74.1% at the last study visit) or alglucosidase alfa/placebo (73.3% at baseline and 70.4% at last study visit).

The percentage of patients in the ERT-naïve population with positive specific anti-rhGAA antibodies and detectable titres increased in both the cipaglucosidase alfa/miglustat (0 at baseline to 87.5% at last study visit) and alglucosidase alfa/placebo (0 at baseline and 100% at the last study visit) treatment arms; however, there was no apparent association between the incidence of anti-rhGAA antibodies or maximum antibody titre, and Aes.

17.2. Alglucosidase alfa (LOTS trial)

Aes were obtained from the randomised, placebo-controlled LOTS trial that estimated the efficacy and safety of alglucosidase alfa (20 mg/kg) in 90 patients with LOPD across America and Europe over a 78-week study period (van der Ploeg 2010).

Aes reported in the LOTS trial were mild or moderate in severity, similar between treatment arms, and not considered related to alglucosidase alfa, and thus were not included in the model. The incidence of SAEs was similar between treatment arms and occurred in less than 3% of patients; SAEs were therefore not included in the base case analysis.

17.3. Alglucosidase alfa (literature review)

Alglucosidase alfa is generally well tolerated in patients with LOPD. A targeted literature review commissioned by Amicus in 2020 reported that almost all patients enrolled in studies experienced an adverse event (AE), but most were mild to moderate in severity and were not considered to be related to alglucosidase alfa (York Health Economics Consortium 2020b). Similar to any protein infusion, alglucosidase alfa can be associated with allergic reactions due to the presence of immunoglobulin G (IgG) antibodies; however, these can be controlled by slowing the infusion rate, temporarily stopping infusion until conditions improve, or using pre-medications including antihistamines and corticosteroids (Bay 2019). Furthermore, safety results in a large Italian cohort of 65 patients with LOPD receiving

alglucosidase alfa confirmed its tolerability: only four patients (6%) discontinued treatment, one owing to Aes, and four patients (5%) experienced Aes, which were mild in severity (Angelini 2012). Other Aes reported by 5–8% of patients with LOPD receiving alglucosidase alfa as part of LOTS (Late-Onset Treatment Study) included anaphylactic, allergic and infusion-associated reactions (IARs) that involved urticaria, flushing, hyperhidrosis, chest discomfort, vomiting and increased blood pressure (van der Ploeg 2010).

The well-established decline in effectiveness of alglucosidase alfa represents a major issue for patients with LOPD, most of whom will have received the same treatment for several years with declining efficacy. Consequently, patients living with Pompe disease represent a population with a substantial unmet need for effective treatments, which may be achieved by addressing the following:

- **Poor uptake:** can be overcome by developing rhGAA with improved CI-MPR-mediated uptake into muscle cells.
- **Stabilisation:** the use of small molecule enzyme stabilisers has been highlighted as a potential method to increase ERT effectiveness by stabilising an rhGAA in the plasma following infusion of the ERT (Hundsberger 2013).

Maximizing activity of rhGAA in the lysosome: Once endocytosed via the CI-MPR, an rhGAA requires a series of proteolytic and N-glycan processing events to yield the mature, most active form of the enzyme with 7–10-fold greater affinity for glycogen than the precursor protein (Wisselaar 1993, Moreland 2005).

17.4. Safety data across studies for the intervention and comparator

Table 67: Table comparing serious TRAEs safety data for PROPEL and LOTS

Number of patients, n (%)	PROPEL		LOTS*	
	Cipaglucosidase alfa/ miglustat (N = 85)	Alglucosidase alfa/ placebo (N = 38)	Alglucosidase alfa (N = 60)	Placebo (N = 30)
Any TEAE	**81 (95.3)**	**37 (97.4)**	**32 (53.3)**	**17 (56.7)**
Any serious TEAEs	**8 (9.4)**	**1 (2.6)**	**13 (22)**	**6 (20)**
Gastrointestinal disorders				
Abdominal pain	1 (1.2)	0	1 (2)	1 (3)
Enteritis	1 (1.2)	0	1 (2)	0
Vomiting	1 (1.2)	0	-	-
General disorders and administration site conditions				
Chills	1 (1.2)	0	-	-
Immune system disorders	1 (1.2)	0	-	-
Anaphylactoid reaction	1 (1.2)	0	-	-
Infections and infestations	0	1 (2.6)	-	-
Diverticulitis	0	1 (2.6)	0	1 (3)
Hypersensitivity	-	-	2 (3)	0
Chest discomfort	-	-	1 (2)	0
Non-cardiac chest pain	-	-	1 (2)	0
Pneumonia	-	-	1 (2)	0
Injury, poisoning and procedural complications				

Accidental overdose	1 (1.2)	0	-	-
Fall	1 (1.2)	0	1 (2)	1 (3)
Fracture (humerus)	-	-	1 (2)	1 (3)
Investigations				
Heart rate irregular	1 (1.2)	0	-	-
Nervous system disorders	0	1 (2.6)	-	-
Cerebrovascular accident	0	1 (2.6)	-	-
Brain-stem ischemia	-	-	1 (2)	0
Headache	-	-	0	1 (3)
Renal and urinary disorders				
Glycosuria	0	1 (2.6)	-	-
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	1 (1.2)	0	-	-
Lung disorder	-	-	1 (2)	0
Throat tightness	-	-	1 (2)	0
Skin and subcutaneous tissue disorders				
Pruritus	1 (1.2)	0	-	-
Urticaria	1 (1.2)	0	-	-
Angioedema	-	-	1 (2)	0
Septal panniculitis	-	-	0	1 (3)
Vascular disorders				
Aortic aneurysm	1 (1.2)	0	-	-
Flushing	1 (1.2)	0	-	-
Aneurysm	-	-	1 (2)	0
Coronary artery disease	-	-	1 (2)	0
Supraventricular tachycardia	-	-	1 (2)	0
Musculoskeletal and connective-tissue disorders				
Intervertebral disk protrusion	-	-	1 (2)	0
Flank pain	-	-	0	1 (3)
Metabolism and nutritional disorders				
Dehydrations	-	-	1 (2)	0

Note: The LOTS study reported serious adverse events during the treatment period.
Abbrevations: TRAE, treatment related adverse events
Source: PROPEL (Schoser 2021b) and LOTS (van der Ploeg 2010)

Appendix F – Comparative analysis of efficacy and safety

Table A4 Meta-analysis of studies comparing cipaglucosidase alfa/miglustat to placebo for patients with Pompe disease

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	*P* value	Difference	CI	*P* value		
6MWD change from baseline at week 52 (Relative effect) (Main analysis)	LOTS OLE (Van der Ploeg 2012)				27.6	(–84.1, 144.4)	0.648	A multi-level network meta regression (ML-NMR) was performed, which is an extension of standard network meta-analyses (NMAs) that take into account the effect of study-level covariates, and that can be applied to any connected network with any mixture of individual patient-level data (IPD) and aggregate data. Single-arm study results were matched to appropriate comparator arms of the comparative studies to allow for inclusion into the network. See section 7.1.5.2.2 for a detailed methods description.	*Yes*
FVC change from baseline at week 52 (Relative effect) (Main analysis)	PROPEL (Schoser 2021b) ATB200-02 (Byrne 2022)				4.7	(–6.0, 16.2)	0.413		*Yes*

Appendix G – Extrapolation

Please refer to section 8.3 for a description of extrapolation.

Appendix H – Literature search for HRQoL data

A *de novo* SLR was conducted with electronic databases searched in September 2022, to identify published economic evidence (including economic evaluations, health-related quality of life [HRQoL] and utility studies, and cost/healthcare resource use studies) in adults with Pompe disease from a global perspective.

The database and hand searches for the economic evaluation evidence stream were conducted alongside those for the HRQoL and utility studies and cost and healthcare resource use (HCRU) studies. Each record identified in these searches was assessed for eligibility across all three data streams, therefore studies could be simultaneously included in one or more of the evidence streams.

The SLR was conducted following current best practices and methodological principles of conduct for SLRs, as recommended by the Cochrane Collaboration and detailed in the University of York's CRD guidelines (University of York Centre for Reviews and Dissemination 2009, Chandler 2019). The reporting of the methods and results of the SLR is in line with the guidance provided by NICE and the PRISMA guidelines (Moher 2010).

The SLR was performed in accordance with a pre-specified protocol. This involved searching electronic databases as well as hand-searching key conference proceedings from the last two years, key HTA body websites and health economics databases, and the bibliographies of any relevant SLRs, NMAs or HTAs identified during the review. Full details of the SLR are provided below.

Search strategy

Identification of studies

Electronic Databases

The following electronic databases were searched from inception:

- MEDLINE®, including MEDLINE® In-Process, MEDLINE® Daily and MEDLINE® Epub Ahead of Print, from 1946 to 10th June 2022 via the Ovid® SP platform (Table 68)
- Embase, from 1974 to 10th June 2022 via the Ovid® SP platform (Table 69)
- The University of York's CRD platform:
    - NHS Economic Evaluation Database (EED), Issue 2 of 4, April 2015 to 8th June 2022 (Table 70)
- International Health Technology Assessment (HTA) database, to 8th June 2022 via the International Network of Agencies for Health Technology Assessment (INAHTA) website (Table 71)

MEDLINE and Embase were searched separately via the Ovid® SP platform. As multiple literature databases were searched, duplicate citations were removed.

Conference Proceedings

Conference proceedings from the following congresses were manually searched in August 2022:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – *International meetings*, 2020–2022
- ISPOR – *European meetings*, 2020–2021
- MDA Conference, 2021–2022
- World Muscle Society, 2020–2022
- WORLD Symposium, 2020–2022

Manual searches for conference abstracts were limited to those published from January 2020–June 2022, justified under the assumption that high-quality studies reported in abstract form before this time will have since been published in a peer-reviewed journal.

Search terms for each conference were devised based on the terms used in the electronic database and the specific format and requirements of each source. The search terms used for conference proceedings can be found in Table 72.

HTA and Economic Websites

To supplement the searches, websites of the following HTA bodies were searched in August 2022 to identify relevant HTAs:

- All Wales Medicines Strategy Group (AWMSG)
- National Centre for Pharmacoeconomics (NCPE)
- NICE
- Scottish Medicines Consortium (SMC)

In line with current best practice guidelines for identifying inputs relevant to cost-effectiveness modelling, a supplementary search of the following economic databases to identify health-state utility values and cost-effectiveness analyses was conducted in August 2022:

- The Cost-Effectiveness Analysis (CEA) Registry, managed by Tufts Medical Center
- The School of Health and Related Research Health Utilities Database (ScHARRHUD), University of Sheffield
- The EQ-5D Publications Database

Bibliography Searches

The bibliographies of all relevant SLRs, NMAs, economic evaluations and HTAs identified during the SLR were hand-searched to identify any additional, relevant studies for inclusion. The studies included in a previous targeted review of the clinical, economic, resource use and utility evidence for Pompe disease, conducted by Amicus in conjunction with the York Health Economics Consortium in 2020 were hand-searched, to ensure that no relevant studies were missed (York Health Economics Consortium 2020a).

Search Terms

The search terms used in the electronic databases are provided below. For all applicable searches (i.e. of databases with complex search functionality) the search terms to capture economic evaluations were based on the validated SIGN filter set (SIGN (Healthcare Improvement Scotland)); the search terms to capture health state utilities/HRQoL were adapted from filters developed by ScHARR (Papaioannou 2013) and YHEC (Arber 2016); and the search terms to capture cost/resource use studies were based on the validated SIGN filter set (SIGN (Healthcare Improvement Scotland)) and the Canadian Agency for Drugs and Technologies in Health (CADTH) search filters database (CADTH 2022).

Table 68: Search terms for MEDLINE (searched via Ovid SP)

Dates searched: 10th June 2022 **Records retrieved: 218**			
Term group	**#**	**Search terms**	**Results 10th June 2022**
Pompe disease	1	exp glycogen storage disease type II/	1,860
	2	(pompe or pompes).ti,ab,kf.	2,189
	3	((glycogen storage disease$ or glycogen storage disorder$ or gsd or glycogenos$) adj (ii or iis or "2" or 2s or two or twos)).ti,ab,kf.	168
	4	((glycogen storage disease$ or glycogen storage disorder$ or gsd or glycogenos$) adj6 (type ii or type iis or type ii or type iis or type 2 or type 2s or type2 or type2s or type two or type twos or type two or type twos or t2 or t2s or t-2 or t-2s)).ti,ab,kf.	749
	5	(gsdii or gsdiis or gsd2 or gsd2s or gsdtwo or gsdtwos).ti,ab,kf.	119
	6	((alpha$ glucosidase$ or alfa$ glucosidase or acid maltase) adj6 deficien$).ti,ab,kf.	825
	7	((alpha$ or alfa$) adj6 glucosidase$ deficien$).ti,ab,kf.	150
	8	(gaa adj6 deficien$).ti,ab,kf.	283
	9	((generali$ed or cardiomuscular or cardio-muscular or diffuse) adj6 (glycogen storage disease$ or glycogen storage disorder$ or gsd or glycogenos$)).ti,ab,kf.	108

	10	(mckusick 23230 or mckusick23230).ti,ab,kf.	1
	11	(iopd or iopds or lopd or lopds or io-pd or io-pds or lo-pd or lo-pds).ti,ab,kf.	364
	12	or/1-11	3,195
Economic evaluations	13	Economics/ or exp "Fees and Charges"/ or exp Budgets/	69,108
	14	exp Models, Economic/ or exp Cost-Benefit Analysis/ or exp "Costs and Cost Analysis"/	264,190
	15	Economics, Nursing/ or exp Economics, Medical/ or Economics, Pharmaceutical/ or exp Economics, Dental/ or exp Economics, Hospital/	50,254
	16	Markov Chains/ or Monte Carlo Method/ or Decision Theory/	45,090
	17	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or consequence$)).ti,ab,kf.	190,042
	18	((economic$ or pharmacoeconomic$ or cost$ or price$ or pricing$ or expenditure$ or financ$) adj2 (evaluat$ or model$ or analys?s or outcome$)).ti,ab,kf.	86,012
	19	(value adj2 (money or monetary)).ti,ab,kf.	2,800
	20	(economic model$ or markov or monte carlo).ti,ab,kf.	80,828
	21	(decision$ adj2 (tree or analys?s or model$)).ti,ab,kf.	28,684
	22	exp Value of Life/ or Quality-Adjusted Life Years/	20,354
	23	(quality adjusted life year$ or quality-adjusted life year$ or qaly$ or disability adjusted life year$ or disability-adjusted life year$ or daly$ or life year$ gained or life year$ equivalent$ or incremental cost effective$ or icer or qald$ or qale$ or qtime$).ti,ab,kf.	27,584
	24	or/13-23	595,390
Health state utilities/HRQoL	25	(health utilit$ or health state$1 or illness state$1 or HSUV or HSUVs or utility assessment$ or preference based or utility based).ti,ab,kf.	11,179
	26	(utility adj3 (score$1 or scoring or valu$ or measur$ or evaluat$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab,kf.	40,117
	27	utility.ab. /freq=2	21,325
	28	(utilities or disutilit$).ti,ab,kf.	8,921
	29	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf.	1,003
	30	(multiattribute$ or multi attribute$).ti,ab,kf.	1,132
	31	(euro qual or euro qual5d or euroqual or euroqual5d or euroqol or euroqol5d or euro qol or euro qol5d or eq-5d or eq5-d or eq5d or eq 5d or eq-sdq or eqsdq).ti,ab,kf.	1,4591
	32	(short form$ or shortform$).ti,ab,kf.	40,243
	33	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	25,001
	34	(sf6 or sf 6 or sf6d or sf 6d or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight or short form 6 or shortform 6 or shortform six or short form six).ti,ab,kf.	3,866
	35	(sf12 or sf 12 or sf twelve or sftwelve or short form 12 or shortform 12 or shortform twelve or short form twelve).ti,ab,kf.	7,022
	36	(sf16 or sf 16 or sf sixteen or sfsixteen or shortform 16 or short form 16 or shortform sixteen or short form sixteen).ti,ab,kf.	37
	37	(sf20 or sf 20 or sf twenty or sftwenty or short form 20 or shortform 20 or shortform twenty or short form twenty).ti,ab,kf.	435
	38	(15D or 15-D or 15 dimension or 15-dimension).ti,ab,kf.	5,852
	39	visual analog$ scale$.ti,ab,kf.	66,791
	40	(standard gamble$ or sg).ti,ab,kf.	12,909
	41	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	2,188
	42	(health$1 year$1 equivalent$1 or hye or hyes).ti,ab,kf.	84
	43	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1,808
	44	*quality of life/ and (quality of life or qol or hrqol).ti,ab,kf.	89,317
	45	quality of life/ and ((quality of life or qol or hrqol) adj (score$1 or measure$1)).ti,ab,kf.	16,964
	46	quality of life/ and health-related quality of life.ti,ab,kf.	40,616
	47	quality of life/ and ec.fs.	10,869
	48	quality of life/ and (health adj3 status).ti,ab,kf.	10,905
	49	(qol or hrqol or quality of life).ti,ab,kf.	344,827

	50	(Rasch-built Pompe-specific Activity or R-PACT or RPACT or PROMIS or Patient-Reported Outcomes Measurement Information System).ti,ab,kf.	3,364
	51	Patient report$.ti,ab,kf.	51,383
	52	or/25-51	537,132
Cost/resource use studies	53	Cost allocation/ or Cost control/ or Cost savings/ or Cost of illness/ or Cost sharing/ or "Deductibles and coinsurance"/ or Medical savings accounts/ or Health care costs/ or Direct service costs/ or Drug costs/ or Employer health costs/ or Hospital costs/ or Health expenditures/ or Capital expenditures/ or Financial management/	160,352
	54	(economic$ or pharmacoeconomic$).ti,ab,kf.	352,891
	55	((healthcare$ or health care or health-care or drug$ or medication$ or treatment$ or physician$ or nurse$ or nursing or hospital$ or illness$) adj2 cost$).ti,ab,kf.	87,111
	56	((unit adj cost$) or (low adj cost$) or (high adj cost$) or (cost adj estimate$) or (cost adj variable$)).ti,ab,kf.	104,081
	57	((resource$ or healthcare$ or health care or health-care or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).ti,ab,kf.	150,096
	58	(price$ or pricing$ or fiscal or funding or financial or finance).ti,ab,kf.	22,4470
	59	Presenteeism/ or Absenteeism/ or exp Employment/	104,254
	60	(absenteeism or presenteeism or employment or unemployment).ti,ab,kf.	8,3664
	61	((patient$ or caregiver$ or carer$ or social$ or society$ or family$ or work$) adj2 (burden$ or productiv$)).ti,ab,kf.	25,350
	62	("length of stay" or utili?ation or "economic burden" or "cost-of-illness" or nursing cost$ or physician cost$ or physician visit$ or "out of pocket").ti,ab,kf.	331,103
	63	or/53-62	1,271,687
Exclusion terms	64	exp animals/ not exp humans/	5,015,361
	65	(comment or editorial or historical article).pt.	1,732,888
	66	or/64-65	6,690,822
Combined	67	12 and (24 or 52 or 63)	228
	68	67 not 66	219

Databases: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to 10th June 2022

Table 69: Search terms for Embase (searched via Ovid SP)

Dates searched: 10th June 2022 Records retrieved: 473			
Term group	#	Search terms	Results 10th June 2022
Pompe disease	1	exp glycogen storage disease type II/	4,670
	2	(pompe or pompes).ti,ab,kw,dq.	3,819
	3	((glycogen storage disease$ or glycogen storage disorder$ or gsd or glycogenos$) adj (ii or iis or "2" or 2s or two or twos)).ti,ab,kw,dq.	247
	4	((glycogen storage disease$ or glycogen storage disorder$ or gsd or glycogenos$) adj6 (type ii or type iis or typeii or typeiis or type 2 or type 2s or type2 or type2s or type two or type twos or typetwo or typetwos or t2 or t2s or t-2 or t-2s)).ti,ab,kw,dq.	906
	5	(gsdii or gsdiis or gsd2 or gsd2s or gsdtwo or gsdtwos).ti,ab,kw,dq.	177
	6	((alpha$ glucosidase$ or alfa$ glucosidase or acid maltase) adj6 deficien$).ti,ab,kw,dq.	1,297
	7	((alpha$ or alfa$) adj6 glucosidase$ deficien$).ti,ab,kw,dq.	229
	8	(gaa adj6 deficien$).ti,ab,kw,dq.	592
	9	((generalized or generalised or cardiomuscular or cardio-muscular or diffuse) adj6 (glycogen storage disease$ or glycogen storage disorder$ or gsd or glycogenos$)).ti,ab,kw,dq.	80
	10	(mckusick 23230 or mckusick23230).ti,ab,kw,dq.	1
	11	(iopd or iopds or lopd or lopds or io-pd or io-pds or lo-pd or lo-pds).ti,ab,kw,dq	754
	12	or/1-11	5,736
Economic evaluations	13	economics/ or exp health economics/ or exp budget/	1,111,342
	14	exp economic model/ or exp economic evaluation/	336,040
	15	economics, nursing/ or economics, medical/ or economics, pharmaceutical/ or economics, dental/ or exp economics, hospital/ or economic aspect/	1,044,643
	16	Markov chains/ or monte carlo method/ or exp decision theory/	55,389

	17	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or consequence$)).ti,ab,kf.	258,942
	18	((economic$ or pharmacoeconomic$ or cost$ or price$ or pricing$ or expenditure$ or financ$) adj2 (evaluat$ or model$ or analys?s or outcome$)).ti,ab,kf.	130,090
	19	(value adj2 (money or monetary)).ti,ab,kf.	3,765
	20	(economic model$ or markov or monte carlo).ti,ab,kf.	91,734
	21	(decision$ adj2 (tree or analys?s or model$)).ti,ab,kf.	39,736
	22	exp socioeconomics/ or quality adjusted life year/	484,634
	23	(quality adjusted life year$ or quality-adjusted life year$ or qaly$ or disability adjusted life year$ or disability-adjusted life year$ or daly$ or life year$ gained or life year$ equivalent$ or incremental cost effective$ or icer or qald$ or qale$ or qtime$).ti,ab,kf.	43,885
	24	or/13-23	1,795,933
Health state utilities/HRQoL	25	(health utilit$ or health state$1 or illness state$1 or HSUV or HSUVs or utility assessment$ or preference based or utility based).ti,ab,kf.	18,634
	26	(utility adj3 (score$1 or scoring or valu$ or measur$ or evaluat$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab,kf.	61,383
	27	utility.ab. /freq=2	32,969
	28	(utilities or disutilit$).ti,ab,kf.	14,452
	29	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf.	1,535
	30	(multiattribute$ or multi attribute$).ti,ab,kf.	1,368
	31	(euro qual or euro qual5d or euroqual or euroqual5d or euroqol or euroqol5d or euro qol or euro qol5d or eq-5d or eq5-d or eq5d or eq 5d or eq-sdq or eqsdq).ti,ab,kf.	26,352
	32	(short form$ or shortform$).ti,ab,kf.	54,563
	33	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	42,790
	34	(sf6 or sf 6 or sf6d or sf 6d or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight or short form 6 or shortform 6 or shortform six or short form six).ti,ab,kf.	5,251
	35	(sf12 or sf 12 or sf twelve or sftwelve or short form 12 or shortform 12 or shortform twelve or short form twelve).ti,ab,kf.	11,174
	36	(sf16 or sf 16 or sf sixteen or sfsixteen or shortform 16 or short form 16 or shortform sixteen or short form sixteen).ti,ab,kf.	64
	37	(sf20 or sf 20 or sf twenty or sftwenty or short form 20 or shortform 20 or shortform twenty or short form twenty).ti,ab,kf.	492
	38	(15D or 15-D or 15 dimension or 15-dimension).ti,ab,kf.	7,315
	39	visual analog$ scale$.ti,ab,kf.	94,143
	40	(standard gamble$ or sg).ti,ab,kf.	19,023
	41	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	3,215
	42	(health$1 year$1 equivalent$1 or hye or hyes).ti,ab,kf.	171
	43	(hui or hui1 or hui2 or hui3).ti,ab,kf.	2,789
	44	*quality of life/ and (quality of life or qol or hrqol).ti,ab,kf.	115,675
	45	quality of life/ and ((quality of life or qol or hrqol) adj (score$1 or measure$1)).ti,ab,kf.	34,815
	46	quality of life/ and health-related quality of life.ti,ab,kf.	70,170
	47	quality of life/ and ec.fs.	52,295
	48	quality of life/ and (health adj3 status).ti,ab,kf.	18,989
	49	(qol or hrqol or quality of life).ti,ab,kf.	549,172
	50	(Rasch-built Pompe-specific Activity or R-PACT or RPACT or PROMIS or Patient-Reported Outcomes Measurement Information System).ti,ab,kf.	6,592
	51	Patient report$.ti,ab,kf.	89,277
	52	or/25-51	850,065
Cost/resource use studies	53	cost control/ or cost of illness/ or health care cost/ or health care financing/ or drug cost/ or hospital cost/ or hospital finance/ or financial management/	469,198
	54	(economic$ or pharmacoeconomic$).ti,ab,kf.	421,598
	55	((healthcare$ or health care or health-care or drug$ or medication$ or treatment$ or physician$ or nurse$ or nursing or hospital$ or illness$) adj2 cost$).ti,ab,kf.	140,277

	56	((unit adj cost$) or (low adj cost$) or (high adj cost$) or (cost adj estimate$) or (cost adj variable$)).ti,ab,kf.	124,976
	57	((resource$ or healthcare$ or health care or health-care or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).ti,ab,kf.	206,480
	58	(price$ or pricing$ or fiscal or funding or financial or finance).ti,ab,kf.	315,987
	59	Presenteeism/ or Absenteeism/ or exp Employment/	130,769
	60	(absenteeism or presenteeism or employment or unemployment).ti,ab,kf.	109,537
	61	("length of stay" or utili?ation or "economic burden" or "cost-of-illness" or nursing cost$ or physician cost$ or physician visit$ or "out of pocket").ti,ab,kf.	480,478
	62	((patient$ or caregiver$ or carer$ or social$ or society$ or family$ or work$) adj2 (burden$ or productiv$)).ti,ab,kf.	41,860
	63	or/53-62	1,813,791
Exclusion terms	64	("conference abstract" or "conference review").pt.	4,434,477
	65	limit 64 to yr="1974-2019"	3,825,475
	66	exp animals/ not exp humans/	4,964,069
	67	editorial.pt.	728,606
	68	editorial/	701,152
	69	or/65-68	9,182,148
Combined	70	12 and (24 or 52 or 63)	701
	71	70 not 69	473

Database: Embase 1974 to 2022 10th June 2022

Table 70: Search terms for NHS EED (via the University of York CRD)

Dates searched: 8th June 2022 **Records retrieved: 2**			
Term group	**#**	**Search terms**	**Results 8th June 2022**
Pompe disease	1	MeSH DESCRIPTOR Glycogen Storage Disease Type II EXPLODE ALL TREES	7
	2	(pompe OR pompes)	16
	3	((glycogen storage disease* OR glycogen storage disorder* OR gsd OR glycogenos*) NEAR1 (ii OR iis OR 2 OR 2s OR two OR twos))	9
	4	((ii OR iis OR 2 OR 2s OR two OR twos) NEAR1 (glycogen storage disease* OR glycogen storage disorder* OR gsd OR glycogenos*))	0
	5	((glycogen storage disease* OR glycogen storage disorder* OR gsd OR glycogenos*) NEAR6 (type ii OR type iis OR typeii OR typeiis OR type 2 OR type 2s OR type2 OR type2s OR type two OR type twos OR typetwo OR typetwos OR t2 OR t2s OR t-2 OR t-2s))	9
	6	((type ii OR type iis OR typeii OR typeiis OR type 2 OR type 2s OR type2 OR type2s OR type two OR type twos OR typetwo OR typetwos OR t2 OR t2s OR t-2 OR t-2s) NEAR6 (glycogen storage disease* OR glycogen storage disorder* OR gsd OR glycogenos*))	0
	7	(gsdii OR gsdiis OR gsd2 OR gsd2s OR gsdtwo OR gsdtwos)	0
	8	((alpha* glucosidase* OR alfa* glucosidase OR acid maltase) NEAR6 deficien*)	0
	9	(deficien* NEAR6 (alpha* glucosidase* OR alfa* glucosidase OR acid maltase))	0
	10	((alpha* OR alfa*) NEAR6 glucosidase* deficien*)	0
	11	(glucosidase* deficien* NEAR6 (alpha* OR alfa*))	0
	12	(gaa NEAR6 deficien*)	0
	13	(deficien* NEAR6 gaa)	0
	14	((generalized OR generalised OR cardiomuscular OR cardio-muscular OR diffuse) NEAR6 (glycogen storage disease* OR glycogen storage disorder* OR gsd OR glycogenos*))	0
	15	((glycogen storage disease* OR glycogen storage disorder* OR gsd OR glycogenos*) NEAR6 (generalized OR generalised OR cardiomuscular OR cardio-muscular OR diffuse))	0
	16	(mckusick 23230 OR mckusick23230)	0
	17	(iopd OR iopds OR lopd OR lopds OR io-pd OR io-pds OR lo-pd OR lo-pds)	0
	18	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)	18
Database		(#18) IN NHSEED	2

Database: NHS EED: Issue 2 of 4, April 2015 to 8th June 2022

Table 71: Search terms for the international HTA database (via INAHTA)

Dates searched: 8th June 2022 Records retrieved: 12			
Term group	**#**	**Search terms**	**Results 8th June 2022**
Pompe disease	1	"glycogen storage disease type II"[mhe]	4
	2	(pompe OR pompes)	7
	3	((glycogen storage disease* OR glycogen storage disorder* OR gsd OR glycogenos*) NEAR1 (ii OR iis OR 2 OR 2s OR two OR twos))	0
	4	((ii OR iis OR 2 OR 2s OR two OR twos) NEAR1 (glycogen storage disease* OR glycogen storage disorder* OR gsd OR glycogenos*))	0
	5	((glycogen storage disease* OR glycogen storage disorder* OR gsd OR glycogenos*) NEAR6 (type ii OR type iis OR typeii OR typeiis OR type 2 OR type 2s OR type2 OR type2s OR type two OR type twos OR typetwo OR typetwos OR t2 OR t2s OR t-2 OR t-2s))	0
	6	((type ii OR type iis OR typeii OR typeiis OR type 2 OR type 2s OR type2 OR type2s OR type two OR type twos OR typetwo OR typetwos OR t2 OR t2s OR t-2 OR t-2s) NEAR6 (glycogen storage disease* OR glycogen storage disorder* OR gsd OR glycogenos*))	0
	7	(gsdii OR gsdiis OR gsd2 OR gsd2s OR gsdtwo OR gsdtwos)	0
	8	((alpha* glucosidase* OR alfa* glucosidase OR acid maltase) NEAR6 deficien*)	0
	9	(deficien* NEAR6 (alpha* glucosidase* OR alfa* glucosidase OR acid maltase))	0
	10	((alpha* OR alfa*) NEAR6 glucosidase* deficien*)	0
	11	(glucosidase* deficien* NEAR6 (alpha* OR alfa*))	0
	12	(gaa NEAR6 deficien*)	0
	13	(deficien* NEAR6 gaa)	0
	14	((generalized OR generalised OR cardiomuscular OR cardio-muscular OR diffuse) NEAR6 (glycogen storage disease* OR glycogen storage disorder* OR gsd OR glycogenos*))	0
	15	((glycogen storage disease* OR glycogen storage disorder* OR gsd OR glycogenos*) NEAR6 (generalized OR generalised OR cardiomuscular OR cardio-muscular OR diffuse))	0
	16	(mckusick 23230 OR mckusick23230)	0
	17	(iopd OR iopds OR lopd OR lopds OR io-pd OR io-pds OR lo-pd OR lo-pds)	4
	18	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)	12

Database: INAHTA up to 8th June 2022

Table 72: Search terms and results of congress searching

Congress	Link	Search strategy	Search terms	Results
ISPOR International	https://www.ispor.org/heor-resources/presentations-database/search	Each international meeting for the years 2020-2022 in turn was selected; all diseases/disorders and all topics were selected; each search term was searched in turn as a keyword using the search bar; abstracts were reviewed for relevance	Pompe	• 2022: 1 result, 0 included • 2021: 2 results, 0 included • 2020: 0 results
			Glycogen storage	• 2022: 3 results, 0 included • 2021: 2 results, 0 included • 2020: 1 result, 0 included
			Acid maltase deficiency	• 2022: 0 results • 2021: 0 results • 2020: 0 results
ISPOR EU	https://www.ispor.org/heor-resources/presentations-database/search	Each European meeting for the years 2020-2022 in turn was selected; all diseases/disorders and all topics were selected; each search term was searched in turn as a keyword using the search bar; abstracts were reviewed for relevance	Pompe	• 2021: 2 results, 0 included • 2020: 1 result, 0 included
			Glycogen storage	• 2021: 1 result, 0 included • 2020: 1 result, 0 included
			Acid maltase deficiency	• 2021: 0 results • 2020: 0 results
MDA	https://www.mdaconference.org/abstracts/202	With any abstract topic selected, each search term was searched in turn as a title/keyword; abstracts were reviewed for relevance	Pompe	• 2022: 5 results, 0 included • 2021: 3 results, 0 included
			Glycogen storage	• 2022: 1 result, 0 included • 2021: 2 results, 0 included

	2-abstract-library/		Acid maltase deficiency	• 2022: 9 results, 0 included • 2021: 17 results, 0 included
World Muscle Society	https://www.worldmusclesociety.org/page/past-world-muscle-society-congresses	Abstract books were searched using each search term in turn with the control + F function in Adobe; abstracts were reviewed for relevance	Pompe	• 2021: 8 results, 1 included • 2020: 8 results, 0 included
			Glycogen storage	• 2021: 0 results • 2020: 0 results
			Acid maltase deficiency	• 2021: 0 results • 2021: 0 results
WORLD Symposium	https://www.sciencedirect.com/search.com/search	Each search term in turn was searched in the 'Molecular Genetics and Metabolism' Journal: • 2022: Volume 135; Issue 2 • 2021: Volume 134; Issue 2 • 2020: Volume 129; Issue 2 Abstracts were reviewed for relevance	Pompe	• 2022: 59 results, 0 included • 2021: 35 results, 0 included • 2020: 49 results, 0 included
			Glycogen storage	• 2022: 10 results, 0 included • 2021: 9 results, 0 included • 2020: 8 results, 0 included
			Acid maltase deficiency	• 2022: 0 results • 2021: 1 result, 0 included • 2020: 1 result, 0 included
All	-	-	-	• **Total hits: 239** • **Total included: 0**

Notes: Congress searches performed between 3rd-5th August 2022.
Abbreviations: EU, European Union; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; MDA, Muscular Dystrophy Association; N/A: not applicable.

Table 73: Search terms and results of HTA website searching

Source	Link	Search strategy	Search terms	Results
AWMSG	http://www.awmsg.org/	Using the search bar, each search term in turn was searched; all records were reviewed for relevance	Pompe	2 results, 0 included
			Glycogen storage	6 results, 0 included
			Acid maltase deficiency	67 results, 0 included
NCPE	http://www.ncpe.ie/	Using the search bar, each search term in turn was searched; all records were reviewed for relevance	Pompe	0 results
			Glycogen storage	0 results
			Acid maltase deficiency	0 results
NICE	https://www.nice.org.uk/	Using the search bar, each search term in turn was searched, limited in the guidance category to "Guidance" AND "NICE Advice"; all records were reviewed for relevance	Pompe	2 results, 0 included
			Glycogen storage	1 result, 0 included
			Acid maltase deficiency	0 results
SMC	https://www.scottishmedicines.org.uk/Home	Using the search bar, each search term in turn was searched; all records were reviewed for relevance	Pompe	1 result, 1 included
			Glycogen storage	0 results
			Acid maltase deficiency	0 results
All	-		-	**Total hits: 79** **Total included: 1**

Abbreviations: AWMSG: All Wales Medicines Strategy Group; N/A: not applicable; NCPE: National Centre for Pharmacoeconomics; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium.

Table 74: Search terms and results of economic website searching

Source	Link	Search strategy	Search terms	Results 4th August 2022
The CEA Registry, managed by Tufts Medical Center	http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/search.aspx	Using the search bar, each search term in turn was searched, with Methods, Ratios and Utility Weights selected in turn; abstracts were reviewed for relevance	Pompe	23 results, 0 included
			Glycogen storage	0 results
			Acid maltase deficiency	1 result, 0 included

The EQ-5D Publications Database	http://eq-5dpublications.euroqol.org/?noheader=true	Using the advanced search function, the search terms were combined with each of the following economic terms in turn and searched in the abstract: • Cost • Economic • Utility • Utilities • Quality of life • Resource Abstracts were reviewed for relevance	Pompe	0 results
			Glycogen storage	0 results
			Acid maltase deficiency	0 results
ScHARRHUD, University of Sheffield	http://www.scharrhud.org/	Using the search function each search term in turn was searched in the abstract; abstracts were reviewed for relevance	Pompe	2 results, 0 included
			Glycogen storage	0 results
			Acid maltase deficiency	0 results
All	-	-	-	**Total hits: 26** **Total included: 0**

Abbreviations: CEA: Cost-effectiveness Analysis; EQ-5D: EuroQoL 5 dimensions; ScHARRHUD: School of Health and Related Research Health Utilities Database.

Study Selection Process

The eligibility criteria presented here are specific to the HRQoL and utility evidence stream (see Table 75).

Table 75: Eligibility criteria for the HRQoL/utility studies

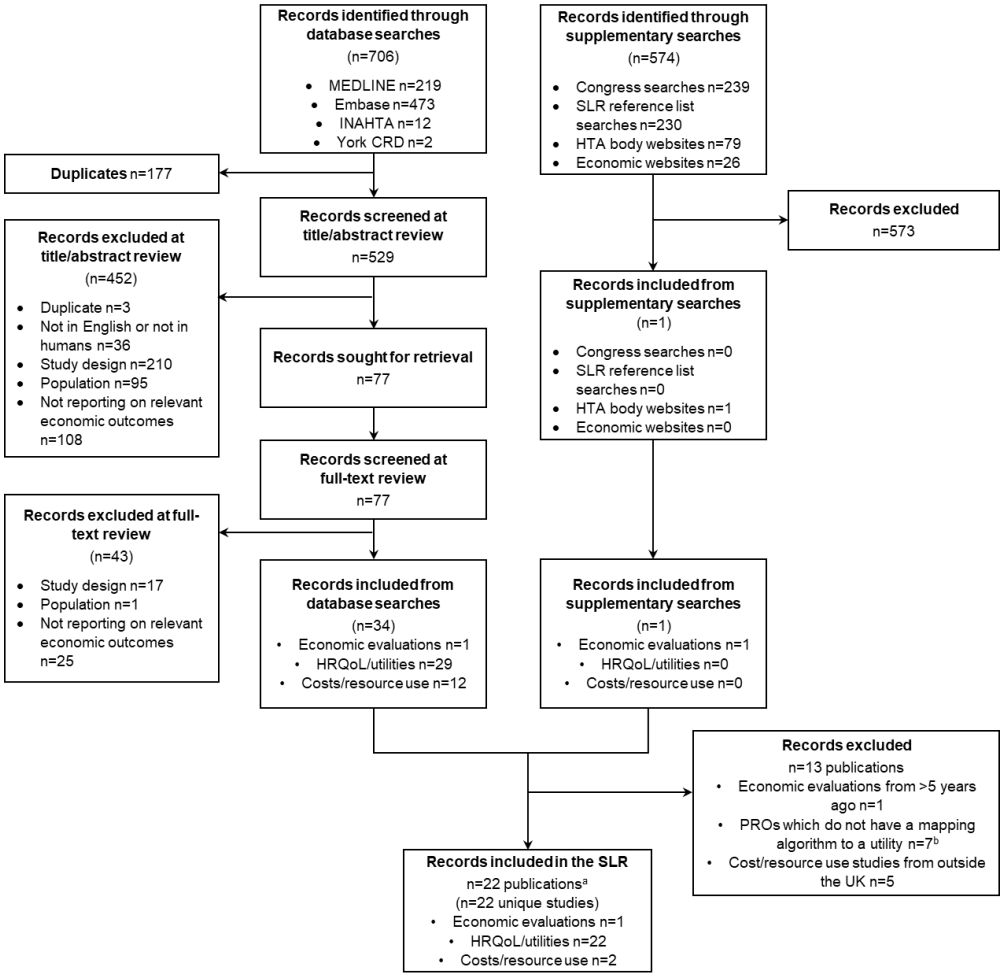
Category	Inclusion Criteria	Exclusion Criteria
Population	• Adults (≥18 years of age) with Pompe disease[a] • Caregivers/family of patients with Pompe disease	• Children (<18 years of age) with Pompe disease[b] • Adults and/or children who do not have Pompe disease
Intervention	Any or none	N/A
Comparators	Any or none	N/A
Outcomes	Health state utility or HRQoL data if measured using a PRO that has a mapping algorithm to a utility, to include[c]: • EQ-5D-5L • SF-36 • SF-6D • SF-12 • PROMIS • St George's Respiratory Questionnaire • Hospital anxiety and Depression scale • PHQ-9 • Nottingham Health Profile • EQ-VAS • R-Pact[d]	Studies not presenting relevant outcomes for the population of interest Studies reporting on PROs that do not have a mapping algorithm to a utility, to include: • CarerQoL • Fatigue Severity Scale • Individualised Neuromuscular QoL questionnaire • MRC-Dyspnoea • PROMIS-GI • Pain detect questionnaire • Rotterdam handicap scale • WHO QoL scale • Brief pain inventory
Study design	• Any original research study	N/A
Publication type	• Peer-reviewed journal articles presenting original research studies including economic evaluations • SLRs[e] • HTAs • Congress abstracts published in or since 2020 • Letters (if they report primary research) • Case studies/reports	• Articles that do not present any original research e.g. narrative reviews, guidelines, commentaries or opinion pieces, editorials • Conference abstracts published before 2020 • Book chapters
Language	• English language	• Studies published in a language other than English[f]
Other	• Any geographic location • Human subjects	• *In vitro*/preclinical studies/animal studies

Note: [a]The population of this SLR was selected to be more inclusive than the population described in the decision problem to ensure that no relevant publications were missed. [b]Studies which reported mixed populations of adults and children with Pompe disease were included if results for adults with Pompe disease were reported separately. [c]Although all HRQoL data were included in the search strategy, HRQoL data most relevant to the

submission were adjusted post-hoc. Therefore, studies investigating PROs that did not have a mapping algorithm to a utility were not eligible for inclusion. Identification of PROs that had a mapping algorithm to a utility was based on a 2018 SLR (Dakin 2018) [d]Records reporting on HRQoL results for the Pompe disease-specific PRO, the Rasch-built Pompe-specific activity (R-Pact) scale, were included in the HRQoL/utilities stream, despite there not being a mapping algorithm to map R-Pact to a utility. This was decided due to the R-Pact's disease-specific nature which was considered of particular value to the SLR. [e]SLRs of relevant primary publications were considered relevant at the title/abstract review stage and hand searched for relevant primary studies but were excluded during the full text review stage unless they presented primary research. [f]Studies with an abstract in English but a full text in a language other than English were screened, and data were extracted, based on the abstract.
Abbreviations: EQ-5D-5L: EuroQol-5-Dimensions 5-Level; HRQoL: health-related quality of life; HTA, health technology assessment; HUI3: Health Utilities Index Mark 3; N/A: not applicable; PROMIS: Patient-Reported Outcomes Measurement Information System; R-Pact: Rasch-built Pompe-specific Activity; SF-36: 36-Item Short-Form Health Survey; SLR, systematic literature review.

The PRISMA flow diagram for the SLR is presented in Figure 31.

Figure 31: PRISMA diagram of studies identified in the SLR



Note: [a]Several records were relevant to multiple streams and therefore the total number of records is not equal to the sum of records included in each individual stream. [b]All PROs which did not have a mapping algorithm to a utility were excluded from the study. However, records reporting on HRQoL results for the Pompe disease-specific PRO, the Rasch-built Pompe-specific activity (R-Pact) scale, were included in the HRQoL/utilities stream, despite there not being a mapping algorithm to map R-Pact to a utility. This was decided due to the R-Pact's disease-specific nature which was considered of particular value to the SLR.
Abbreviations: CRD: Centre for Reviews and Dissemination; HRQoL: health-related quality of life; HTA: health technology assessment; INAHTA: International Network of Agencies for Health Technology Assessment; PROs: patient-reported outcomes; R-Pact scale: Rasch-built Pompe-specific activity SLR: systematic literature review; UK: United Kingdom.

A total of 706 records were retrieved from the electronic databases, of which 177 were duplicates, resulting in 529 novel records that were screened at the title/abstract review stage. Subsequently, 77 full publications were screened against the HRQoL/utility eligibility criteria at full text review, with 22 articles ultimately meeting the inclusion criteria. No additional articles were retrieved from supplementary searches, resulting in a total of 22 articles reporting on 22 unique studies included in the HRQoL/utility stream of the SLR.

A full list of studies included in the HRQoL/utility stream of the SLR is presented in Table 76.

Table 76: HRQoL/utility studies included in the economic SLR

#	Study name	Reference
1	Aslan 2016	Aslan, GK; Huseyinsinoglu, BE; Oflazer, P et al. Inspiratory Muscle Training in Late-Onset Pompe Disease: The Effects on Pulmonary Function Tests, Quality of Life, and Sleep Quality. Lung. 2016;194(4):555-561.
2	Boentert 2016	Boentert, M; Drager, B; Glatz, C et al. Sleep-disordered breathing and effects of noninvasive ventilation in patients with late-onset pompe disease. Journal of Clinical Sleep Medicine. 2016;12(12):1623-1632.
3	Boentert 2015	Boentert, M; Karabul, N; Wenninger, S et al. Sleep-related symptoms and sleep-disordered breathing in adult Pompe disease. European Journal of Neurology. 2015;22(2):369-376.
4	Favejee 2015	Favejee, MM; van den Berg, LE; Kruijshaar, ME et al. Exercise training in adults with Pompe disease: the effects on pain, fatigue, and functioning. Arch Phys Med Rehabil. 2015;96(5):817-822.
5	Gungor 2016	Gungor, D; Kruijshaar, ME; Plug, I et al. Quality of life and participation in daily life of adults with Pompe disease receiving enzyme replacement therapy: 10 years of international follow-up. Journal of Inherited Metabolic Disease. 2016;39(2):253-260.
6	Gungor 2013	Gungor, D; Schober, AK; Kruijshaar, ME et al. Pain in adult patients with Pompe disease: A cross-sectional survey. Molecular Genetics and Metabolism. 2013;109(4):371-376.
7	Hagemans 2004	Hagemans, ML; Janssens, AC; Winkel, LP et al. Late-onset Pompe disease primarily affects quality of life in physical health domains. Neurology. 2004;63(9):1688-1692.
8	Harfouche 2020	Harfouche, M; Kishnani, PS; Krusinska, E et al. Use of the patient-reported outcomes measurement information system (PROMIS R) to assess late-onset Pompe disease severity. J. 2020;4(1):83.
9	Hu 2021	Hu, J; Zhu, L; He, J et al. The usage of enzyme replacement treatments, economic burden, and quality of life of patients with four lysosomal storage diseases in Shanghai, China. Intractable and Rare Diseases Research. 2021;10(3):190-197.
10	Jones 2020	Jones, HN; Kuchibhatla, M; Crisp, KD et al. Respiratory muscle training in late-onset Pompe disease: Results of a sham-controlled clinical trial. Neuromuscular Disorders. 2020;30(11):904-914.
11	Kanters 2011	Kanters, TA; Hagemans, ML; van der Beek, NA et al. Burden of illness of Pompe disease in patients only receiving supportive care. Journal of Inherited Metabolic Disease. 2011;34(5):1045-1052.
12	Kanters 2015a	Kanters, TA; Redekop, WK; Kruijshaar, ME et al. Comparison of EQ-5D and SF-6D utilities in Pompe disease. Quality of Life Research. 2015;24(4):837-844.
13	Kanters 2015b	Kanters, TA; Redekop, WK; Rutten-Van Molken, MP et al. A conceptual disease model for adult Pompe disease. Orphanet Journal Of Rare Diseases. 2015;10:112.
14	Kanters 2017	Kanters, TA; van der Ploeg, AT; Kruijshaar, ME et al. Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in adult patients with Pompe disease. Orphanet Journal Of Rare Diseases. 2017;12(1):179.
15	Kuperus 2017	Kuperus, E; Kruijshaar, ME; Wens, SCA et al. Long-term benefit of enzyme replacement therapy in Pompe disease: A 5-year prospective study. Neurology. 2017;89(23):2365-2373.
16	Kuperus 2018	Kuperus, E; van der Meijden, JC; In 't Groen, SLM et al. The ACE I/D polymorphism does not explain heterogeneity of natural course and response to enzyme replacement therapy in Pompe disease. PloS ONE. 2018;13(12):e0208854.
17	Malottki 2022	Malottki, K; Wilson, K; Fournier, M et al. POSA272 Using Real World Evidence to Characterise Utility in Patients with a Rare Disease: Analysis of Pompe Registry Data. Value in Health. 2022;25(1 Supplement):S173.
18	Pollissard 2021	Pollissard, L; DasMahapatra, P; Baranowski, E et al. POMPE DISEASE: EP.203 Mobility, usual activities and EQ-5D visual analogue score improvement with avalglucosidase alfa in Late-onset Pompe disease during the COMET trial. Neuromuscular Disorders. 2021;31(Supplement 1):S111.
19	Sechi 2020	Sechi, A; Zuccarelli, L; Grassi, B et al. Exercise training alone or in combination with high-protein diet in patients with late onset Pompe disease: Results of a cross over study. Orphanet Journal of Rare Diseases. 2020;15(1) (no pagination).
20	Simon 2019	Simon, NJ; Richardson, J; Ahmad, A et al. Health utilities and parental quality of life effects for three rare conditions tested in newborns. J. 2019;3(1):4.
21	Vaeggemose 2021	Vaeggemose, M; Mencagli, RA; Hansen, JS et al. Function, structure and quality of striated muscles in the lower extremities in patients with late onset Pompe Disease – An MRI study. Peerj. 2021;9 (no pagination).
22	Wyatt 2012	Wyatt, K; Henley, W; Anderson, L et al. The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: A longitudinal cohort study of people with lysosomal storage disorders. Health Technology Assessment. 2012;16(39):1-566.

Quality assessment and generalizability of estimates

The quality of all included economic evaluations was assessed using the Drummond checklist (Drummond 2015), which was completed by one individual and verified by another individual. Critical appraisals of cost, resource use and utility studies were not conducted, in line with NICE requirements.

Unpublished data

The unpublished data used in this submission are all sourced from the PROPEL study clinical trials.

Appendix I – Mapping of HRQoL data

The HRQoL estimates used in the analysis is presented in detail in section 8.4.

Appendix J – Probabilistic sensitivity analyses

The detailed values for the PSA are described in Table 77 Detailed probabilistic sensitivity analysis values below.

Table 77 Detailed probabilistic sensitivity analysis values

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
General						
Patient age	47	1.197	Normal	N/A	N/A	E14
Patient weight	75	1.670	Normal	N/A	N/A	E15
Patient height	171	0.905	Normal	N/A	N/A	E16
Baseline 6MWT (overall): No correlation	356	12.356	Normal	N/A	N/A	E17
Baseline 6MWT (ERT-experienced): No correlation	343	13.764	Normal	N/A	N/A	E18
Baseline 6MWT (ERT- naïve): No correlation	398	25.844	Normal	N/A	N/A	E19
Baseline 6MWT (overall): Correlation	356	12.356	Normal	N/A	N/A	E20
Baseline 6MWT (ERT-experienced): Correlation	351	13.764	Normal	N/A	N/A	E21

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
Baseline 6MWT (ERT- naïve): Correlation	370	25.844	Normal	N/A	N/A	E22
Baseline sitting %pred FVC (overall)	70.5%	0.022	Normal	N/A	N/A	E23
Baseline sitting %pred FVC (ERT-experienced)	67.7%	0.024	Normal	N/A	N/A	E24
Baseline sitting %pred FVC (ERT-naïve)	80.0%	0.042	Normal	N/A	N/A	E25
Effectiveness (6MWT): ITC						
6MWT: Alglucosidase alfa: initial change from baseline (relative to cipaglucosidase alfa)	-16.29	3.754	Normal	N/A	N/A	E27
6MWT: Alglucosidase alfa: subsequent % change from baseline	-2.3%	0.003	Normal	N/A	N/A	E28
6MWT: Cipaglucosidase alfa w. miglustat: initial change from baseline	20.79	4.639	Normal	N/A	N/A	E29
6MWT: BSC: initial change from baseline (relative to cipaglucosidase alfa)	-30.88	8.275	Normal	N/A	N/A	E31

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
Effectiveness (FVC): ITC				N/A	N/A	E32
FVC: Alglucosidase alfa: initial change from baseline (relative to cipaglucosidase alfa)	-3.1%	0.009	Normal	N/A	N/A	E33
FVC: Alglucosidase alfa: subsequent % change from baseline	-0.9%	0.001	Normal	N/A	N/A	E34
FVC: Cipaglucosidase alfa w. miglustat: initial change from baseline	-0.9%	0.007	Normal	N/A	N/A	E35
FVC: BSC: initial change from baseline (relative to cipaglucosidase alfa)	-5.5%	0.008	Normal	N/A	N/A	E37
Effectiveness (6MWT): CT						
6MWT: Alglucosidase alfa: change from baseline to year 1	7.24	6.621	Normal	N/A	N/A	E39
6MWT: Alglucosidase alfa: change from year 1 to year 2	1.4%	0.003	Normal	N/A	N/A	E40
6MWT: Alglucosidase alfa: change from year 2 to year 3	-2.3%	0.003	Normal	N/A	N/A	E41

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
6MWT: Alglucosidase alfa: change from year 3 to year 4	-2.3%	0.003	Normal	N/A	N/A	E42
6MWT: Cipaglucosidase alfa w. miglustat: change from baseline to year 1 (phase two)	20.79	4.639	Normal	N/A	N/A	E43
6MWT: Cipaglucosidase alfa w. miglustat: change from year 1 to year 2 (phase two)	12.68	16.677	Normal	N/A	N/A	E44
6MWT: Cipaglucosidase alfa w. miglustat: change from year 2 to year 3 (phase two)	-14.08	23.464	Normal	N/A	N/A	E45
6MWT: Cipaglucosidase alfa w. miglustat: change from year 3 to year 4 (phase two)	10.22	30.669	Normal	N/A	N/A	E46
6MWT: Cipaglucosidase alfa w. miglustat: change from baseline to year 1 (propel)	20.79	4.639	Normal	N/A	N/A	E47
6MWT: Cipaglucosidase alfa w. miglustat: change from year 1 to year 2 (propel)	-0.28	8.330	Normal	N/A	N/A	E48
6MWT: Cipaglucosidase alfa w. miglustat: change from year 2 to year 3 (propel)	-0.02	0.003	Normal	N/A	N/A	E49

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
6MWT: Cipaglucosidase alfa w. miglustat: change from year 3 to year 4 (propel)	-0.02	0.003	Normal	N/A	N/A	E50
6MWT: BSC: change from baseline to year 1	-2.99	10.913	Normal	N/A	N/A	E55
6MWT: BSC: change from year 1 to year 2	-2.99	10.913	Normal	N/A	N/A	E56
6MWT: BSC: change from year 2 to year 3	-2.99	10.913	Normal	N/A	N/A	E57
6MWT: BSC: change from year 3 to year 4	-2.99	10.913	Normal	N/A	N/A	E58
Effectiveness (FVC): CT						
FVC: Alglucosidase alfa: change from baseline to year 1	-4.0%	0.008	Normal	N/A	N/A	E60
FVC: Alglucosidase alfa: change from year 1 to year 2	-0.9%	0.001	Normal	N/A	N/A	E61
FVC: Alglucosidase alfa: change from year 2 to year 3	-0.9%	0.001	Normal	N/A	N/A	E62
FVC: Alglucosidase alfa: change from year 3 to year 4	-0.9%	0.001	Normal	N/A	N/A	E63

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
FVC: Cipaglucosidase alfa w. miglustat: change from baseline to year 1 (phase two)	-0.9%	0.007	Normal	N/A	N/A	E64
FVC: Cipaglucosidase alfa w. miglustat: change from year 1 to year 2 (phase two)	3.4%	0.022	Normal	N/A	N/A	E65
FVC: Cipaglucosidase alfa w. miglustat: change from year 2 to year 3 (phase two)	-0.4%	0.019	Normal	N/A	N/A	E66
FVC: Cipaglucosidase alfa w. miglustat: change from year 3 to year 4 (phase two)	1.6%	0.025	Normal	N/A	N/A	E67
FVC: Cipaglucosidase alfa w. miglustat: change from baseline to year 1 (propel)	-0.9%	0.007	Normal	N/A	N/A	E68
FVC: Cipaglucosidase alfa w. miglustat: change from year 1 to year 2 (propel)	-0.5%	0.012	Normal	N/A	N/A	E69
FVC: Cipaglucosidase alfa w. miglustat: change from year 2 to year 3 (propel)	-0.8%	0.001	Normal	N/A	N/A	E70

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
FVC: Cipaglucosidase alfa w. miglustat: change from year 3 to year 4 (propel)	-0.8%	0.001	Normal	N/A	N/A	E71
FVC: BSC: initial change from baseline	-2.2%	0.010	Normal	N/A	N/A	E76
FVC: BSC: change from year 1 to year 2	-2.2%	0.010	Normal	N/A	N/A	E77
FVC: BSC: change from year 2 to year 3	-2.2%	0.010	Normal	N/A	N/A	E78
FVC: BSC: change from year 3 to year 4	-2.2%	0.010	Normal	N/A	N/A	E79
Relative risk of mortality						
Intermittent mobility support	2.87	0.547	Lognormal	N/A	N/A	E81
Wheelchair dependent	2.87	0.547	Lognormal	N/A	N/A	E82
Intermittent respiratory support	2.05	0.610	Lognormal	N/A	N/A	E83
Intermittent mobility support and intermittent respiratory support	5.32	0.439	Lognormal	N/A	N/A	E84

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
Intermittent respiratory support and wheelchair dependent	5.32	0.439	Lognormal	N/A	N/A	E85
Wheelchair and respiratory support dependent (non-invasive ventilation)	5.32	0.439	Lognormal	N/A	N/A	E86
Wheelchair and respiratory support dependent (invasive ventilation)	5.32	0.439	Lognormal	N/A	N/A	E87
Health state disutility values						
No ambulatory or ventilation support (0-5) years	0.17	0.02	Gamma	124.32	0.00	E89
No ambulatory or ventilation support (6-15) years	0.17	0.02	Gamma	124.32	0.00	E90
No ambulatory or ventilation support (>15) years	0.17	0.02	Gamma	124.32	0.00	E91
Intermittent mobility support	0.38	0.03	Gamma	209.40	0.00	E92
Wheelchair dependent	0.75	0.03	Gamma	555.47	0.00	E93
Intermittent respiratory support	0.44	0.03	Gamma	252.86	0.00	E94

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
Intermittent mobility support and respiratory support	0.53	0.03	Gamma	244.23	0.00	E95
Intermittent respiratory support and wheelchair dependent	0.78	0.03	Gamma	656.49	0.00	E96
Wheelchair and respiratory support dependent (non-invasive ventilation)	0.78	0.03	Gamma	656.49	0.00	E97
Wheelchair and respiratory support dependent (invasive ventilation)	0.93	0.03	Gamma	809.68	0.00	E98
Societal costs: % patients stopping work completely						
No wheelchair use or respiratory support	0.0%	0.1	Beta	0	-1	E100
Intermittent mobility support	5.0%	0.1	Beta	0	4	E101
Wheelchair dependent	25.0%	0.1	Beta	4	13	E102
Intermittent respiratory support	5.0%	0.1	Beta	0	4	E103

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
Intermittent mobility support and intermittent respiratory support	10.0%	0.1	Beta	1	7	E104
Intermittent respiratory support and wheelchair dependent	40.0%	0.1	Beta	9	14	E105
Wheelchair and respiratory support dependent (non-invasive ventilation)	40.0%	0.1	Beta	9	14	E106
Wheelchair and respiratory support dependent (invasive ventilation)	40.0%	0.1	Beta	9	14	E107
Societal costs: % patients required to reduce hours						
No wheelchair use or respiratory support	0.0%	0.1	Beta	0	-1	E109
Intermittent mobility support	5.0%	0.1	Beta	0	4	E110
Wheelchair dependent	10.0%	0.1	Beta	1	7	E111
Intermittent respiratory support	5.0%	0.1	Beta	0	4	E112

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
Intermittent mobility support and intermittent respiratory support	20.3%	0.1	Beta	3	12	E113
Intermittent respiratory support and wheelchair dependent	20.3%	0.1	Beta	3	12	E114
Wheelchair and respiratory support dependent (non-invasive ventilation)	20.3%	0.1	Beta	3	12	E115
Wheelchair and respiratory support dependent (invasive ventilation)	20.3%	0.1	Beta	3	12	E116
Societal costs: number of reduced hours per week per patient						
No wheelchair use or respiratory support	14.00	1.4	Gamma	100	0.140	E118
Intermittent mobility support	14.00	1.4	Gamma	100	0.140	E119
Wheelchair dependent	14.00	1.4	Gamma	100	0.140	E120
Intermittent respiratory support	14.00	1.4	Gamma	100	0.140	E121

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
Intermittent mobility support and intermittent respiratory support	14.00	1.4	Gamma	100	0.140	E122
Intermittent respiratory support and wheelchair dependent	14.00	1.4	Gamma	100	0.140	E123
Wheelchair and respiratory support dependent (non-invasive ventilation)	14.00	1.4	Gamma	100	0.140	E124
Wheelchair and respiratory support dependent (invasive ventilation)	14.00	1.4	Gamma	100	0.140	E125
Societal costs: % patients requiring informal care						
No wheelchair use or respiratory support	0.00	0.0	Beta	100	999,799	E127
Intermittent mobility support	0.05	0.0	Beta	95	1,804	E128
Wheelchair dependent	0.05	0.0	Beta	95	1,804	E129
Intermittent respiratory support	0.05	0.0	Beta	95	1,804	E130

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
Intermittent mobility support and intermittent respiratory support	0.05	0.0	Beta	95	1,804	E131
Intermittent respiratory support and wheelchair dependent	0.10	0.0	Beta	90	809	E132
Wheelchair and respiratory support dependent (non-invasive ventilation)	0.50	0.1	Beta	50	50	E133
Wheelchair and respiratory support dependent (invasive ventilation)	0.50	0.1	Beta	50	50	E134
Societal costs: number care hours required per week						
No wheelchair use or respiratory support	17.69	1.8	Gamma	100	0.177	E136
Intermittent mobility support	17.56	1.8	Gamma	100	0.176	E137
Wheelchair dependent	17.76	1.8	Gamma	100	0.178	E138
Intermittent respiratory support	17.71	1.8	Gamma	100	0.177	E139

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
Intermittent mobility support and intermittent respiratory support	17.77	1.8	Gamma	100	0.178	E140
Intermittent respiratory support and wheelchair dependent	17.78	1.8	Gamma	100	0.178	E141
Wheelchair and respiratory support dependent (non-invasive ventilation)	17.78	1.8	Gamma	100	0.178	E142
Wheelchair and respiratory support dependent (invasive ventilation)	17.75	1.8	Gamma	100	0.178	E143
Societal costs: number of work hours substituted for informal care time						
No wheelchair use or respiratory support	0.28	0.0	Gamma	100	0.003	E145
Intermittent mobility support	0.38	0.0	Gamma	100	0.004	E146
Wheelchair dependent	0.19	0.0	Gamma	100	0.002	E147
Intermittent respiratory support	0.21	0.0	Gamma	100	0.002	E148

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
Intermittent mobility support and intermittent respiratory support	0.34	0.0	Gamma	100	0.003	E149
Intermittent respiratory support and wheelchair dependent	0.34	0.0	Gamma	100	0.003	E150
Wheelchair and respiratory support dependent (non-invasive ventilation)	0.23	0.0	Gamma	100	0.002	E151
Wheelchair and respiratory support dependent (invasive ventilation)	0.33	0.0	Gamma	100	0.003	E152
Costs and resource use						
No wheelchair use or respiratory support	[redacted]	[redacted]	Gamma	100	[redacted]	E154
Intermittent mobility support (new to wheelchair)	[redacted]	[redacted]	Gamma	100	[redacted]	E155
Intermittent mobility support (ongoing wheelchair)	[redacted]	[redacted]	Gamma	100	[redacted]	E156
Wheelchair dependent (new to wheelchair)	[redacted]	[redacted]	Gamma	100	[redacted]	E157

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
Wheelchair dependent (ongoing wheelchair)	[redacted]	[redacted]	Gamma	100	[redacted]	E158
Intermittent respiratory support required	[redacted]	[redacted]	Gamma	100	[redacted]	E159
Intermittent mobility support (new) and intermittent respiratory support	[redacted]	[redacted]	Gamma	100	[redacted]	E160
Intermittent mobility support (ongoing) and intermittent respiratory support	[redacted]	[redacted]	Gamma	100	[redacted]	E161
Intermittent respiratory support and wheelchair dependent (new)	[redacted]	[redacted]	Gamma	100	[redacted]	E162
Intermittent respiratory support and wheelchair dependent (ongoing)	[redacted]	[redacted]	Gamma	100	[redacted]	E163
Wheelchair (new) and respiratory support dependent (new)	[redacted]	[redacted]	Gamma	100	[redacted]	E164
Wheelchair (ongoing) and respiratory support dependent (new)	[redacted]	[redacted]	Gamma	100	[redacted]	E165

	Mean	Variation	Probability distribution	Parameter distribution (Alpha)	Parameter distribution (Beta)	Refers to cell (in the Excel model) Sheet: 'PSA Inputs'!
Wheelchair (ongoing) and respiratory support dependent (ongoing)	[redacted]	[redacted]	Gamma	100	[redacted]	E166

Appendix K- PROPEL Endpoints and statistical analysis

Baseline data on 6MWD and FVC were available for all patients; however, for multi-component/multi-item endpoints (e.g. GSGC and MMT), if a baseline value was partially missing, the average value for all patients with recorded baseline values across both treatment arms combined replaced the missing score, and the same applied for total baseline score. Patients who permanently discontinued the study treatment also discontinued the study; however, if patients returned for an end of study/end of treatment visit, efficacy assessments collected at that visit replaced the missing endpoint value, i.e. the last available observation was carried forward to replace the missing value at week 52.

The primary endpoint was tested for superiority of cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo in the intention-to-treat (ITT)-observed population, using a mixed-effect model for repeated measures (MMRM) and pre-specified non-parametric test in case of violation of normality; all secondary endpoints were analysed using an analysis of covariance (ANCOVA) model with last observation carried forward. The efficacy and safety measurements used in PROPEL are widely used and recognised as reliable, accurate and relevant, reflecting the patient impact of LOPD, including pulmonary function, muscle strength and motor function as well as PROs and patient and physician impressions of change.

All inferential statistical tests for the primary and key secondary efficacy endpoints were one-sided and were performed at an alpha level of 0.025 unless otherwise specified. The test for the primary endpoint was conducted first at the one-sided 0.025 significance level, and if significant, key secondary endpoints were similarly tested at the same significance level using a hierarchical testing order. If at any point the null hypothesis failed to be rejected, that comparison and any other comparison below it could not be claimed as statistically significant in terms of superiority, and subsequent analyses were needed to assess nominal significance on superiority.

A non-parametric, randomisation-based ANCOVA was specified as the first sensitivity analysis for 6MWD and FVC and was conducted formally if the primary parametric analyses failed to meet assumptions of normality. Post-hoc robustness analysis carried out at the request of the CHMP

Due to the COVID-19 pandemic and restrictions on access to study centres, some visits could not be done at the scheduled times as per the PROPEL study protocol. At the request of the CHMP, a post-hoc robustness analysis based on the mixed-effect model for repeated measures (MMRM) method was performed, using the actual date of each visit as a continuous variable. As such, these results have been additonally presented as found in the EMA European Public Assessment Report (EPAR), to support the efficacy of cipaglucosidase alfa/miglustat (European Medicines Agency 2023).

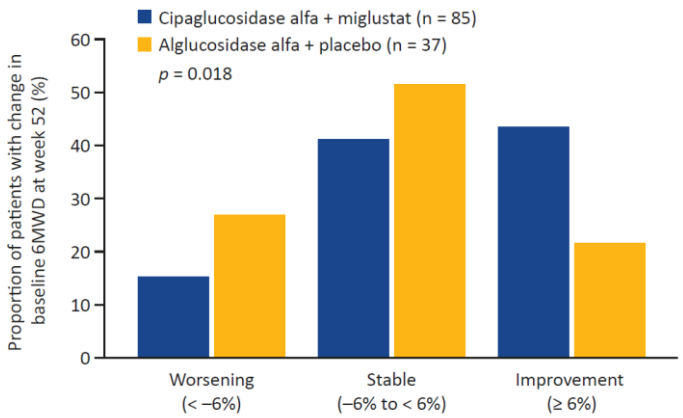
Appendix L – Clinical relevance of improvements in 6MWD and percent predicted FVC

The thresholds for clinically relevant changes in 6MWD and % predicted FVC in Pompe disease are not well-established; however, a large body of evidence is available on other neuromuscular and chronic respiratory diseases. Based on the literature,(du Bois 2011, Lachmann 2013, Schrover 2017, Baschung Pfister 2018) an increase in 6MWD greater than 6% (range, 3–11%) and a change in % predicted FVC greater than 3% (range, 2–6%) are considered clinically relevant using both anchor- and distribution-based methodologies. These thresholds were applied in a pre-specified composite patient-level responder analysis that considered 6MWD, % predicted FVC and MMT lower extremity score in the context of clinically meaningful response thresholds of ± 6%, ± 3% and ± 7%, respectively.

When these thresholds were applied to the PROPEL data, a greater proportion of patients in the cipaglucosidase alfa/miglustat arm of the ITT population reported a clinically meaningful improvement in 6MWD, % predicted FVC and MMT lower extremity score compared with alglucosidase alfa/placebo (two-sided $p = 0.012$), and a lower proportion demonstrated clinically meaningful worsening. Similarly, a pre-specified comparison of clinically meaningful improvement in 6MWD and % predicted FVC yielded a statistically significant two-sided p value of 0.041.

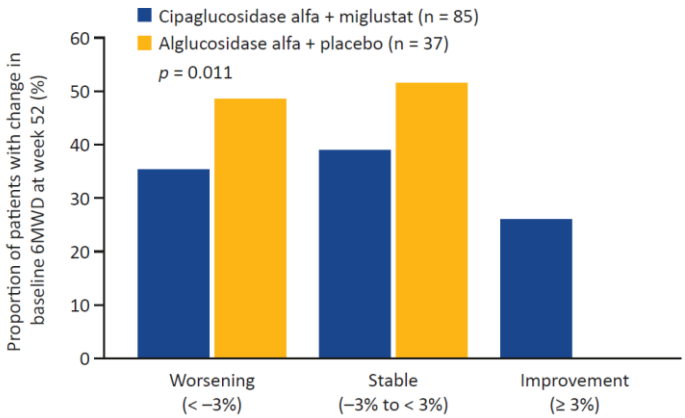
Additional *post hoc* patient-level analyses were conducted using the same thresholds for 6MWD (± 6%) and % predicted FVC (± 3%) separately. A higher proportion of patients receiving cipaglucosidase alfa/miglustat demonstrated clinically meaningful improvement, and fewer reported clinically meaningful worsening than those receiving alglucosidase alfa/placebo for 6MWD ($p = 0.018$) and % predicted FVC ($p = 0.011$). Similar results were seen when 6MWD and FVC thresholds were combined (data not shown; $p = 0.002$). Further sensitivity analyses showed that generally across a range of thresholds (6MWD, ± 30 m, ± 20 m, ± 10 m; FVC, ± 9%, ± 6%, ± 3%) a higher proportion of patients receiving cipaglucosidase alfa/miglustat experienced a clinically meaningful improvement, and fewer patients reported clinically meaningful worsening, in 6MWD and % predicted FVC than in the alglucosidase alfa/placebo arm.

Figure 32: PROPEL proportion of patients with change in baseline 6MWD at week 52 grouped by consolidated ranges (Overall population [ERT-experienced and ERT-naïve]; LOCF)



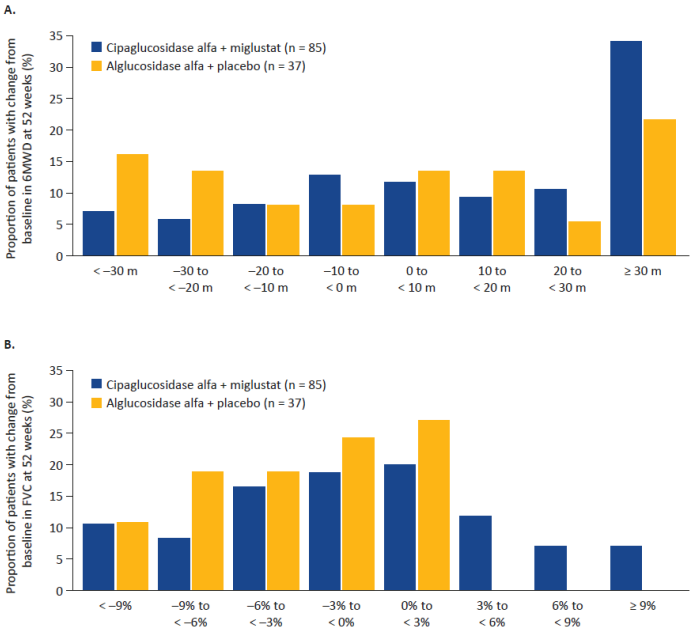
Abbreviations: 6MWD, 6-minute walk distance; ERT, enzyme replacement therapy; ITT, intention-to-treat; LOCF, last observation carried forward.

Figure 33: PROPEL proportion of patients with change in baseline sitting % predicted FVC at week 52 grouped by consolidated ranges (Overall population [ERT-experienced and ERT-naïve], LOCF)



Abbreviations: 6MWD, 6-minute walk distance; ERT, enzyme replacement therapy; FVC, forced vital capacity; ITT, intention-to-treat; LOCF, last observation carried forward.

Figure 34: PROPEL proportion of patients with a change from baseline 6MWD and percentage FVC at 52 weeks grouped by clinical meaningfulness threshold (Overall population [ERT-experienced and ERT-naïve]; LOCF). A. 6-minute walk distance. B. Percentage forced vital capacity.



Abbreviations: 6MWD, 6-minute walk distance; FVC, forced vital capacity; ITT, intention-to-treat; LOCF, last observation carried forward.

Appendix M – Secondary endpoints

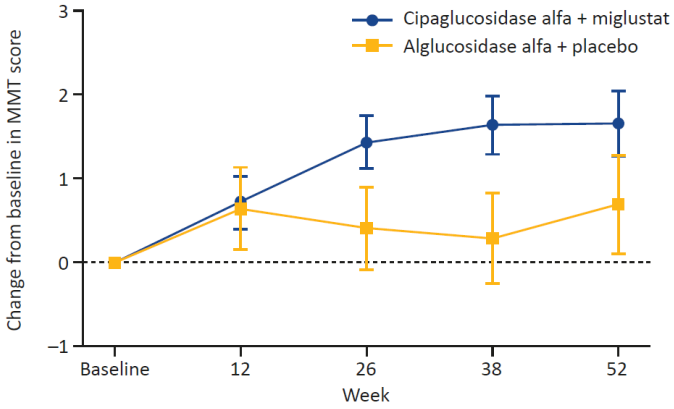
Other secondary endpoints, including those assessing motor function, pulmonary function, muscle strength, PROs and biomarkers, are summarised along with the primary and key secondary endpoints in sections 25.1, 25.2, 0 and 25.4 below.

25.1. Key secondary endpoint: change from baseline to week 52 in the MMT score for lower extremities

25.1.1. Change from baseline in MMT score for lower extremities at 52 weeks in the overall population (ERT-experienced and ERT-naïve)

An improvement in motor function was reported in both treatment arms of the overall population at 52 weeks, as demonstrated by change from baseline MMT lower extremities score at 52 weeks). At week 52, cipaglucosidase alfa/miglustat was associated with a mean improvement in baseline MMT lower extremities score of 1.56 points (SD, 3.78), compared with a mean 0.9-point (SD, 2.58) improvement in the alglucosidase alfa/placebo arm (ANCOVA LS mean treatment difference, 0.96 [95% CI, −0.48, 2.40]; nominal two-sided p = [redacted]). Mean baseline MMT lower extremities scores were 28.0 (SD, 5.76) and 27.7 (SD, 6.17) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at 52 weeks (LOCF) were 29.7 (SD, 6.04) and 28.5 (SD, 7.0), respectively.

Figure 35: PROPEL key secondary endpoint: LS mean of change in baseline MMT lower extremities score at week 52 (overall population [ERT-experienced and ERT-naïve]).



Population	Treatment	n	Mean baseline MMT lower extremities score (SD), m	n	Mean LOCF MMT lower extremities score at week 52 (SD), m	Mean CFB MMT lower extremities score at 52 weeks (SD)	
Overall	**Cipaglucosidase alfa/miglustat**	84	27.96 (5.76)	80	29.73 (6.04)	1.56 (3.78)	↑
	Alglucosidase alfa/placebo	34	27.65 (6.17)	34	28.53 (7.00)	0.88 (2.58)	↑
	ANCOVA difference in LS mean (95% CI)				0.96 (−0.48, 2.40); nominal two-sided *p* = [redacted]		

Note: ↑ denotes improvement from baseline. Blue shading indicates treatment group is favoured.
Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; LOCF, last observation carried forward; LS, least-squares; MMT, manual muscle test; SD, standard deviation.

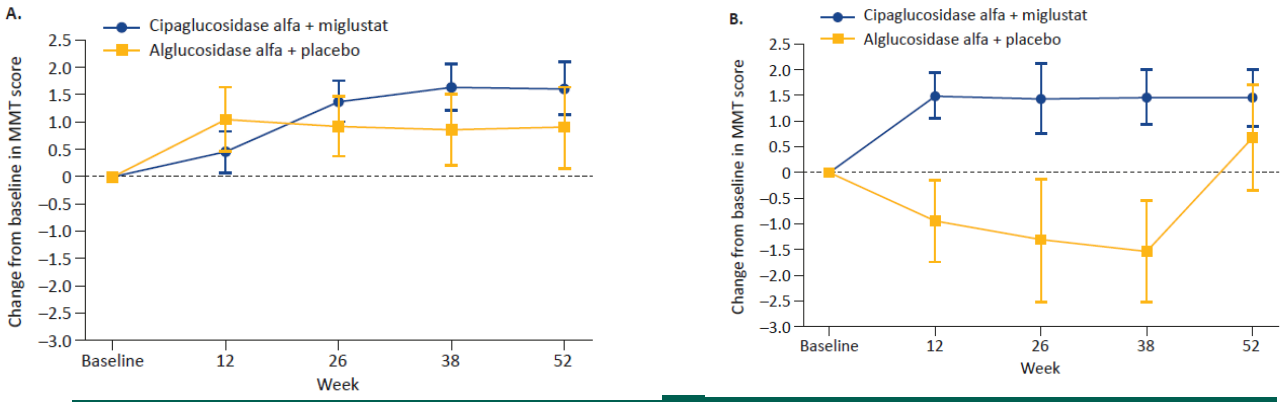
25.1.2. Change from baseline in MMT score for lower extremities at 52 weeks stratified by ERT status

An improvement in MMT lower extremity scores occurred in both treatment arms of the **ERT-experienced population**, directionally favouring cipaglucosidase alfa/miglustat over alglucosidase alfa/placebo. Patients

enrolled in the cipaglucosidase alfa/miglustat arm reported a 1.6-point improvement (SD, 4.13) in MMT lower extremities score, and those in the alglucosidase alfa/placebo arm a 0.9-point improvement (SD, 2.81; ANCOVA LS mean treatment difference, 0.70 [95% CI, −1.08, 2.49]; nominal two-sided *p* = [redacted]). Mean baseline MMT lower extremities scores were 26.4 (SD, 5.1) in the cipaglucosidase alfa/miglustat arm and 26.1 (SD, 5.8) in the alglucosidase alfa/placebo arm; at 52 weeks (LOCF) mean scores were 28.2 (SD, 5.6) and 27.0 (SD, 6.8), respectively.

A similar improvement in MMT lower extremity score was reported in both treatment arms of the **ERT-naïve population**. Mean improvement from baseline MMT lower extremity score was 1.36 points (SD, 2.55) in the cipaglucosidase alfa/miglustat arm and 1.00 point (SD, 1.53) in the alglucosidase alfa/placebo arm (ANCOVA LS mean treatment difference, 0.78 [95% CI, −1.79, 3.34]; nominal two-sided p = [redacted]). At baseline, mean MMT lower extremity scores were 33.00 (SD, 4.69) and 33.57 (SD, 3.36) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at 52 weeks (LOCF) were 34.35 (SD, 4.98) and 34.57 (SD, 3.91), respectively.

Figure 36: PROPEL LS mean change in baseline MMT lower extremity score at week 52 stratified by ERT status. A. ERT-experienced. B. ERT-naïve.



Population	Treatment	n	Mean baseline MMT lower extremities score (SD), m	n	Mean LOCF MMT lower extremities score at week 52 (SD), m	Mean CFB MMT lower extremities score at 52 weeks (SD)	
ERT-experienced	Cipaglucosidase alfa/miglustat	64	26.38 (5.14)	60	28.18 (5.59)	1.63 (4.13)	↑
	Alglucosidase alfa/placebo	27	26.11 (5.81)	27	26.96 (6.80)	0.85 (2.81)	↑
	ANCOVA difference in LS mean (95% CI)				0.70 (−1.08, 2.49); nominal two-sided *p* = [redacted]		
ERT-naïve	Cipaglucosidase alfa/miglustat	20	33.00 (4.69)	20	34.35 (4.98)	1.36 (2.55)	↑
	Alglucosidase alfa/placebo	7	33.57 (3.36)	7	34.57 (3.91)	1.00 (1.53)	↑
	ANCOVA difference in LS mean (95% CI)				0.78 (−1.79, 3.34); nominal two-sided *p* = [redacted]		

Note: ↑ denotes improvement from baseline. Blue shading indicates treatment group is favoured.
Abbreviations: ANCOVA; analysis of covariance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; LOCF, last observation carried forward; LS, least-squares; MMT, manual muscle test; SD, standard deviation.

Post-hoc robustness analysis carried out at the request of the CHMP for MMT score for lower extremities

For the MMT score for lower extremities at 52 weeks, the results of the post-hoc robustness analysis were consistent with those of the main analysis, showing improvements in favour of the cipaglucosidase alfa/miglustat (European Medicines Agency 2023):

- For the ITT population, least squares mean difference of +1.1 point (95% CI. -0.1, 2.3)
- For the ERT-experienced population, least squares mean difference of +0.9 point (95% CI -0.6, 2.3)

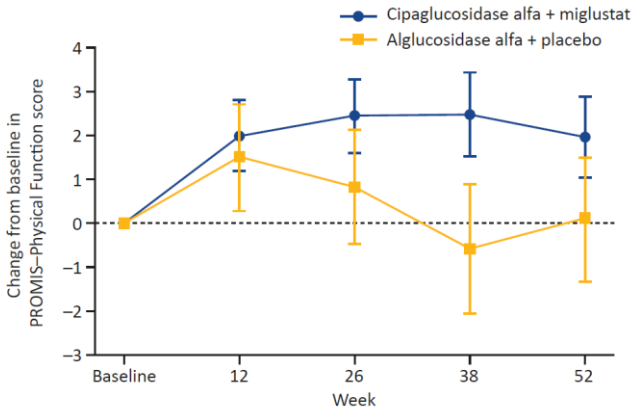
For a summary of the MMT score fo lower extremities outcomes, see Section 34 Appendix V.

25.2. Key secondary endpoint: change from baseline in PROMIS–Physical Function domain score at week 52

25.2.1. Change from baseline in PROMIS–Physical Function score at week 52 in the overall population (ERT-experienced and ERT-naïve)

Cipaglucosidase alfa/miglustat was associated with a numerically greater improvement in PROMIS–Physical Function score than alglucosidase alfa/placebo; however, these improvements were not considered clinically significant. Mean improvement from baseline PROMIS–Physical Function score at week 52 was 1.9 points (SD, 7.50) in the cipaglucosidase alfa/miglustat arm and 0.2 points (SD, 10.82) in the alglucosidase alfa/placebo arm (ANCOVA LS mean treatment difference, 1.87 [95% CI, −1.51, 5.25]; nominal two-sided p = [redacted]). PROMIS–Physical Function scores were 66.9 (SD, 12.26) and 68.0 (SD, 13.09) at baseline in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and 68.8 (SD, 12.95) and 68.2 (SD, 16.27) at week 52 (LOCF), respectively.

Figure 37: PROPEL key secondary endpoint: change from baseline PROMIS–Physical Function score at week 52 (overall population [ERT-experienced and ERT-naïve])



Population	Treatment	n	Mean baseline PROMIS–Physical Function score (SD)	n	Mean LOCF PROMIS–Physical Function score at week 52 (SD)	Mean CFB PROMIS–Physical Function score at 52 weeks (SD)	
Overall	Cipaglucosidase alfa/miglustat	84	66.86 (12.26)	84	68.80 (12.95)	1.94 (7.50)	↑
	Alglucosidase alfa/placebo	37	67.97 (13.09)	37	68.16 (16.27)	0.19 (10.82)	↑
	ANCOVA difference in LS mean (95% CI)				1.87 (−1.51, 5.25); two-sided *p* = [redacted]		

Note: ↑ denotes improvement from baseline. Blue shading indicates treatment group is favoured.
Abbrevations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; LOCF, last observation carried forward; LS, least-squares; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation

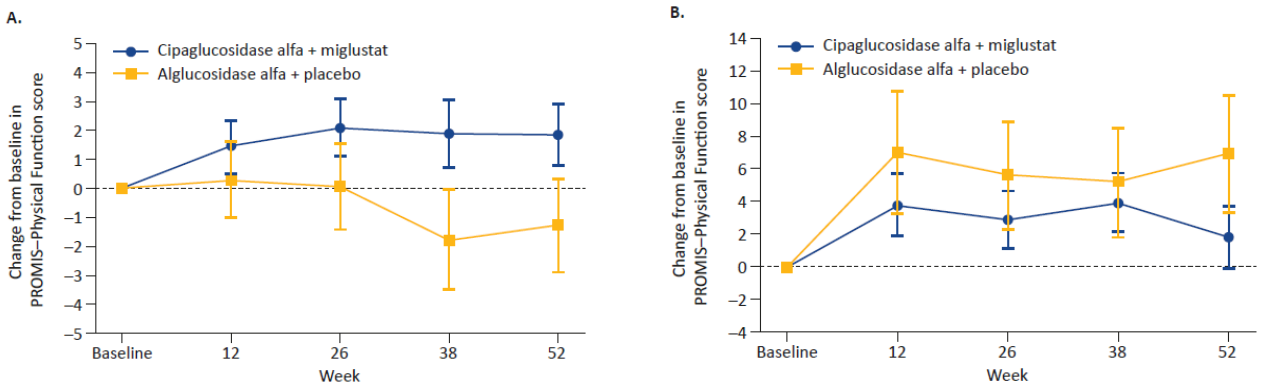
25.2.2. Change from baseline in PROMIS–Fatigue score at week 52 stratified by ERT status

In the **ERT-experienced** population, cipaglucosidase alfa/miglustat was associated with an improvement in PROMIS–Physical Function score that was directionally favoured over alglucosidase alfa/placebo (two-sided p = [redacted]). Mean change from baseline PROMIS–Physical Function score was 1.76 points (SD, 7.18) in the cipaglucosidase alfa/miglustat arm and −0.97 points (SD, 11.20) in the alglucosidase alfa/placebo arm. Mean

baseline PROMIS–Physical Function scores were 64.4 (SD, 11.38) and 65.9 (SD, 12.29) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at week 52 (LOCF) were 66.19 (SD, 12.33) and 65.90 (SD, 15.79), respectively).

An improvement from baseline PROMIS–Physical Function score was reported in both treatment arms of the ERT-naïve population at week 52. Patients enrolled in the cipaglucosidase alfa/miglustat arm reported a 2.50-point (SD, 8.62) improvement in baseline PROMIS–Physical Function score at 52 weeks compared with a 5.14-point (SD, 7.82) improvement reported by those in the alglucosidase alfa/placebo arm (ANCOVA LS mean treatment difference, −5.09 [95% CI, −14.04, 3.85]; nominal two-sided p = [redacted]). Mean baseline PROMIS–Physical Function scores were 74.65 (SD, 11.98) and 72.71 (SD, 16.32) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at week 52 (LOCF) were 77.15 (SD, 11.54) and 77.86 (SD, 15.74), respectively.

Figure 38: PROPEL change from baseline PROMIS–Physical Function score at week 52 stratified by ERT status. A. ERT-experienced. B. ERT-naïve



Population	Treatment	n	Mean baseline PROMIS–Physical Function score (SD)	n	Mean LOCF PROMIS–Physical Function score at week 52 (SD)	Mean CFB PROMIS–Physical Function score at 52 weeks (SD)	
ERT-experienced	Cipaglucosidase alfa/miglustat	64	64.43 (11.38)	64	66.19 (12.33)	1.76 (7.18)	↑
	Alglucosidase alfa/placebo	30	66.87 (12.29)	30	65.90 (15.79)	−0.97 (11.20)	↓
	ANCOVA difference in LS mean (95% CI)				3.14 (−0.73, 7.02); nominal two-sided *p* = [redacted]		
ERT-naïve	Cipaglucosidase alfa/miglustat	20	75.65 (11.98)	20	77.15 (11.54)	2.50 (8.62)	↑
	Alglucosidase alfa/placebo	7	72.71 (16.32)	7	77.86 (15.74)	5.14 (7.82)	↑
	ANCOVA difference in LS mean (95% CI)				−5.09 (−14.04, 3.85); nominal two-sided *p* = 0.249		

Note: ↑ denotes improvement from baseline; ↓ worsening from baseline. Blue shading indicates treatment group is favoured.
Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; LOCF, last observation carried forward; LS, least-squares; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.

Post-hoc robustness analysis carried out at the request of the CHMP for PROMIS-Physical function score

For the PROMIS-Physical function score at 52 weeks, the results of the post-hoc robustness analysis were consistent with those of the main analysis ITT (95% CI -0.6, +5.7) and ERT-experienced (95% CI -0.1, +7.1) populations (European Medicines Agency 2023).

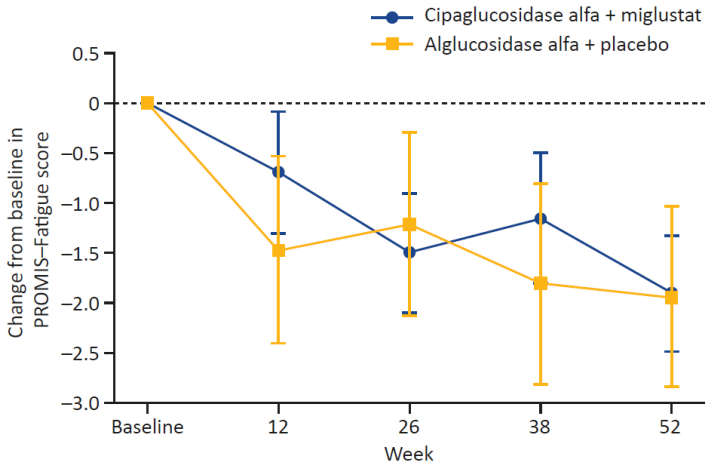
For a summary of the PROMIS-Physical function outcomes, see Section 34 Appendix V.

25.3. Key secondary endpoint: change from baseline PROMIS–Fatigue domain score at 52 weeks

25.3.1. Change from baseline in PROMIS–Fatigue score at week 52 in the overall population (ERT-experienced and ERT-naïve)

A similar improvement in PROMIS–Fatigue score was reported in both treatment arms. Patients allocated to the cipaglucosidase alfa/miglustat arm reported a −2.0-point (SD, 5.8) improvement from baseline in PROMIS–Fatigue score at week 52 compared with a −1.7-point (SD, 6.6) improvement in the alglucosidase alfa/placebo arm (ANCOVA treatment difference in LS mean, 0.04 [95% CI, −2.12, 2.20]; nominal two-sided p = [redacted]). Baseline PROMIS–Fatigue scores were 22.3 (SD, 8.3) and 21.1 (SD, 6.1) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at week 52 (LOCF) were 20.2 (SD, 7.5) and 19.4 (SD, 6.7), respectively).

Figure 39: PROPEL key secondary endpoint: change from baseline PROMIS–Fatigue score at week 52 (overall population [ERT-experienced and ERT-naïve])



Population	Treatment	n	Mean baseline PROMIS–Fatigue score[a] (SD)	n	Mean LOCF PROMIS–Fatigue score[a] at week 52 (SD)	Mean CFB PROMIS–Fatigue score[a] at 52 weeks (SD)
Overall	Cipaglucosidase alfa/miglustat	85	22.26 (8.30)	85	20.24 (7.49)	−2.02 (5.76) ↑
	Alglucosidase alfa/placebo	37	21.08 (6.10)	37	19.41 (6.74)	−1.67 (6.62) ↑
	ANCOVA difference in LS mean (95% CI)				0.04 (−2.12, 2.20); nominal two-sided *p* = [redacted]	

Note: ↑ denotes improvement from baseline. Blue shading indicates treatment group is favoured.
[a]A higher score represents more fatigue, i.e. an increase in score indicates worsening and a decrease in score represents improvement.
Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; LOCF, last observation carried forward; LS, least-squares; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.

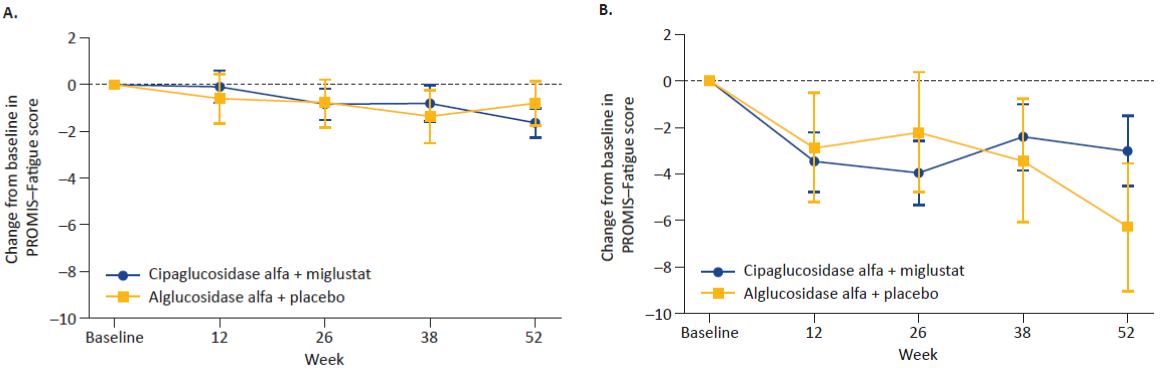
25.3.2. Change from baseline in PROMIS–Fatigue score at week 52 in the overall population (ERT-experienced and ERT-naïve)

A similar improvement in PROMIS–Fatigue score was reported in both treatment arms of the ERT-experienced population. Mean improvement from baseline PROMIS–Fatigue score at 52 weeks was −1.87 points (SD, 5.84) in the cipaglucosidase alfa/miglustat arm and −0.27 points (SD, 5.27) in the alglucosidase alfa/placebo arm (ANCOVA LS mean treatment difference, −0.84 [95% CI, −3.16, 1.49]; nominal two-sided p = [redacted]); note, a lower score indicates an improvement in fatigue. Mean PROMIS–Fatigue scores at baseline were 22.00 (SD, 7.92)

and 20.37 (SD, 5.38) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at week 52 were 10.13 (SD, 6.77) and 20.10 (SD, 6.55), respectively.

An improvement from baseline in PROMIS–Fatigue score was reported in both treatment arms in the ERT-naïve population. Mean change from baseline in PROMIS–Fatigue score at week 52 was −2.50 (SD, 5.63) in the cipaglucosidase alfa/miglustat arm and −7.70 (SD, 8.77) in the alglucosidase alfa/placebo arm (ANCOVA LS mean treatment difference, 3.29 [95% CI, −3.69, 10.27]; nominal two-sided p = [redacted]). Baseline PROMIS–Fatigue scores were 23.10 (SD, 9.61) and 24.13 (SD, 8.36) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at week 52 (LOCF) were 20.60 (SD, 9.68) and 16.43 (SD, 7.23), respectively.

Figure 40: PROPEL change from baseline PROMIS–Fatigue score at week 52 stratified by ERT status. A. ERT-experienced. B. ERT-naïve



Population	Treatment	n	Mean baseline PROMIS–Fatigue score[a] (SD)	n	Mean LOCF PROMIS–Fatigue score[a] at week 52 (SD)	Mean CFB PROMIS–Fatigue score[a] at 52 weeks (SD)	
ERT-experienced	Cipaglucosidase alfa/miglustat	65	22.00 (7.92)	65	20.13 (6.77)	−1.87 (5.84)	↑
	Alglucosidase alfa/placebo	30	20.37 (5.38)	30	20.10 (6.55)	−0.27 (5.27)	↑
	ANCOVA difference in LS mean (95% CI)				−0.84 (−3.16, 1.49); nominal two-sided *p* = [redacted]		
ERT-naïve	Cipaglucosidase alfa/miglustat	20	23.10 (9.61)	20	20.60 (9.68)	−2.50 (5.63)	↑
	Alglucosidase alfa/placebo	7	24.13 (8.36)	7	16.43 (7.23)	−7.70 (8.77)	↑
	ANCOVA difference in LS mean (95% CI)				3.29 (−3.69, 10.27); nominal two-sided *p* = [redacted]		

Note: ↑ denotes improvement from baseline. Blue shading indicates treatment group is favoured.
[a]A higher score represents more fatigue, i.e. an increase in score indicates worsening and a decrease in score represents improvement.
Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; LOCF, last observation carried forward; LS, least-squares; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.

Post-hoc robustness analysis carried out at the request of the CHMP for PROMIS-Fatigue score

For the PROMIS-Fatigue score at 52 weeks, the results of the post-hoc robustness analysis were consistent with those of the main analysis ITT (95% CI -2.4, +1.8) and ERT-experienced (95% CI -3.5, +1.1) populations (European Medicines Agency 2023).

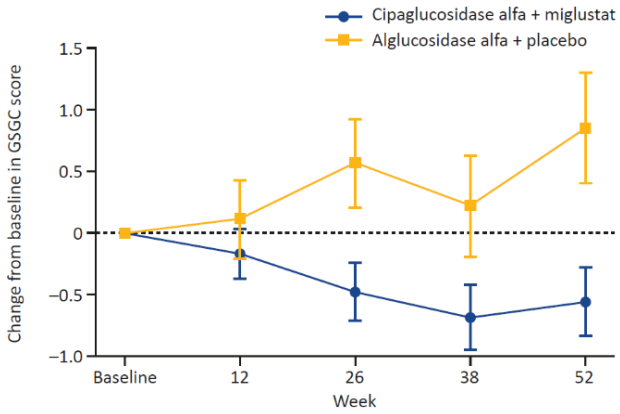
For a summary of the PROMIS-Fatigue score outcomes, see Section 34 Appendix V.

25.4. Key secondary endpoint: change from baseline to week 52 in the GSGC score

25.4.1. Change from baseline in GSGC score at week 52 in the overall population (ERT-experienced and ERT-naïve)

Cipaglucosidase alfa/miglustat was associated with a nominally statistically significant improvement in GSGC score compared with alglucosidase alfa/placebo; note, a lower score represents better functionality. Mean change from baseline GSGC score was −0.53 (SD, 2.54) in the cipaglucosidase alfa/miglustat arm and 0.77 (SD, 1.81) in the alglucosidase alfa/placebo arm (ANCOVA treatment difference in LS mean, −1.41 [95% CI, −2.46, −0.36]; nominal two-sided p = [redacted]). Mean baseline GSGC scores were 14.51 (SD, 5.17) and 14.50 (SD, 4.72) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at week 52 (LOCF) were 13.74 (SD, 5.37) and 15.00 (SD, 4.49), respectively.

Figure 41: PROPEL key secondary endpoint: change from baseline GSGC score at week 52 (overall population [ERT-experienced and ERT-naïve]).



Population	Treatment	n	Mean baseline GSGC score[a] (SD)	n	Mean LOCF GSGC score[a] at week 52 (SD)	Mean CFB GSGC score[a] at 52 weeks (SD)	
Overall population	Cipaglucosidase alfa/miglustat	74	14.51 (5.17)	72	13.74 (5.37)	−0.53 (2.54)	↑
	Alglucosidase alfa/placebo	37	14.50 (4.72)	30	15.00 (4.49)	0.77 (1.81)	↑
	ANCOVA difference in LS mean (95% CI)				−1.41 (−2.46, −0.36); nominal two-sided *p* = [redacted]		

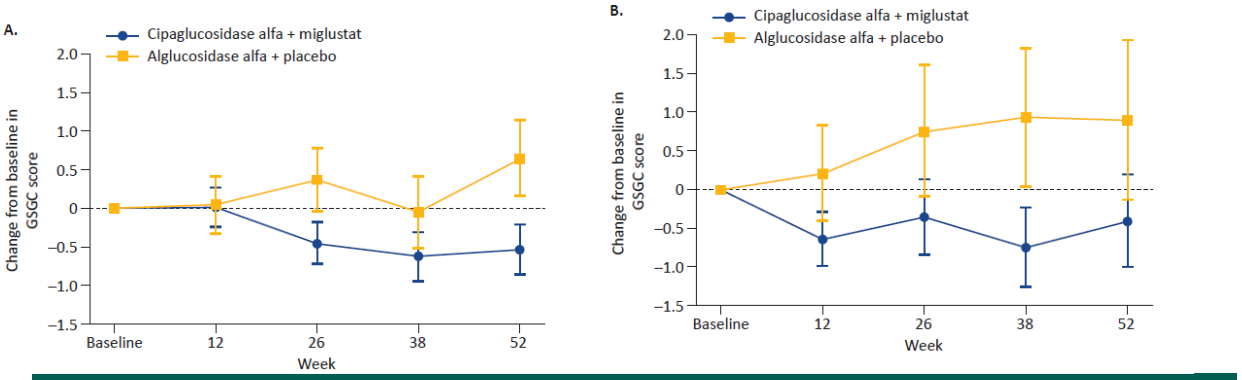
Note: ↑ denotes improvement from baseline.
[a]Lower score denotes better functionality.
Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; GSGC, gait, stairs, Gower's manoeuvre, chair; LOCF, last observation carried forward; LS, least-squares; SD, standard deviation

25.4.2. Change from baseline in GSGC score at week 52 stratified by ERT status

Similar to the overall population, cipaglucosidase alfa/miglustat was associated with a nominally statistically significant improvement in GSGC score compared with alglucosidase alfa/placebo in the **ERT-experienced population**. Mean change from baseline in GSGC score was −0.53 points (SD, 2.53) in the cipaglucosidase alfa/miglustat arm and 0.61 points (SD, 1.83) in the alglucosidase alfa/placebo arm (ANCOVA difference in LS mean, −1.19 [95% CI, −2.38, 0]; nominal two-sided *p* = [redacted]; note, a lower score represents better functionality. At baseline, mean GSGC scores were 15.61 (SD, 4.07) and 15.52 (SD, 4.35) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at week 52 were 14.96 (SD, 4.81) and 15.87 (SD, 4.17), respectively.

In the **ERT-naïve population**, mean change from baseline in GSGC score was −0.6 points (SD, 2.64) in the cipaglucosidase alfa/miglustat arm and 1.3 points (SD, 1.80) in the alglucosidase alfa/placebo arm (ANCOVA difference in LS mean [redacted] [95% CI, [redacted]]; nominal two-sided *p* = [redacted]; note, a lower score represents better functionality. At baseline, mean GSGC scores were 11.3 (SD, 6.65) and 10.9 (SD, 4.41) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at week 52 were 10.1 (SD, 5.41) and 12.1 (SD, 4.60), respectively.

Figure 42: PROPEL change from baseline GSGC score at week 52 stratified by ERT status. A. ERT-experienced. B. ERT-naïve



Population	Treatment	n	Mean baseline GSGC score[a] (SD)	n	Mean LOCF GSGC score[a] at week 52 (SD)	Mean CFB GSGC score[a] at 52 weeks (SD)	
ERT-experienced	Cipaglucosidase alfa/miglustat	55	15.61 (4.07)	54	14.96 (4.81)	−0.53 (2.53)	↑
	Alglucosidase alfa/placebo	54	15.52 (4.35)	23	15.87 (4.17)	0.61 (1.83)	↑
	ANCOVA difference in LS mean (95% CI)				−1.19 (−2.38, 0); nominal two-sided *p* = [redacted]		
ERT-naïve	Cipaglucosidase alfa/miglustat	19	11.32 (6.65)	18	10.06 (5.41)	−0.56 (2.64)	↑
	Alglucosidase alfa/placebo	7	10.86 (4.41)	7	12.14 (4.60)	1.29 (1.80)	↓
	ANCOVA difference in LS mean (95% CI)				−1.32 (−4.03, 1.39); nominal two-sided *p* = [redacted]		

Note: ↑ denotes improvement from baseline; ↓ worsening from baseline.
[a]Lower score denotes better functionality.
Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; GSGC, gait, stairs, Gower's manoeuvre, chair; LOCF, last observation carried forward; LS, least-squares; SD, standard deviation.

Post-hoc robustness analysis carried out at the request of the CHMP for GSGC score

For the GSGC score at 52 weeks, the results of the post-hoc robustness analysis were consistent with those of the main analysis, showing an improvement in in favour of the cipaglucosidase alfa/miglustat group between baseline and week 52 in the ITT and ERT-experienced populations (European Medicines Agency 2023):

- For the ITT population, least squares mean difference of -1.5 point (95% CI -2.4, -0.6)
- For the ERT-experienced population, least squares mean difference of -1.2 point (95% CI -2.2, -0.1)

For a summary of the GSGC outcomes, see Section 34 Appendix V.

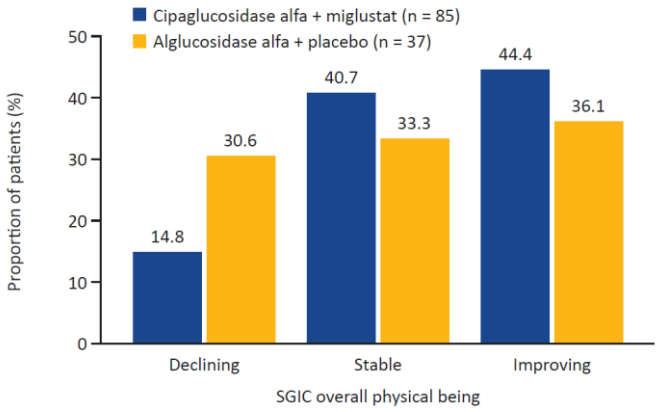
Appendix N – Patient-reported outcomes

In addition to PROMIS–Physical Function and PROMIS–Fatigue, differences in PROMIS–Dyspnoea, PROMIS–Upper Extremity, R-Pact, EQ-5D-5L, subject global impression of change (SGIC) and physician's global impression of change (PGIC) outcomes were assessed between treatment arms. A similar improvement in PROMIS–Dyspnoea, PROMIS–Upper Extremity, R-Pact and EQ-5D-5L was reported in both treatment arms, but SGIC and PGIC demonstrated a consistently greater improvement favouring cipaglucosidase alfa/miglustat over alglucosidase alfa/placebo in the overall population.

26.1. Subject's Global Impression of Change

SGIC comprises eight distinct endpoints: overall physical well-being, effort of breathing, muscle strength, muscle function, ability to move around, ADLs, energy level and muscular pain. A higher percentage of patients in the cipaglucosidase alfa/miglustat arm of the overall population considered themselves improving (overall physical well-being at week 52, 44.4% vs 36.1% (difference of 8.3%)) or stable (40.7% vs 33.3% (difference of 7.4%)) compared with the alglucosidase alfa/placebo arm, and a lower proportion of patients reported themselves as declining (14.8% vs 30.6% (difference of 15.8%)). Similar results were reported for the PGIC. Overall physical well-being change from baseline at week 52, shown in Figure 43, is considered representative of the benefits reported across these measures.

Figure 43: PROPEL patient-reported outcomes: change from baseline SGIC overall physical well-being score at 52 weeks (overall population [ERT-experienced and ERT-naïve])



Abbreviations: SGIC, Subject's Global Impression of Change.

26.2. XXXXXXXXXXXXXXXXXXXXXXXX

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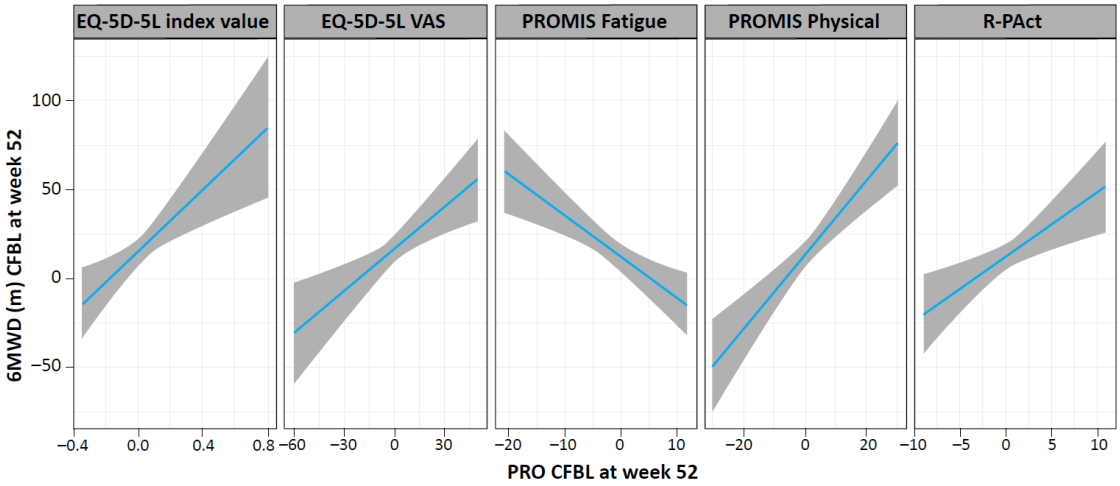
26.3. Correlation between walking distance and quality of life

As discussed in Section 0, statistically significant correlations were observed between physician-measured functional outcomes in rare muscular, skeletal and neurodegenerative diseases, including 6MWD and % predicted FVC, and patient-reported health-related quality of life (HRQoL) (Shohet 2021). Potential correlations between 6MWD and PROs (EQ-5D-5L index value, EQ-5D-5L visual analogue scale (VAS), PROMIS–Fatigue, PROMIS–Physical Function and the R-Pact score) were explored using data from PROPEL. A linear regression was performed using patient-level data from 123 patients enrolled in the PROPEL trial, regardless of treatment, with and without adjusting for baseline covariates (age, sex, body mass index, ERT duration and treatment), and revealed that change from baseline in 6MWD at week 52 was associated with statistically significant gains in EQ-5D-5L index value and VAS, and improvements in other PROs (including PROMIS–Fatigue, PROMIS–Physical Function and R-Pact) (Raza 2022a). This suggests that improved walking ability in LOPD may have a meaningful impact on patient experience, as measured by PRO and quality-of-life instruments. These associations were also significant at baseline with the exception of PROMIS Fatigue and 6MWD (Figure 46; Table 82) (Raza 2022a).

Figure 46: Linear regression illustrating association between 6MWD and PROs – CFBL to week 52



Note: Regression lines in blue are generated from linear regression models without adjusting for baseline covariates, and the shaded grey areas represent their 95% confidence intervals.
Abbreviations: 6MWD, 6-minute walk distance; CFBL, change from baseline; EQ-5D-5L, 5-dimension, 5-level EuroQol questionnaire; EQ-5D-5L VAS, 5-dimension, 5-level EuroQol questionnaire visual analogue scale; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; R-Pact, Rasch-built Pompe-specific Activity.
Source: (Raza 2022a)

Table 82: Heat map for strength of associations (R) between 6MWD and PROs

	6MWD			
			R (unadjusted)	**R (adjusted)**
EQ-5D-5L	Index value	At baseline	**0.295**	0.690
		CFBL	**0.306**	**0.512**
	VAS	At baseline	**0.282**	**0.673**
		CFBL	**0.306**	0.481
PROMIS	Fatigue	At baseline	−0.056	−0.312
		CFBL	**−0.327**	**−0.434**
	Physical Function	At baseline	**0.532**	**0.565**

		CFBL	**0.422**	**0.483**
R-Pact		At baseline	**0.640**	**0.779**
		CFBL	**0.296**	**0.514**

Key						
R: −1 to <−0.5	R: −0.5 to <−0.3	R: −0.3 to <−0.1	R: −0.1 to < 0.1	R: 0.1 to ≤ 0.3	R: 0.3 to ≤ 0.5	R: 0.5 to ≤ 1
Strong negative correlation	Moderate negative correlation	Weak negative correlation	No correlation	Weak positive correlation	Moderate positive correlation	Strong positive correlation

Note: Values in **bold** indicate significance of the association between 6MWD and the PRO (i.e. significance of the regression coefficient B of the PRO in the linear models). 'Unadjusted' and 'adjusted' mean the correlation coefficient R is derived from the model without and with adjusting for baseline covariates, respectively. All statistical tests were two-sided and assessed at 5% level of significance, without adjustment for multiplicity.
Abbreviations: 6MWD, 6-minute walk distance; CFBL, change from baseline; EQ-5D-5L, 5-dimension, 5-level EuroQol questionnaire; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; R, Pearson R value; R-Pact, Rasch-built Pompe-specific Activity; VAS, visual analogue scale.
Source: (Raza 2022a)

26.4. Responder analysis of PRO outcomes

Using parameters obtained from the literature (Table 83) (Kishnani 2022), a post hoc patient- and group-level responder analysis performed using PRO data obtained from PROPEL revealed an improvement in HRQoL in patients receiving cipaglucosidase alfa with miglustat compared with alglucosidase alfa, as measured by the EQ-5D-5L, SGIC and PROMIS instruments. In the patient-level analysis, cipaglucosidase alfa with miglustat was statistically or numerically favoured in most PRO domains in the overall (ERT-experienced and ERT-naïve) and ERT-experienced populations, using a Chi-square or Fisher exact test. Results of the group-level analysis that compared change from baseline PRO measures at week 52 using an ANCOVA adjusted for baseline covariates, including ERT status (naïve or experienced), age, gender, height and weight, showed that, in the overall population, cipaglucosidase alfa with miglustat was numerically favoured in the majority of domains, and numerically or statistically favoured in the majority of domains in the ERT-experienced population. These analyses suggest that, compared with alglucosidase alfa, cipaglucosidase alfa with miglustat improves PROs relevant to patients with Pompe disease (Hagemans 2007a, van der Beek 2013, Rampakakis 2015, Harfouche 2020, Berger 2021), and this is consistent with trends seen in PROPEL. Interestingly, on an individual patient level, cipaglucosidase alfa with miglustat was favoured in more domains than in the group-level analysis, suggesting that the level of improvement is patient-specific; a concept discussed as part of the FDA's patient-focused drug development. While between-group difference is frequently used in clinical trials to determine the relevant benefit of treatment, with benefit benchmarked as minimal clinically important difference and minimum important difference, it does not take into account the impact on the individual patient. Instead, the FDA intends to provide guidance on measuring meaningful within-patient change (FDA 2019), which may be relevant for patients with rare, heterogeneous and often debilitating diseases.

Table 83: Responder analysis of PRO data obtained from the PROPEL trial

PRO measure	Definition of improvement
EQ-5D-5L	
Index[a]	EQ-5D-5L index value change from baseline at week 52 > 0
Mobility[b]	EQ-5D-5L mobility change from baseline at week 52 < 0, or if patient does not show any problems at baseline and at week 52 (i.e. = 1 for both visits)
Self-care[b]	
Usual activities[b]	

Pain/discomfort[b]	
Anxiety/depression[b]	
VAS[a]	EQ-5D-5L VAS percentage change from baseline at week 52 ≥ 10
Subject's Global Impression of Change	
Overall well-being	Subject's Global Impression of Change overall well-being at week 52 ≥ 5
Ability to move around	
Effort of breathing	
Muscle strength	
R-Pact	R-Pact change from baseline at week 52 > 0
PROMIS	
Physical	PROMIS–Physical change from baseline at week 52 > 0
Fatigue	PROMIS–Fatigue l change from baseline at week 52 > 0

Abbreviations: EQ-5D-5L, 5-dimension, 5-level EuroQoL questionnaire; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; R-Pact, Rasch-built Pompe-specific Activity; VAS, visual analogue scale.
Source: (Kishnani 2022)

Appendix O – Biomarkers: change in baseline absolute values of key biomarkers at 52 weeks

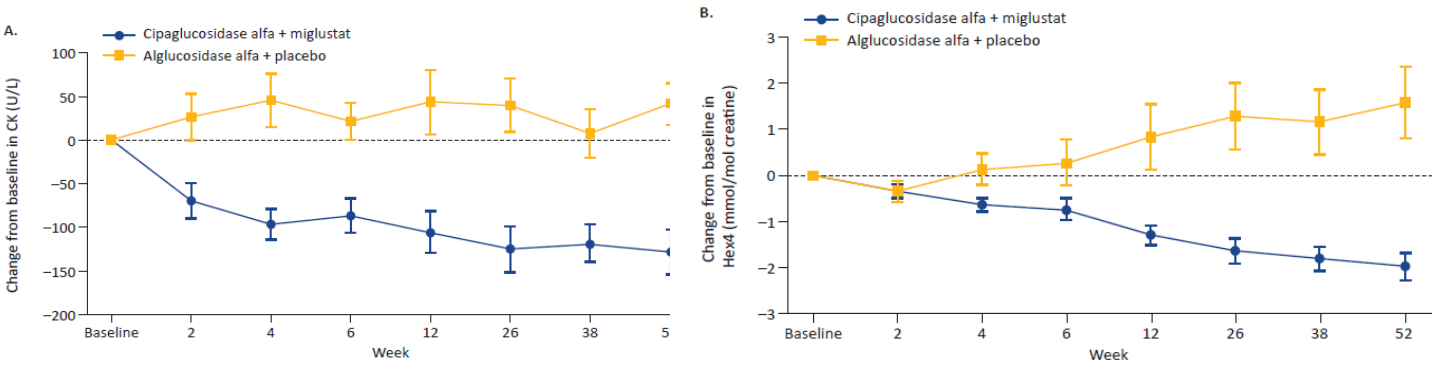
27.1. Change from baseline in absolute values of key biomarkers at 52 weeks in the overall population (ERT-experienced and ERT-naïve)

Levels of biomarkers representative of muscle damage (CK) and disease substrate (Hex4) were significantly reduced ($p < 0.001$) in the cipaglucosidase alfa/miglustat arm compared with the alglucosidase alfa/placebo arm.

Mean change from baseline absolute CK value was −130.5 U/L (SD, 231.2) in the cipaglucosidase alfa/miglustat arm and 60.2 U/L in the alglucosidase alfa/placebo arm (ANCOVA LS mean treatment difference, −176.0 U/L [95% CI, −244.4, −107.6]; nominal one-sided $p < 0.001$; Figure 47). Absolute values at baseline were 447.0 U/L (SD, 399.5) and 527.8 U/L (SD, 426.6) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at 52 weeks (LOCF) were 316.5 U/L (SD, 277.2) and 588.0 U/L (SD, 482.2), respectively (Figure 47).

Mean change from baseline in absolute Hex4 value was −1.88 mmol/mol creatine (SD, 2.38) in the cipaglucosidase alfa/miglustat arm and 1.22 mmol/mol creatine (SD, 4.43) in the alglucosidase alfa/placebo arm (ANCOVA LS mean treatment difference, −2.49 mmol/mol [95% CI, −3.66, −1.32]; nominal one-sided $p < 0.001$; Figure 47). Absolute values at baseline were 4.61 mmol/mol creatinine (SD, 3.37) and 6.92 mmol/mol creatinine (SD, 6.94) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at 52 weeks (LOCF) were 2.74 mmol/mol creatinine (SD, 1.66) and 8.14 mmol/mol creatinine (SD, 10.50), respectively (Figure 47).

Figure 47: PROPEL secondary endpoint: mean change (± standard error) from absolute baseline values of CK and Hex4 at week 52 (overall population [ERT-experienced and ERT-naïve]). A. Creatine kinase. B. Hexose tetrasaccharide.



Population	Treatment	n	Mean absolute value at baseline (SD)	n	Mean LOCF absolute value at week 52 (SD)	Mean CFB absolute value at 52 weeks (SD)	
Overall	**Creatine kinase U/L**						
	Cipaglucosidase alfa/miglustat	85	447.0 (399.5)	85	316.5 (277.20)	−130.5 (231.2)	↑
	Alglucosidase alfa/placebo	37	527.8 (426.6)	35	588.0 (482.23)	60.2 (159.5)	↓
	ANCOVA difference in LS mean (95% CI)				−176.0 (−244.4, −107.6); **nominal one-sided $p < 0.001$**		
	Hex4						
	Cipaglucosidase alfa/miglustat	84	4.61 (3.37)	85	2.74 (1.66)	−1.88 (2.38)	↑

Alglucosidase alfa/placebo	37	6.92 (6.94)	37	8.14 (10.501)	1.22 (4.43)	↓
ANCOVA difference in LS mean (95% CI)				−2.49 (−3.66, −1.32); **nominal one-sided $p < 0.001$**		

Note: ↑ denotes improvement from baseline; ↓ worsening from baseline. Blue shading indicates treatment group is favoured
Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; CK, creatine kinase; ERT, enzyme replacement therapy; Hex4, hexose tetrasaccharide; ITT, intention-to-treat; LOCF, last observation carried forward; LS, least-squares; SD, standard deviation.

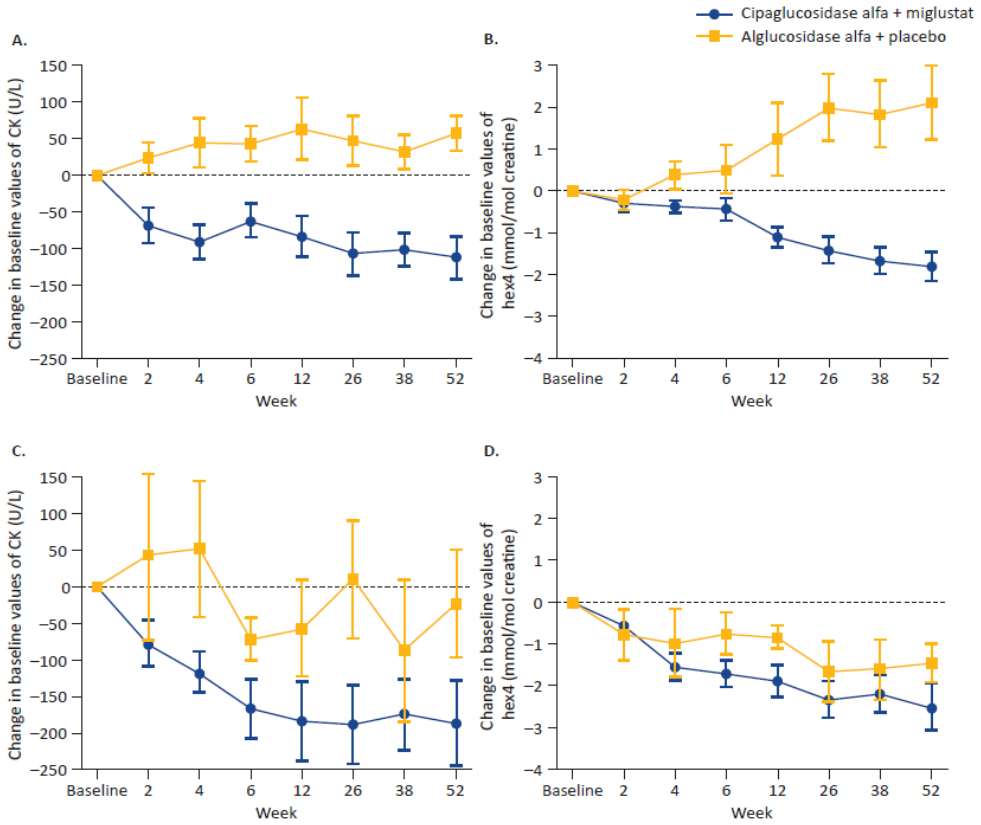
27.2. Change from baseline in absolute values of key biomarkers at 52 weeks stratified by ERT status

As reported for the overall population, a nominally statistically significant reduction in CK and Hex4, a marker of muscle damage and a disease-specific marker, was observed in both the **ERT-experienced** and **ERT-naïve populations**.

In the **ERT-experienced population**, mean changes in absolute CK and Hex4 values were −118.0 U/L (SD, 228.8) and −1.69 mmol/mol creatinine (SD, 2.41) in the cipaglucosidase alfa/miglustat arm, respectively, and 79.6 U/L (SD, 147.5) and 1.89 mmol/mol creatinine (SD, 4.61) in the alglucosidase alfa/placebo arm, respectively (ANCOVA LS mean treatment difference, CK: −179.7 (−253.9, −105.5); nominal one-sided $p < 0.001$; HEX4: −2.68 (−4.0, −1.33); nominal one-sided $p < 0.001$; Figure 48). Mean absolute CK values at baseline were 441.8 U/L (SD, 402.9) and 492.3 U/L (SD, 442.7) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at 52 weeks (LOCF) were 323.8 U/L (SD, 276.2) and 571.9 U/L (SD, 522.7), respectively (Figure 48). Mean absolute Hex4 values at baseline were 4.55 mmol/mol creatinine (SD, 3.50) and 7.17 mmol/mol creatinine (SD, 7.62), respectively, and at 52 weeks were 2.86 mmol/mol creatinine (SD, 1.76) and 9.06 mmol/mol creatinine (SD, 11.48), respectively (Figure 48).

In the **ERT-naïve population**, mean changes in absolute CK and Hex4 values in the cipaglucosidase alfa/miglustat arm were −171.3 U/L (SD, 240.2) and −2.48 mmol/mol creatinine (SD, 2.25) in the cipaglucosidase alfa/miglustat arm, respectively, and in the alglucosidase alfa/placebo arm were −23.1 U/L (SD, 193.8) and −1.64 mmol/mol creatinine (SD, 1.85), respectively (ANCOVA LS mean treatment difference, CK: −209.3 [−311.9, −106.6]; nominal one-sided $p < 0.001$; Hex4: −1.93 [−2.58, −1.29]; nominal one-sided $p < 0.001$; Figure 48). Mean absolute CK values at baseline were 464.1 U/L (SD, 398.1) and 680.3 U/L (SD, 333.1) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at 52 weeks (LOCF) were 292.8 U/L (SD, 286.4) and 657.1 U/L (SD, 260.4), respectively (Figure 48). Mean absolute Hex4 values at baseline were 4.81 mmol/mol creatinine (SD, 3.00) and 5.84 mmol/mol creatinine (SD, 2.50) in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo arms, respectively, and at 52 weeks (LOCF) were 2.33 mmol/mol creatinine (SD, 1.24) and 4.20 mmol/mol creatinine (SD, 1.49), respectively (Figure 48).

Figure 48: PROPEL secondary endpoint: mean change (± standard error) from absolute baseline values of CK and Hex4 at week 52 (observed). A. ERT-experienced: CK. B. ERT-experienced: Hex4. C. ERT-naïve: CK. D. ERT-naïve: Hex4



Population	Treatment	n	Mean absolute value at baseline (SD)	n	Mean LOCF absolute value at week 52 (SD)	Mean CFB absolute value at 52 weeks (SD)	
ERT-experienced	**CK, U/L**						
	Cipaglucosidase alfa/miglustat	65	441.8 (402.90)	65	323.8 (276.18)	−118.0 (228.79)	↑
	Alglucosidase alfa/placebo	30	492.3 (442.73)	30	571.9 (522.71)	79.6 (147.46)	↓
	ANCOVA difference in LS mean (95% CI)				−179.7 (−253.9, −105.5); **nominal one-sided $p < 0.001$**		
	Hex4, mmol/mol creatine						
	Cipaglucosidase alfa/miglustat	64	4.55 (3.50)	65	2.86 (1.76)	−1.69 (2.41)	↑
	Alglucosidase alfa/placebo	30	7.17 (7.62)	30	9.06 (11.48)	1.89 (4.61)	↓
	ANCOVA difference in LS mean (95% CI)				−2.68 (−4.03, −1.33); **nominal one-sided $p < 0.001$**		
ERT-naïve	**CK, U/L**						
	Cipaglucosidase alfa/miglustat	20	464.1 (398.1)	20	292.8 (286.4)	−171.3 (240.2)	↑
	Alglucosidase alfa/placebo	7	680.3 (333.1)	7	657.1 (260.4)	−23.1 (193.8)	↑

ANCOVA difference in LS mean (95% CI)			−209.3 (−311.9, −106.6); **nominal one-sided *p* < 0.001**			
Hex4, mmol/mol creatine						
Cipaglucosidase alfa/miglustat	20	4.81 (2.30)	20	2.33 (1.24)	−2.48 (2.25)	↑
Alglucosidase alfa/placebo	7	5.84 (2.50)	7	4.20 (1.49)	−1.64 (1.85)	↑
ANCOVA difference in LS mean (95% CI)			−1.93 (−2.58, −1.29); **nominal one-sided *p* < 0.001**			

Note: ↑ denotes improvement from baseline; ↓ worsening from baseline. Blue shading indicates treatment group is favoured.
Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CK, creatine kinase; CI, confidence interval; Hex4, hexose tetrasaccharide; ERT, enzyme replacement therapy; LOCF, last observation carried forward; LS, least-squares; SD, standard deviation.

Appendix P – Diagnostic path and disease management in Pompe disease Denmark

Figure 49: Diagnostic path and disease management in Pompe disease Denmark

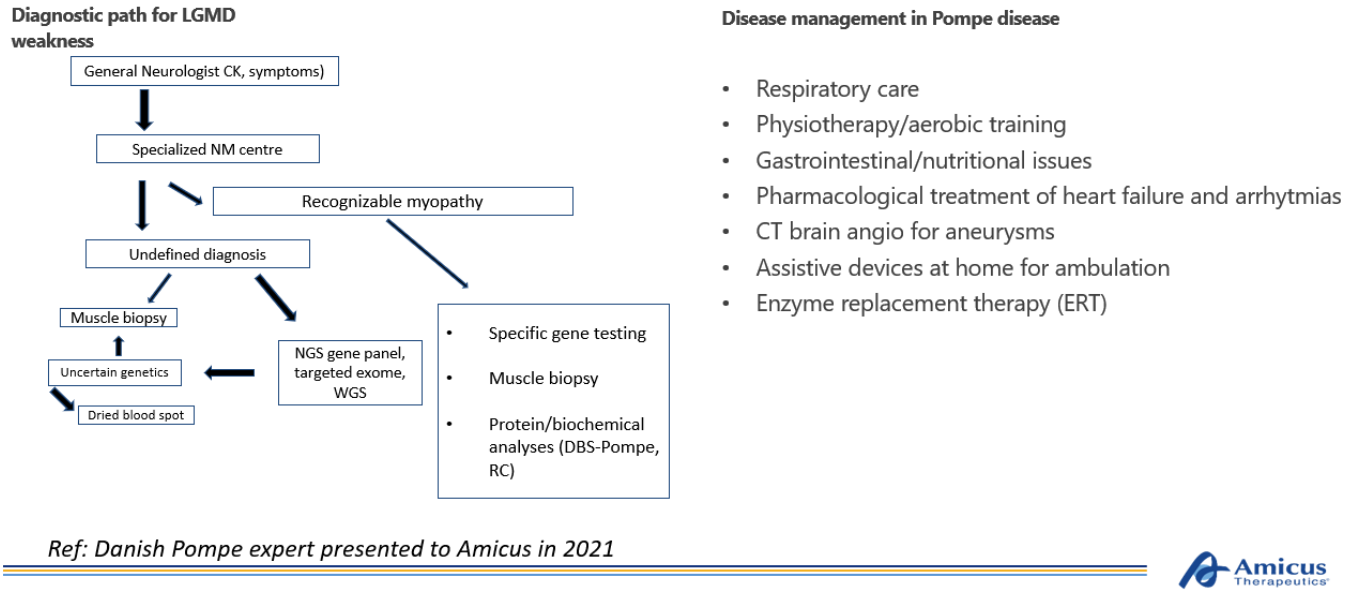
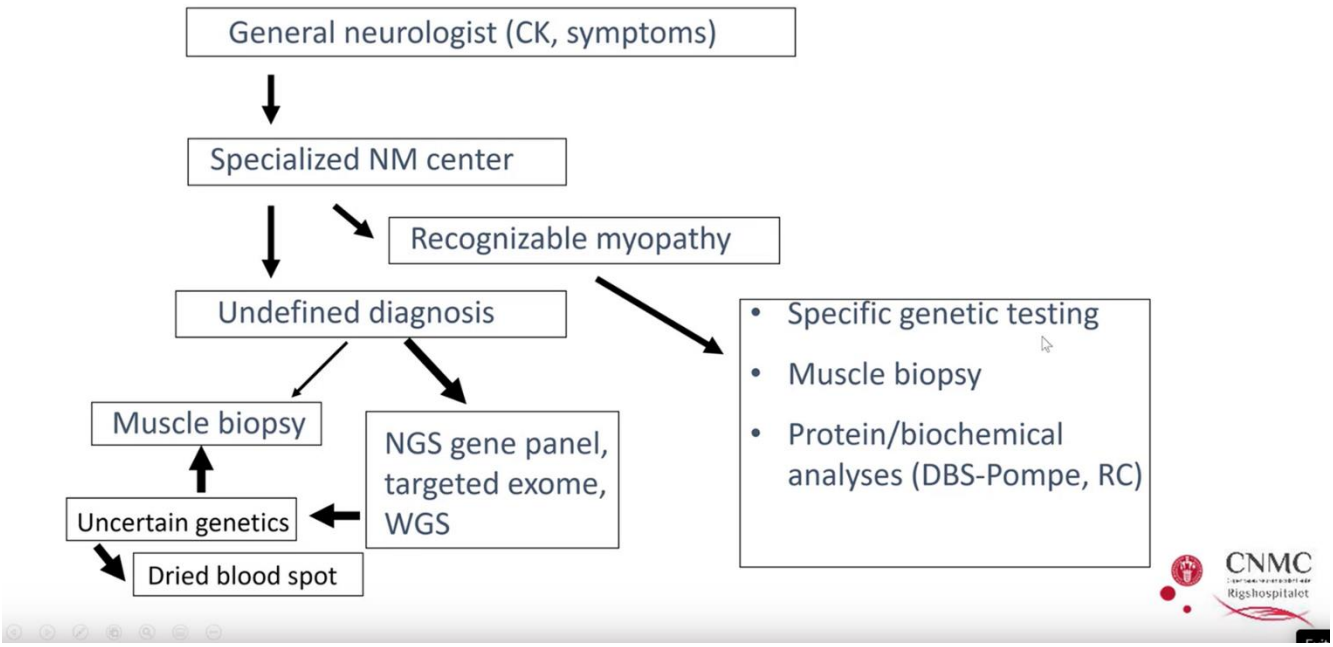


Figure 50: Diagnostic path for LGMD weakness



Appendix Q – Supporting studies ATB200-02 and ATB200-07

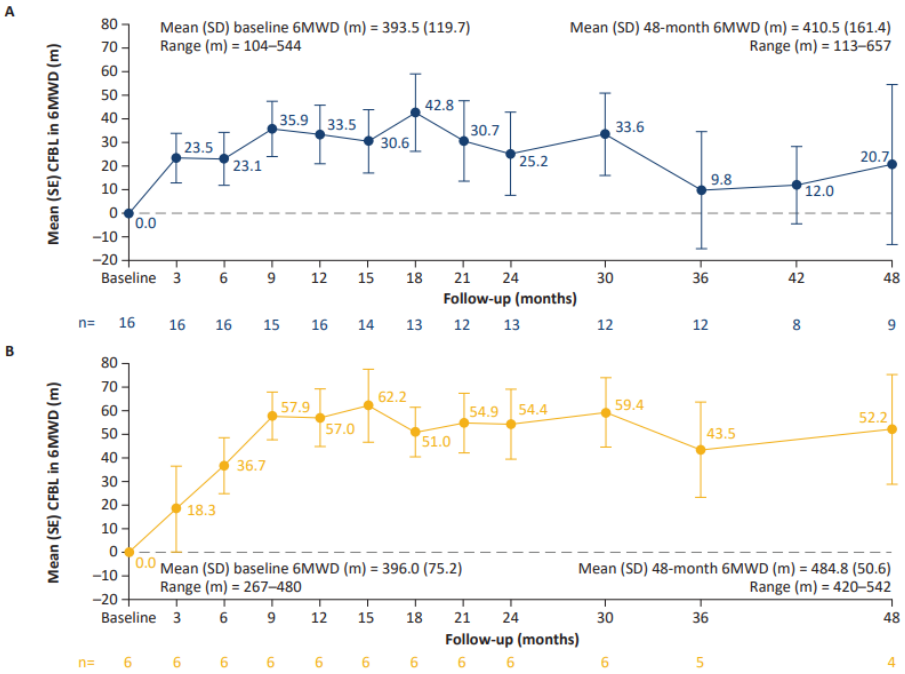
29.1. Supporting study ATB200-02 – phase 1/2 single-arm trial

There is strong evidence starting to emerge of the durability of response with cipalglucosidase alfa/miglustat: 48-month follow-up data from the phase 2 Study ATB200-02 trial showed sustained or improved walking distance and respiratory function in patients receiving cipaglucosidase alfa/ miglustat , which may address the decline in efficacy as experienced with alglucosidase alfa treatment after 2 to 5 years (Semplicini 2020, Gutschmidt 2021). Study ATB200-02 is an ongoing phase ½, open-label, single-arm, fixed-sequence, ascending-dose, first-in-human trial (NCT02675465), which evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of cipaglucosidase alfa/miglustat in 29 adult patients with LOPD.

29.1.1.1. Motor function – 6MWD

Cipaglucosidase alfa/miglustat was associated with durable mean improvements from baseline in 6MWD up to 48 months in both ERT-experienced and ERT-naïve patients (Figure 51).

Figure 51: CFBL in 6MWD in (A) ERT-experienced and (B) ERT-naïve patients

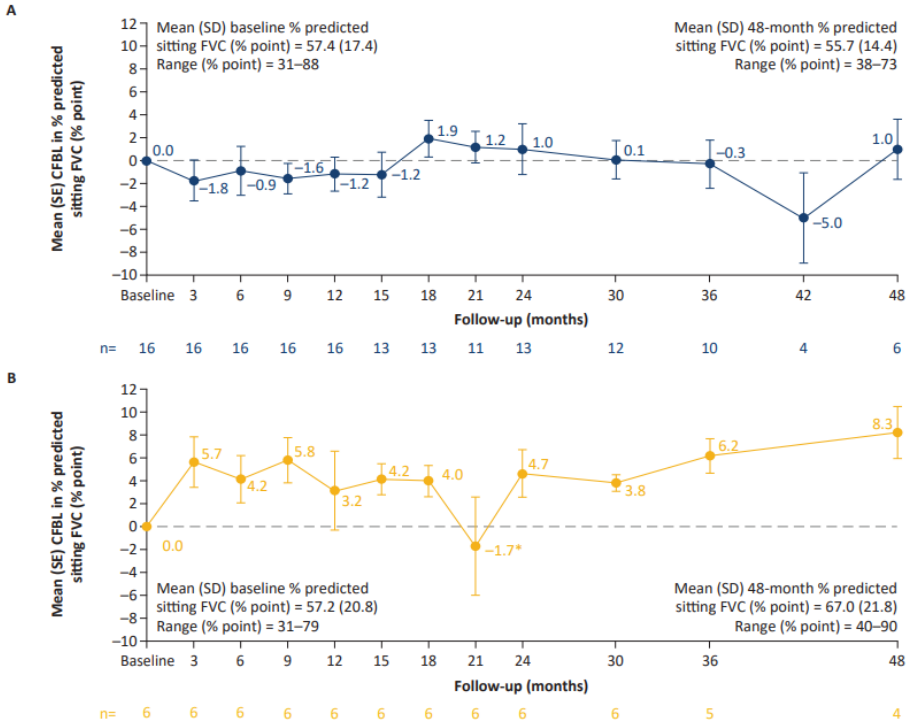


Abbrevations: 6MWD, 6-minute walk distance; BL, baseline; CFBL, change from baseline; ERT, enzyme replacement therapy; SE, standard error.

29.1.1.2. Respiratory function – FVC

The mean change from baseline (CFBL) in FVC was generally stable for up to 48 months of follow-up in ERT-experienced patients receiving cipaglucosidase alfa/miglustat. In ERT-naïve patients, cipaglucosidase alfa/miglustat was associated with a numerical improvement in mean CFBL in FVC for up to 48 months of follow-up (Figure 52).

Figure 52: CFBL in FVC in (A) ERT-experienced and (B) ERT-naïve patients



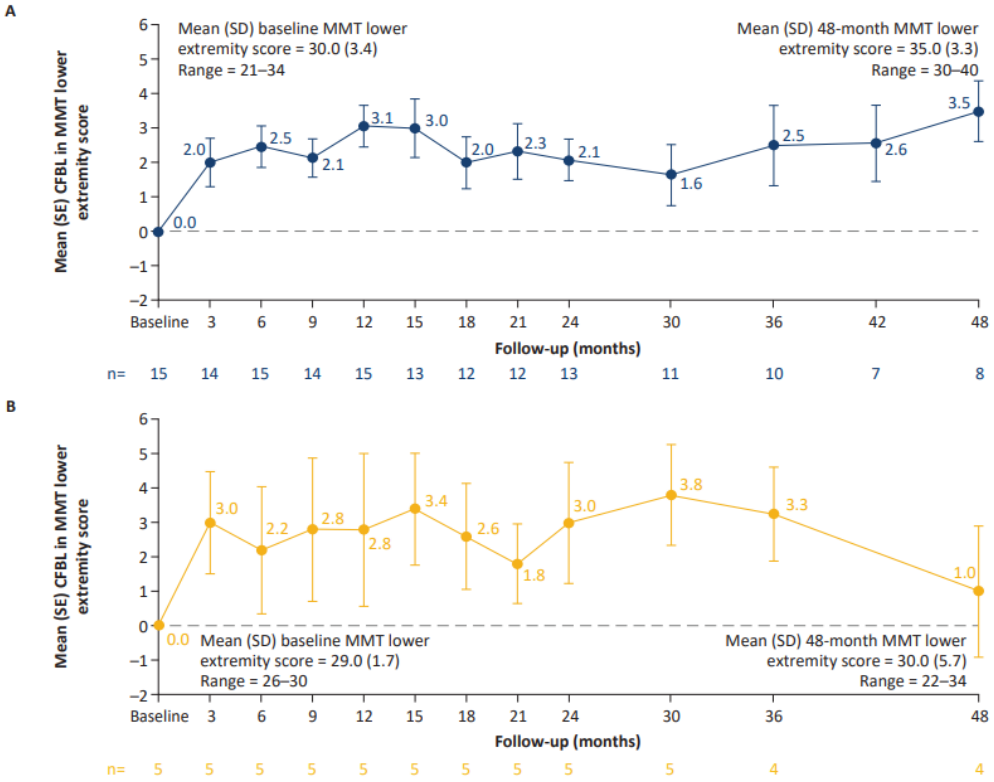
Note: One patient in the ERT-naïve cohort experienced a large drop in % predicted FVC at month 21, which returned to previous levels at the following visit (month 24).

Abbrvations: BL, baseline; CFBL, change from baseline; ERT, enzyme replacement therapy; FVC, forced vital capacity; SE, standard error.

29.1.1.3. Muscle strength – MMT lower extremity score

Cipaglucosidase alfa/miglustat was associated with a numerical improvement in mean CFBL in MMT lower extremity score, with improvements maintained for up to 48 months of follow-up in both ERT-experienced and ERT-naïve cohorts (Figure 53).

Figure 53: CFBL in MMT lower extremity score in (A) ERT-experienced and (B) ERT-naïve patients

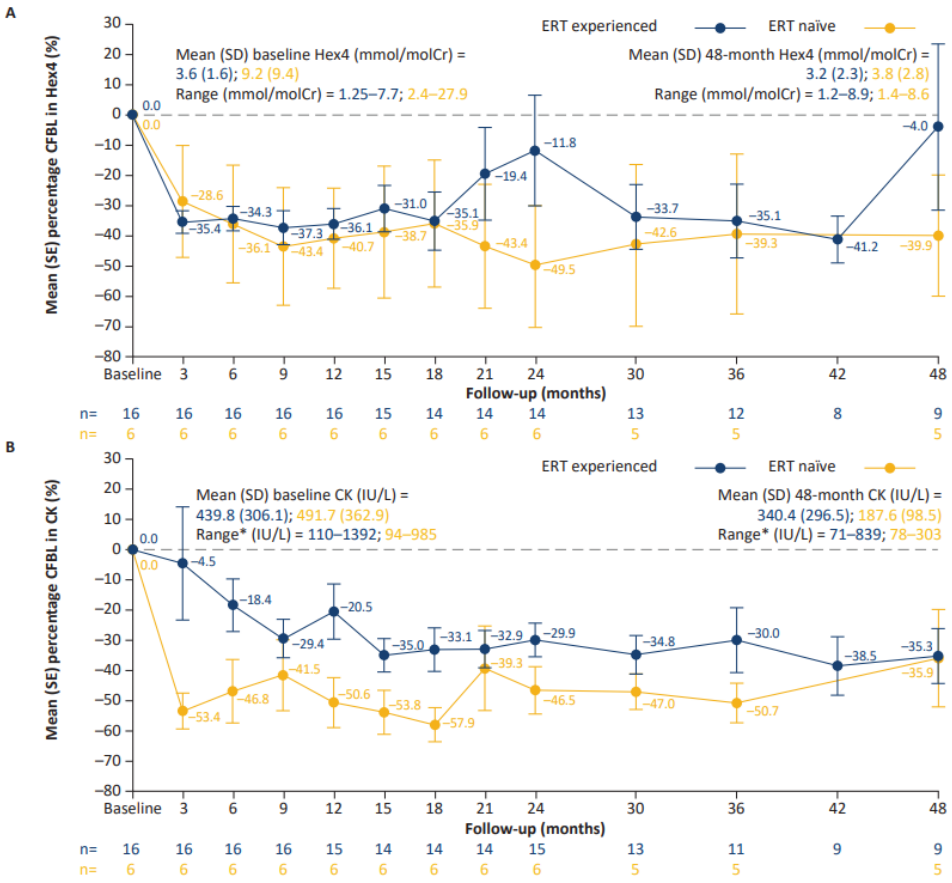


Abbreviation: BL, baseline; CFBL, change from baseline; ERT, enzyme replacement therapy; MMT, manual muscle test; SE, standard error.

29.1.1.4. Biomarkers

During the 48 months of follow-up, cipaglucosidase alfa/miglustat was generally associated with mean reductions from baseline in urine Hex4, especially in ERT-naïve patients (Figure 54). Cipaglucosidase alfa/miglustat was associated with either stable levels or mean reductions from baseline in plasma CK, with greater reductions in ERT-naïve patients (Figure 54).

Figure 54: Percentage CFBL in Hex4 and CK levels



Abbreviations: BL, baseline; CFBL, change from baseline; CK, creatine kinase; ERT, enzyme replacement therapy; Hex4, hexose tetrasaccharide; SE, standard error.

29.1.1.5. Safety

Table 84 summarises the TEAEs associated with cipaglucosidase alfa/miglustat during the 36-month follow-up; the safety profile of cipaglucosidase alfa/miglustat was similar to that reported for alglucosidase alfa (van der Ploeg 2010). The mean (SD) duration of treatment was 37.2 (SD, 14.48), 19.9 (SD, 4.13) and 36.9 (SD, 12.14) months in cohorts 1 (prior ERT 2–6 years), 4 (prior ERT ≥ 7 years) and 3 (ERT-naïve), respectively. The most frequently reported TEAEs included fall, nasopharyngitis and arthralgia; most TEAEs were mild or moderate in severity and did not lead to study withdrawal.

Table 84: Summary of TEAEs

	ERT experienced n = 17	ERT naïve n = 6	Overall N = 23
TEAEs	17 (100)	6 (100)	23 (100)
TEAEs potentially related to treatment	11 (65)	3 (50)	14 (61)
Serious TEAEs	3 (18)	2 (33)	5 (22)
Serious TEAEs potentially related to treatment	1 (6)	1 (17)	2 (9)
TEAEs leading to study withdrawal	1 (6)[a]	0 (0)	1 (4)
TEAEs leading to death	0 (0)	0 (0)	0 (0)
IARs	7 (41)	2 (33)	9 (39)

Note: All data are presented as n (%). TEAEs have an onset date on or after first dose of study drug. [a]Diffuse large B-cell lymphoma.

Abbreviations: ERT, enzyme replacement therapy; IAR, infusion-associated reaction; TEAE, treatment-emergent adverse event.

29.2. Supporting study ATB200-07 – open-label extension of the PROPEL study

ABT200-07 (NCT04138277) is an open-label extension to assess the long-term safety and tolerability (primary endpoint), and the efficacy (secondary endpoint), of cipaglucosidase alfa/miglustat in patients who participated in the phase 3 PROPEL study.

Patients who participated in the PROPEL study were scheduled to undergo an infusion approximately 2 weeks after their last visit for the PROPEL study, and every 2 weeks thereafter, ensuring the treatment regimen investigated in PROPEL was maintained. Study treatment will be continued until 31 December 2023 or until study termination, and after a 30-day safety follow-up. Patients discontinuing treatment for any reason will undergo immunogenicity testing for up to 12 months.

In line with PROPEL, the efficacy endpoints include assessment of ambulatory function (6MWT), motor function (GSGC and timed up and go [TUG]), muscle strength (manual [MMT] and quantitative muscle test [QMT]) and pulmonary function (FVC, slow vital capacity [SVC], MIP, maximum expiratory pressure [MEP] and sniff nasal inspiratory pressure [SNIP]) as well as patient-reported outcomes (PROs; R-PAct, 5-dimension, 5-level EuroQol questionnaire [EQ-5D-5L], PROMIS (Fatigue, Physical Function, Dyspnoea and Upper Extremities), SGIC and Physician's Global Impression of Change [PGIC]).

At the interim data cut-off on 1 April 2021, a total of 117 patients who had completed PROPEL were enrolled and treated in Study ATB200-07; an additional patient who discontinued PROPEL was permitted to enter ATB200-07 (118 patients in total). The efficacy population comprised 111 patients (94.1%): 46 (41.4%) had at least 3–6 months' additional exposure to cipaglucosidase alfa/miglustat and 36 (32.4%) had at least 6–9 months additional exposure. Of the 118 patients enrolled in ATB200-07, 81 patients were allocated cipaglucosidase alfa/miglustat in PROPEL, and 37 received alglucosidase alfa/placebo. A single patient (switched from alglucosidase alfa/placebo to cipaglucosidase alfa/miglustat) discontinued treatment owing to two serious AEs (SAEs; urticaria and hypotension).

Baseline demographics were similar between patients who had received cipaglucosidase alfa/miglustat during PROPEL and those who had received alglucosidase alfa/placebo. Of the 111 patients who comprised the efficacy population, 27 (24.3%) were ERT-naïve in PROPEL and 84 (75.4%) were ERT-experienced. Prior exposure to ERT was similar between patients who remained on cipaglucosidase alfa/miglustat and those who switched from alglucosidase alfa/placebo.

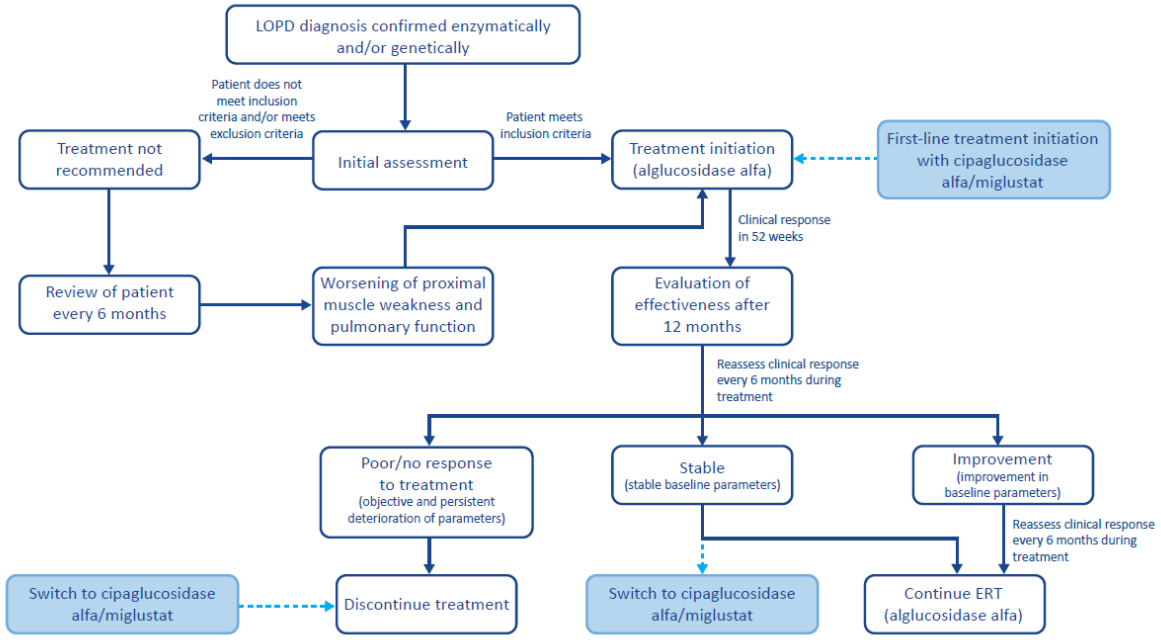
A total of 55 patients had reached week 26 by data cut-off (1 April 2021). Mean change from baseline (baseline defined as start of open-label extension study) 6MWD was 1.5 m (SD, 34.9 m): the benefits observed with cipaglucosidase alfa/miglustat in PROPEL were maintained in patients who continued to receive cipaglucosidase alfa/miglustat in ATB200-07 (mean change from baseline at week 26 [SD], –2.0 m [37.80]) and those who switched to cipaglucosidase/miglustat demonstrated similar improvements to those reported in PROPEL (mean change from baseline [SD], +9.3 m [26.5]). Mean change from baseline % predicted FVC was stable at week 26 (+1.1 [SD, +7.0]): +1.2 (SD, +8.1) in patients who remained on cipaglucosidase alfa/miglustat and +0.9 (SD, +4.1) in patients who switched to cipaglucosidase alfa/miglustat (Schoser 2023).

Appendix R – International treatment guidelines

Most guidelines recommend that ERT is initiated soon after symptom onset, although it can still benefit patients with advanced disease (van der Ploeg 2017). Conversely, for patients who are asymptomatic, initiation of ERT is not recommended; instead patients should be monitored every 6 months in the first year and once per year thereafter for signs of disease progression that would prompt initiation of ERT. Monitoring of disease progression of both untreated and treated patients should include (van der Ploeg 2017):

- MMT using the Medical Research Council grading scale
- 6-MWT
- Timed tests (10-metre walk, four-step climb, stand up from supine and stand from chair [chair test])
- FVC in sitting and supine positions
- MIP/MEP
- Ventilation use

Figure 55: Proposed positioning of cipaglucosidase alfa/miglustat in LOPD treatment pathway based on guidelines analysis



Abbreviations: ERT, enzyme replacement therapy; LOPD, late-onset Pompe disease.
Source: (Amicus data on file 2021b)

Kishnani *et al.* (2006) created the first official Pompe disease diagnosis/treatment guideline with the American College of Medical Genetics and Genomics, which is largely based on experiences in the USA (Kishnani 2006). Several other consensus recommendation guidelines have been published, capturing new information, emerging experiences and/or non-US experiences. The current treatment themes for the management of patients with Pompe disease are summarised in Table 85 and Table 86.

Table 85: Overarching guideline themes for the management of Pompe disease

Theme	Details
Screening and diagnosis	• Within Europe, as of 2018 onwards, most of the diagnostic recommendations follow the Van der Ploeg *et al*. 2017 guidelines: initial screening using DBS is recommended, but only after diagnostic suspicion of Pompe disease

	• The diagnostic 'gold standard' is currently GAA assays performed on skin fibroblast (preferred tissue) or muscle biopsy; these can render a definitive diagnosis of Pompe disease, when combined with clinical and laboratory data (Al Jasmi 2015)
Initiation and discontinuation of ERT	• There are well-defined and accepted recommendations on when to initiate and stop alglucosidase alfa, (van der Ploeg 2017) which at the time the guidelines were issued was the only approved ERT for the treatment of Pompe disease • European consensus literature provides criteria for starting and stopping ERT; (van der Ploeg 2017) however, the exact recommended criteria are vague • Given the unmet need and current treatment decline in efficacy after a few years, new guidelines for the initiation, termination and switching treatment may be necessary to describe the treatment landscape pending the approval of additional treatment options • Longer term data are needed before official clinical switch criteria can be established (long-term according to Danish expert is considered 3 to 5 years, section 11 List of experts)
Monitoring	• As discussed in Section 5.2.2, the management of Pompe disease requires a multidisciplinary team, with Pompe management relying heavily on symptomatic management and supportive care depending on phenotype • Patients undergoing ERT also require monitoring of disease progression (5.2.2.3), involving frequent laboratory and function outcome assessments. A monitoring schedule by classification and phenotype is presented by Kronn 2017, (Kronn 2017) albeit a standardised process across treatment centres is lacking • There is consistency between local and international sources in recommended monitoring measures, with a core set of assessments including muscle strength, muscle function, pulmonary function and patient-reported outcomes • The 6MWT is considered the gold standard for measuring muscle function; however, this test does not reflect reality for many patients when improvements may not be perceived as clinically significant to them • Measuring FVC in a sitting and supine position, along with measuring MIP and MEP, are considered the gold standards for measuring pulmonary function • Patient-reported outcomes are infrequently recommended within guidelines as measures for monitoring disease progression; however, these have been identified as key in other literature and through Amicus advice-seeking activities • When monitoring patient symptoms and disease progression, it is important to consider multiple parameters. Physicians in the Nordics working with LOPD have noted that a worsening in one parameter (e.g., 6MWT) will not on its own lead to treatment switching, if other parameters are stable or improving; all the clinical parameters should be weighed and evaluated together (AMICUS data on file 2022a).
Future guidelines/clarifications required	Guidelines are required that clarify: • prognosis and genotype-phenotype correlations in asymptomatic LOPD • whether to initiate ERT in patients with asymptomatic LOPD with laboratory signs of disease • recommendations on 'next-generation' ERTs • start/stop/switch recommendations for alglucosidase alfa • use of cipaglucosidase alfa plus miglustat (pending approval) and avalglucosidase alfa (FDA and EMA approvals received) In patients who do not initially respond to treatment or who start to decline after initial response with alglucosidase alfa, more frequent (off-label) dosing is often considered in the absence of new and more efficacious treatment (Kronn 2017, Semplicini 2020).

Abbreviations: 6MWT, 6-minute walk test; DBS, dried blood spot; ERT, enzyme replacement therapy; FDA, Food and Drug Administration; FVC, forced vital capacity; GAA, α-1,4-glucosidase; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; MENA, Middle East and Northern Africa; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; NBS, newborn screening

Table 86: Region-specific guidelines for the management of Pompe disease

Region/area (Year of publication)	Key guidance	Recommendation on ERT initiation	Recommendation on when to stop ERT
Europe (van der Ploeg 2017, van Kooten 2020)	Treatment should consist of: ERT (Q2W IV alglucosidase alfa; Myozyme®/Lumizyme®, Sanofi Genzyme), initiated for a 2-year period then evaluated monitoring (residual skeletal and respiratory function tests) The EPOC agreed that a regular diet and exercise should be recommended as a complementary strategy for patients with LOPD undergoing ERT (Angelini 2021)	Treatment should be initiated in patients who: have a confirmed diagnosis; and are symptomatic (skeletal muscle weakness or respiratory muscle involvement)	Treatment should only be stopped if: patients experience a severe infusion-associated reaction high anti-ERT antibody titres the patient wishes to stop ERT patient does not comply with regular infusions/assessments the patient has, or develops, another life-threating condition no indication of skeletal muscle function and/or respiratory function stabilisation or improvement in first 2-year period (using ENMC criteria) If the patient deteriorates after stopping treatment, re-initiation can be considered

Abbreviations: ENMC, European Neuromuscular Centre; EPOC, European POmpe Consortium; ERS, European Respiratory Society; ERT, enzyme replacement therapy; IV, intravenous; LOPD, late-onset Pompe disease; Q2W, every 2 weeks.

Appendix S – Pompe disease-related parameters routinely measured in clinical practice

Table 87: Pompe disease-related parameters routinely measured in clinical practice (van der Ploeg 2017)

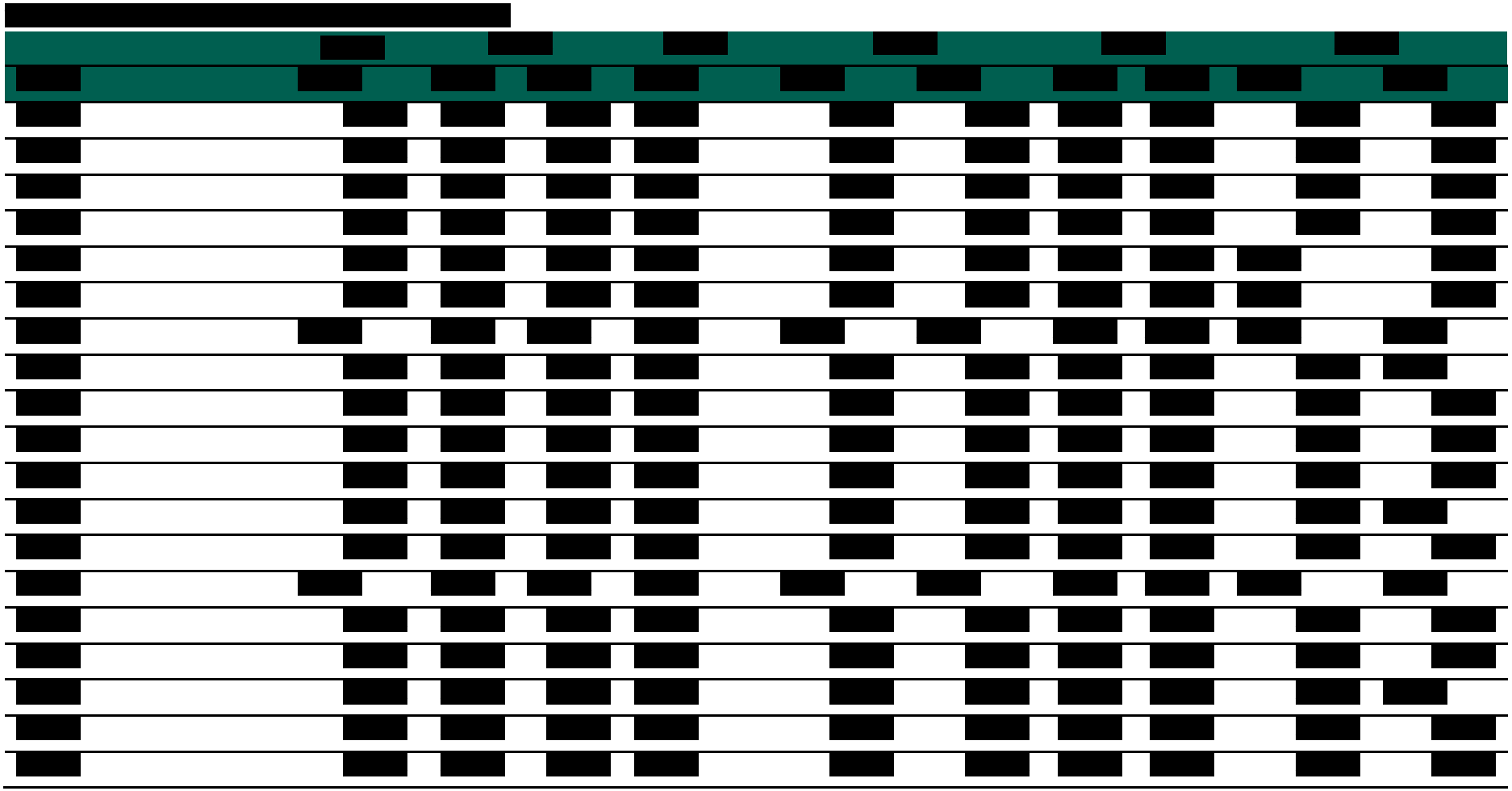
Clinical domain	Measurable endpoint	Definition
Motor function 	6-min walk distance (6MWD) (*primary endpoint in PROPEL*)	Measures the distance that patient can quickly walk on a flat, hard surface in a period of 6 minutes Requires a 30-metre indoor, quiet, straight corridor Evaluates the pulmonary and cardiovascular systems, systemic circulation, neuromuscular units and muscle metabolism Reflects the functional exercise associated with patient's ADLs An increasing number from baseline to week 52 is a positive response (American Thoracic Society 2002)
	(Gait, Stairs, Gowers', Chair) (GSGC)	The GSGC score is a composite test of motor function used to qualitatively assess the patient's ability to complete four motor performances: Gait – 10-metre walk Stairs – four-stair climb Gowers' manoeuvre – supine to standing position Chair – sitting to standing position The patient is rated on ability to complete the four motor performances and is assigned a score of 1–7 for gait, stairs and Gower and 1–6 for stairs, with high total scores reflecting more impairment A mean decrease in Global GSGC score from baseline is a positive response (Angelini 2012)
	Time to complete GSGC test	Time taken to complete GSGC test (above) A decrease in time from baseline to week 52 considered a positive response (improvement) (Angelini 2012)
	Timed Up & Go (TUG) test	Assesses functional mobility, balance and gait Patients are required to rise from a chair to a standard position, walk 3 metres forward, turn around, walk back to the chair and sit back down A decrease in time from baseline to week 52 is considered a positive response (Dunaway 2014)
Pulmonary function 	Forced Vital Capacity (FVC) (% predicted sitting) (*first key secondary endpoint in PROPEL)*	A volitional measure of respiratory function, and a commonly reported outcome assessed in LOPD A spirometer measures the volume of air (litres) that can be forcibly exhaled from the lungs after taking a deep breath FVC data are primarily reported as the percentage of predicted normal An increase in the percentage change from baseline to week 52 is considered a positive response (Berger 2019)
	Slow Vital Capacity (SVC)/max VC	In addition to FVC (above), SVC and max VC are measures of lung volume and are measured using a spirometer An increase in volume from baseline to week 52 is considered a positive response (Amicus data on file)
	Maximal inspiratory pressure (MIP)/ maximal expiratory pressure (MEP)	MIP and MEP are measures of negative and positive pressure, respectively A respiratory pressure meter (MicroRPM; CareFusion, Basingstoke, UK) is used for measurement An increase in pressure from baseline to week 52 is considered a positive response (improvement) (Amicus data on file)
	sniff nasal-inspiratory pressur e (SNIP)	SNIP is a similar measure to MIP/MEP (above) but measures negative pressure through the nostril

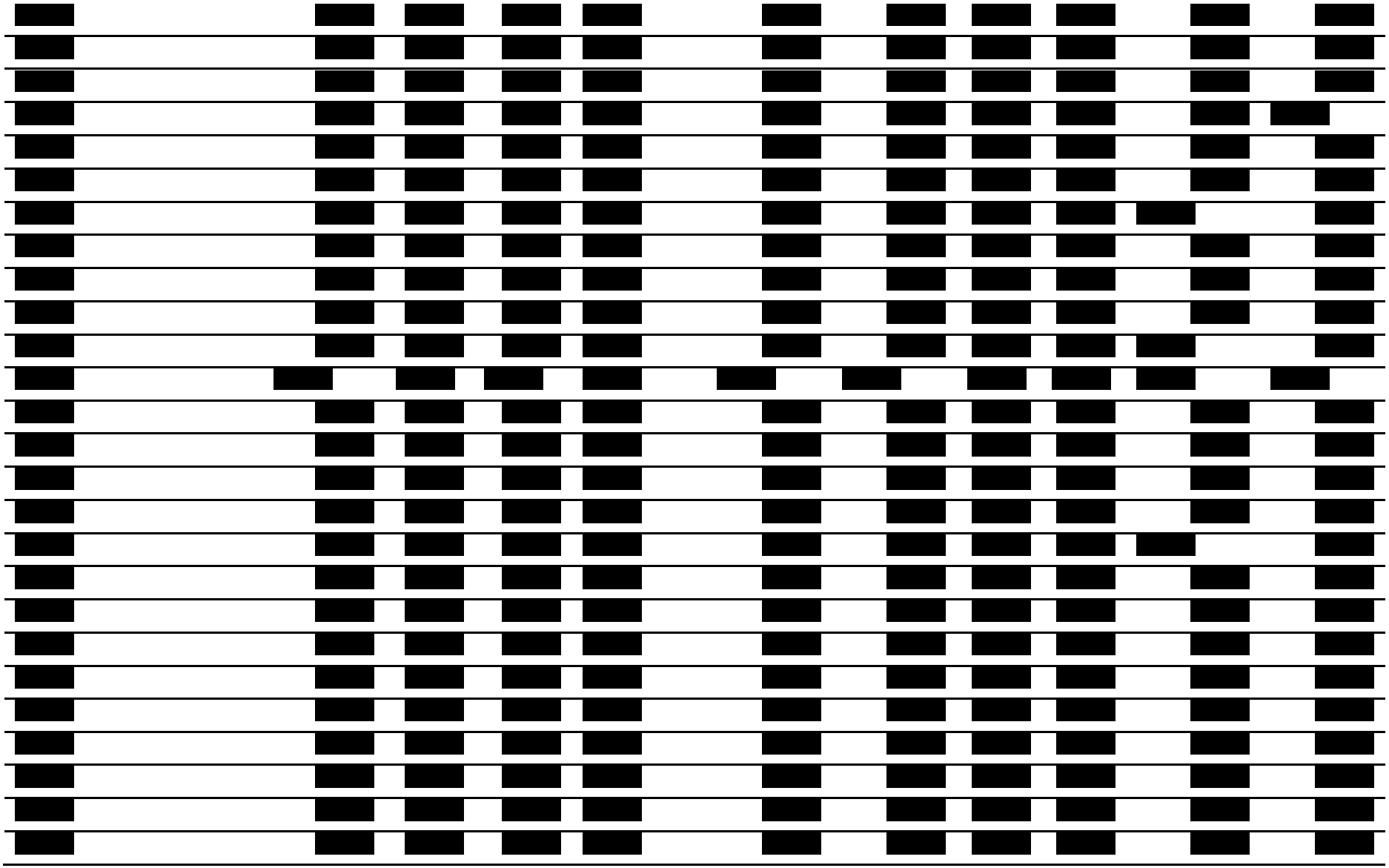
Muscle strength 	Manual Muscle Test (MMT)	A qualitative test of strength of specific muscle group(s), tested in isolation using a Medical Research Council scale Evaluates the musculoskeletal system Both the upper (e.g., shoulder adduction, elbow extension) and the lower extremities (e.g., hip abduction, hip flexion and knee flexion/extension) can be evaluated using MMT Change from baseline to week 52 was investigated; a positive response/improvement from baseline is represented by an increasing number (Schoser 2021c)
	Quantitative Muscle Testing (QMT)	Quantitative test of strength of specific muscle group(s), tested in isolation using the MicroFET2™ Hand-held Dynamometer The evaluator applies resistance to each muscle group and records the weight resisted by the patient An increase in resistance weight from baseline to week 52 is considered a positive response (improvement) (Amicus data on file)
PROs and quality of life 	PROMIS®–Physical Function	A multi-item questionnaire to assess patient perspective regarding overall physical function It assesses the ability to complete select ADLs that require varying levels of physical function based on patient-reported experience. Each of the 20 items on the questionnaire is rated on a scale of 1–5, where: 5 = patient reports they can complete the action without any difficulty 1 = patient reports they are unable to complete the activity A mean increase in PROMIS–Physical Function from baseline is positive and represents improvement (Rose 2014, Harfouche 2020)
	PROMIS®–Fatigue	A multi-item questionnaire to assess patient perspective regarding overall fatigue Each of the eight items on the questionnaire is rated on a scale of 1–5, where: 5 = patient reports a great amount of limitation due to fatigue 1 = patient reports no limitations due to fatigue A mean decrease in PROMIS–Fatigue total score from baseline is a positive response (Harfouche 2020)
	PROMIS®–Dyspnoea and PROMIS®–Upper Extremities	Multi-item questionnaires to assess patient perspective regarding incidence of dyspnoea and upper extremity function, respectively All items on each questionnaire are rated as mentioned previously (Harfouche 2020)
	EQ-5D-5L	A PRO tool used to assess quality of life It addresses five different dimensions, including mobility, self-care (ability to wash and dress oneself), usual activities (of daily life), pain/discomfort and anxiety/depression Each dimension is assigned one of five different levels, including no problem, slight problems, moderate problems, severe problems and extreme problems The patient is also asked to rate their overall health on a visual analogue scale (EQ-VAS) of 0–100 (100, best possible health; 0, worst possible health) (EuroQol 2023)
	Rasch-built Pompe-specific activity (R-Pact)	A patient reported outcome tool designed to quantify the impact of Pompe disease on ADLs and social participation. Consists of 18 different tasks ordered by increasing difficulty, of which the patient reports whether they can complete the given task (2, yes and without difficulty; 1, yes but with difficulty; 0, no) (van der Beek 2013)
	Subject Global Impression of Change (SGIC)	A patient-reported metric used to measure the effects of the study drug on different areas of life Eight different areas of life are measured, including overall physical well-being, effort of breathing, muscle strength, muscle function, ability to move around, ADLs, energy level and level of muscular pain

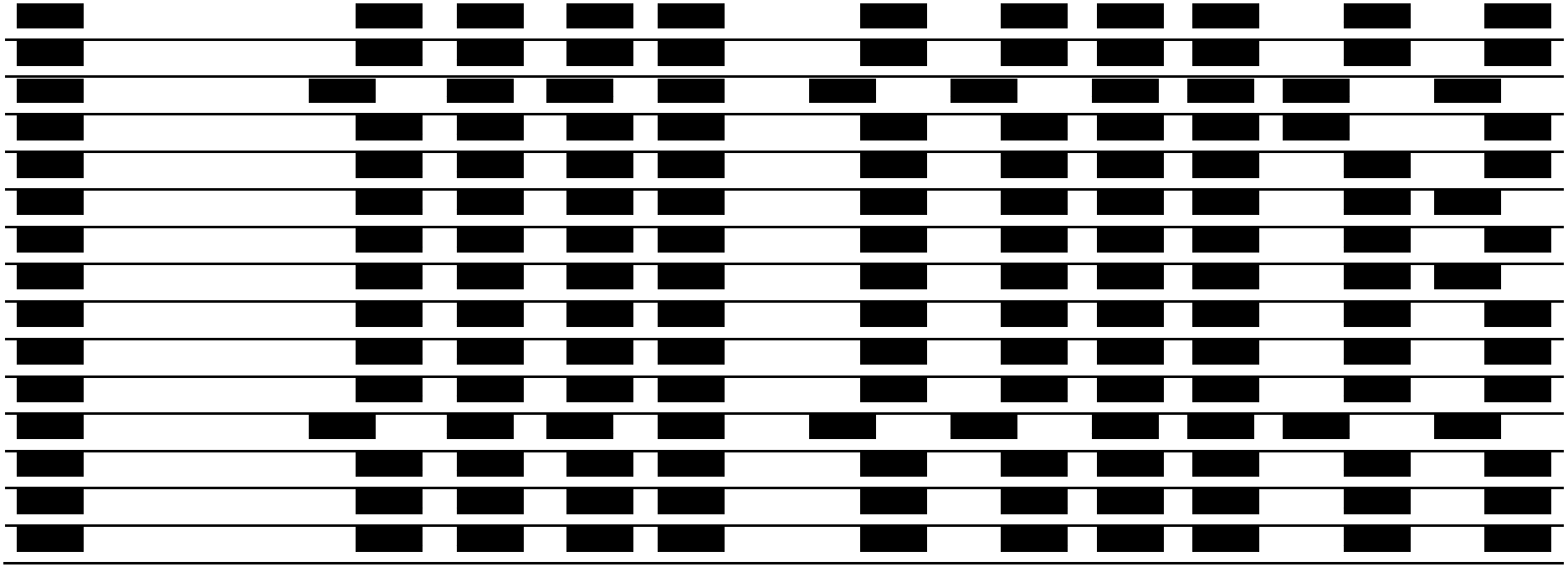
		The patient ranks each of the eight areas of life from 1 to 7 (7, very much improved; 1, very much worse) An increase in value of functional status from baseline to week 52 is considered a positive response (improvement) (Amicus data on file. ATB200-03 Clinical Study Protocol)
	Physician's Global Impression of Change (PGIC)	This is a measurement of the patient's functional status based on the physician's impression (improving, stable or declining) An increase in value of functional status from baseline to week 52 is considered a positive response (improvement) (Amicus data on file. ATB200-03 Clinical Study Protocol)
Biomarkers 	Creatine Kinase (CK)	An enzyme found within the muscles; injury to the membrane surrounding muscle cells allows CK to leak into the bloodstream and is indicative of muscle damage Serum CK levels are often elevated in patients with LOPD Percentage change in CK (U/L) can be measured; a mean increase from baseline is a positive response (American Association of Neuromuscular & Electrodiagnostic Medicine 2009, Spada 2013)
	Hex4	Used as an indirect measure of glycogen clearance in Pompe disease A laboratory assay is used to target the Glc_4, which is a biomarker of glycogen storage Glc_4 is separated from urine by ultra-performance liquid chromatography and quantified by stable isotope dilution. Glc_4 concentrations are compared with age-matched control ranges Percentage change in urinary Hex4 (mmol/mol creatinine) from baseline to week 52 can be measured, and a mean decrease in urinary Hex4 from baseline is a positive response (Chien 2015)

Abbreviations: 6MWD, 6-minute walk distance; ADL, activity of daily living; CK, creatine kinase; EQ-5D-5L, 5-dimension, 5-level EuroQol questionnaire; EQ-VAS, EuroQol visual analogue scale; FVC, forced vital capacity; Glc_4, glucose tetrasaccharide; GMFM 88/66, Gross Motor Function Measure 88/66; GSGC, gait, stairs, Gower's manoeuvre, chair; Hex4, hexose tetrasaccharide; LOPD, late-onset Pompe disease; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; MMT, manual muscle test; PGIC, Physician's Global Impression of Change; PRO, patient-reported outcome; PROMIS®, Patient-Reported Outcomes Measurement Information System; QMT, quantitative muscle test; R-PAct, Rasch-built Pompe-specific Activity; SGIC, Subject's Global Impression of Change; SNIP, sniff nasal inspiratory pressure; SVC, slow vital capacity; TUG, timed up and go; VC, vital capacity.

[redacted]







Appendix U – Utility values

In a targeted review (2020) of literature (Kanters 2011, Kanters 2013, Kanters 2014, Kanters 2015) reporting HRQoL and healthcare resource use (HCRU) associated with Pompe disease, utility values of patients appeared to decline with disease duration among adults who used a wheelchair and those who needed respiratory support (Table 89).

Table 89 Studies providing estimates of utility values for patients with Pompe disease

Study	IOPD/LOPD (n)	Method of elicitation (tools)	Utilities: valuation method	Source of perspective of the values	Mean or median utility with standard error or confidence intervals	
(Castro-Jaramillo 2012)	IOPD; n = NR	EQ-5D: version (3L or 5L) was not stated	Not stated	Symptomatic patients with Pompe disease	EQ-5D, middle state (range): 0.587 (0.189–0.814)	
(Kanters 2011)	NR; n = 80	EQ-5D: version (3L or 5L) was not stated	Dutch tariff	Patients with Pompe disease		**EQ-5D, all patients (no ERT)**
					Overall	0.72 (SE, 0.18)
					With ambulatory support	0.67 (SE, 0.21)
					With respiratory support	0.61 (SE, 0.26)
					Disease duration ≤ 5 years	0.74 (SE, 0.15)
					Disease duration 6–15 years	0.70 (SE, 0.16)
					Disease duration > 15 years	0.69 (SE, 0.23)
(Kanters 2013)	NR; n = 67	EQ-5D: version (3L or 5L) was not stated	Dutch tariff	Patients with Pompe disease	EQ-5D, mean (range) 0.70 (–0.13 to 1.00)	
(Kanters 2015)	NR; n = 80	EQ-5D: version (3L or 5L) was not stated SF-6D	Dutch tariff	Patients with Pompe disease		**EQ-5D** **SF-6D**
					Overall:	0.670 (SE, 0.201) 0.699 (SE, 0.092)
					With wheelchair:	0.533 0.666
					Without wheelchair:	0.729 0.713
					With ventilation:	0.593 0.688
					Without ventilation:	0.693 0.704

(Kanters 2017)	LOPD; n = NA	Regression analysis of multiple QoL tools and VAS	Dutch tariff		Patient's estimated health perceptions and patient characteristics (age, disease duration, enzyme activity and treatment)	ERT: 0.45 No ERT: 0.42	
(Simon 2019)	IOPD and LOPD; n = 862	TTO method applied to Pompe disease health states that were described	TTO		General population	Mild symptoms, ≥ 18 years of age: 0.853 (0.811–0.892) Moderate symptoms, ≥ 18 years of age: 0.683 (0.634–0.729) Severe symptoms, ≥ 18 years of age: 0.536 (0.480–0.594) ERT treatment, ≥ 18 years of age: 0.673 (0.621–0.723)	
(Wyatt 2012)	IOPD: early onset, n = 12; late onset, n = 3 LOPD: adults, n = 62; children, n = 3	EQ-5D: version (3L or 5L) was not stated	UK tariff		Patients with Pompe disease	EQ-5D: No statistically significant difference in EQ-5D utility found by duration of ERT; no mean score provided	
(Hubig 2023)		EQ-5D and TTO vignette study of Pompe disease health states	Vignette and TTO study		**General population**	**EQ-5D (vignette study)**	**TTO (vignette study)**
					No wheelchair use or respiratory support (>15 years alive from treatment initiation)	0.608	0.754
					Intermittent mobility support	0.433	0.614
					Intermittent respiratory support (non-invasive ventilation)	0.361	0.558
					Intermittent mobility support and intermittent respiratory support (non-invasive ventilation)	0.289	0.412
					Wheelchair dependent	0.108	0.338
					Intermittent respiratory support and wheelchair dependent (non-invasive ventilation)	0.080	0.243
					Wheelchair and respiratory support dependent (non-invasive ventilation)	-0.078	0.132
					Wheelchair and respiratory support dependent (invasive ventilation)	-0.078	0.132

Abbreviations: ERT, enzyme replacement therapy; EQ-5D (3L or 5L), 5-dimension EuroQol questionnaire (3-level or 5-level version); IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; NR, not recorded; QoL, quality of life; SE, standard error; SF-6D, Short-Form Six-Dimension questionnaire; TTO, time trade-off.
Source: (York Health Economics Consortium 2020b)

Appendix V – Summary of primary and key secondary endpoints, request of the CHMP vs CSR analyses

presents the post-hoc analysis outcomes as requested by the CHMP and report on the EMA EPAR, as well as the outcomes per the CSR.

Figure 56 Summary of primary and key secondary endpoints in the overall (ERT-experienced and ERT-naïve), ERT-experienced and ERT-naïve populations

Endpoints	Overall population			ERT-experienced			ERT-naïve		
	CFB at week 52		LS mean treatment difference (95% CI)	CFB at week 52		LS mean treatment difference (95% CI)	CFB at week 52		LS mean treatment difference (95% CI)
	Cipaglucosidase alfa with miglustat (n = 85)	Alglucosidase alfa/placebo (n = 37)		Cipaglucosidase alfa with miglustat (n = 65)	Alglucosidase alfa/placebo (n = 30)		Cipaglucosidase alfa with miglustat (n = 20)	Alglucosidase alfa/placebo (n = 7)	
Primary endpoint[a]									
6MWD (observed), m	EMA analysis: 20.0 (13.1, 26.9)	EMA analysis 8.3 (-2.2, 18.8)	EMA analysisa: 11.7 (-1.0, 24.4) CSR analysis[b]: 14.2 (-2.6, 31.0)	EMA analysis: 15.9 (8.3, 23.4)	EMA analysis: 1.0 (−10.2, 12.2)	EMA analysis: 14.9 (1.2, 28.6) CSR analysis: 16.5 (−1.9, 34.8)	EMA analysis: 28.5 (12.4, 44.7)	EMA analysis: 52.7 (23.2, 82.3)	EMA analysis: −24.2 (−60.0, 11.7) CSR analysis: −6.6 (−48.2, 35.1)
	EMA analysis: nominal two-sided p = 0.07[c] ↑ CSR analysis: nominal two-sided p = [redacted]			EMA analysis: nominal two-sided p = 0.033[c] ↑ CSR analysis: nominal two-sided p = [redacted]			EMA analysis: nominal two-sided p = 0.178[c] ↓ CSR analysis: nominal two-sided p = [redacted]		
Sensitivity analysis of the primary endpoint (CSR analysis)									
6MWD (LOCF), m	20.8 (42.8)	7.2 (40.3)	CSR analysis: 13.7 (−1.2, 28.5)	16.9 (40.4)	−0.02 (39.4)	CSR analysis: 16.8 (0.2, 33.3)	33.4 (48.7)	38.2 (29.3)	CSR analysis: −9.0 (−46.5, 35.0)
	CSR analysis: two-sided p = 0.071 ↑			CSR analysis: two-sided p = 0.047 ↑			CSR analysis: two-sided p = 0.60 ↓		
Key secondary endpoint									

% predicted FVC	EMA analysis: −1.4 (−2.5, −0.3)	EMA analysis: −3.7 (−5.4, −2.0)	EMA analysis: 2.3 (0.2, 4.4) CSR analysis: 2.7 (0.4, 5.0)	EMA analysis: −0.2 (−1.5, 1.1)	EMA analysis: −3.8 (−5.7, −1.9)	EMA analysis: 3.6 (1.3, 5.9) CSR analysis: 3.5 (1.0, 6.0)	EMA analysis: −5.2 (−7.5, −2.9)	EMA analysis: −2.40 (−6.7, 1.8)	EMA analysis: −2.8 (−7.8, 2.3) CSR analysis: -2.0 (-8.9, 5.0)
	EMA analysis: nominal two-sided p = 0.031[c] ↑ CSR analysis: nominal two-sided p = [redacted]			EMA analysis: nominal two-sided p = 0.002[c] ↑ CSR analysis: nominal two-sided p = [redacted]			EMA analysis: nominal two-sided p = 0.271[c] ↓ CSR analysis: nominal two-sided p = [redacted]		
Additional key secondary endpoints ordered by statistical hierarchy[d]									
MMT lower extremity score	EMA analysis: 1.7 (1.1, 2.4)	EMA analysis 0.70 (−0.4, 1.7)	EMA analysis: 1.1 (−0.10, 2.3) CSR analysis: 1.0 (−0.5, 2.4) ↑	EMA analysis: 1.8 (1.0, 2.6)	EMA analysis: 0.9 (−0.3, 2.1)	EMA analysis: 0.9 (−0.6, 2.3) CSR analysis: 0.7 (−1.1, 2.5) ↑	EMA analysis: 1.40 (0.40, 2.5)	EMA analysis −0.0 (−1.9, 1.9)	EMA analysis: 1.5 (−0.8, 3.7) CSR analysis: 0.8 (−1.8, 3.3) ↑
PROMIS–Physical Function total score	EMA analysis: 2.2 (0.5, 3.9)	EMA analysis: −0.3 (−2.9, 2.3)	EMA analysis: 2.5 (−0.6, 5.7) CSR analysis: 1.9 (−1.5, 5.3) ↑	EMA analysis: 2.0 (−0.0, 4.0)	EMA analysis: −1.6 (−4.5, 1.4)	EMA analysis: 3.5 (−0.1, 7.1) CSR analysis: 3.1 (−0.7, 7.0) ↑	EMA analysis 2.6 (−1.0, 6.3)	EMA analysis: 5.8 (−0.9, 12.4)	EMA analysis: −3.1 (−11.2, 4.9) CSR analysis: −5.1 (−14.0, 3.9) ↓
PROMIS–Fatigue total score	EMA analysis: −2.0 (−3.2, −0.9)	EMA analysis: −1.7 (−3.4, 0.0)	EMA analysis: −0.3 (−2.4, 1.8) CSR analysis: 0.04	EMA analysis: −1.9 (−3.2, −0.6)	EMA analysis: −0.7 (−2.6, 1.2)	EMA analysis: −1.2 (−3.5, 1.1) CSR analysis: −0.8	EMA analysis: −3.0 (−5.7, −0.2)	EMA analysis: −4.9 (−9.9, 0.0)	EMA analysis: 2.0 (−4.1, 8.0) CSR analysis: 3.3

			(−2.1, 2.2) ↑			(−3.2, 1.5) ↑			(−3.7, 10.3) ↑
GSGC total score	EMA analysis: −0.7 (−1.2, −0.2)	EMA analysis: 0.8 (0.0, 1.5)	EMA analysis: −1.5 (−2.4, −0.6) CSR analysis: −1.4 (−2.5, −0.4) ↓	EMA analysis: −0.7 (−1.3, −0.1)	EMA analysis: 0.5 (−0.4, 1.4)	EMA analysis: −1.2 (−2.2, −0.1) CSR analysis: −1.2 (−2.4, 0) ↓	EMA analysis: −0.6 (−1.6, 0.4)	EMA analysis: 1.3 (−0.4, 3.1)	EMA analysis: −1.9 (−4.1, 0.2) CSR analysis: −1.3 (−4.0, 1.4) ↓

Blue highlight indicates the EMA analysis. Blue shading indicates that cipaglucosidase alfa/miglustat is directionally favoured over alglucosidase alfa with placebo. Yellow shading indicates that alglucosidase alfa with placebo is directionally favoured over cipaglucosidase alfa/miglustat. ↑ denotes improvement from baseline; ↓ worsening from baseline.

[a]EMA analysis on primary and secondary endpoints used MMRM (actual time point of assessment ITT-OBS population excluding outlier).

[b]CSR analysis on primary endpoint used MMRM (delayed visits mapped to planned; ITT-OBS; prespecified) and for secondary endpoints was ANCOVA (ITT-LOCF; prespecified)

[c]The study failed to demonstrate superiority for the primary endpoint, therefore all other endpoints can only be claimed to be nominal and exploratory, and p-values presented cannot be considered statistically valid and are for reference only

[d]p-values for the EMA analysis were not reported in the EPAR for these endpoints; therefore, we have not presented the p-values from the CSR analysis

Abbreviation: 6MWD, 6-minute walk distance; ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; ERT, enzyme replacement therapy; FVC, forced vital capacity; GSGC, gait, stairs, Gowers' manoeuvre, chair; ITT, intention-to-treat; LOCF, last observation carried forward; LS, least-squares; MMRM, mixed model for repeated measures; MMT, manual muscle test; NR, not reported; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.

Source:

Amicus Therapeutics®
www.amicusrx.co.uk

Response to the DMC additional questions received 231206

1) Can you inform how many patients went through measurement of residual enzyme activity?
2) Can you inform about the baseline residual enzyme activity?
   If possible it would be informative to hear if response to cipaglucosidase alfa was connected to residual enzyme activity
3) Can you inform why there is no cipaglucosidase alfa arm (i.e. not in combination with miglustat) included in the PROPEL-study?
4) Is there any data from the open-label-extensions-study available at this time? It would be information to see if effect of cipaglucosidase alfa is maintained over time.

Response

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   Can you inform about the baseline residual enzyme activity?
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[redacted]

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[redacted]

[redacted]

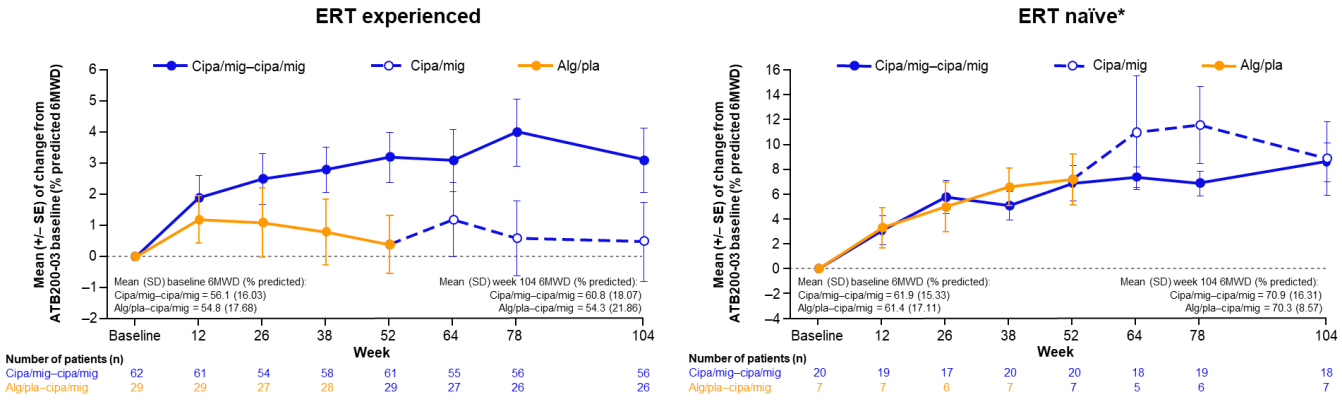
3) Can you inform why there is no cipaglucosidase alfa arm (i.e. not in combination with miglustat) included in the PROPEL-study?

[redacted]

4) Is there any data from the open-label-extensions-study available at this time? It would be information to see if effect of cipaglucosidase alfa is maintained over time.

There is ongoing data developing from the OLE study ATB200-007. Up to 78 week data is reported in the dossier already submitted. At the WORLD *symposium* congress in February 2023 up to 104 week data was presented (Schoser et al 2023). The key results are summarised below.

ERT-experienced and -naïve patients treated with cipaglucosidase alfa /miglustat throughout showed durable improvements in % predicted 6 minute walking distance (6MWD) in PROPEL that were maintained throughout the OLE to week 104.
ERT-experienced and -naïve patients who received alglucosidase alfa /placebo in PROPEL and switched to cipaglucosidase alfa /miglustat in the OLE showed stability in % predicted 6MWD throughout the OLE.



ERT-experienced patients treated with cipaglucosidase alfa /miglustat throughout remained stable, while patients who received alglucosidase alfa/placebo in PROPEL experienced a decline in sitting % predicted forced vital capacity (FVC) that stabilized after switching to cipaglucosidase alfa /miglustat in the OLE.

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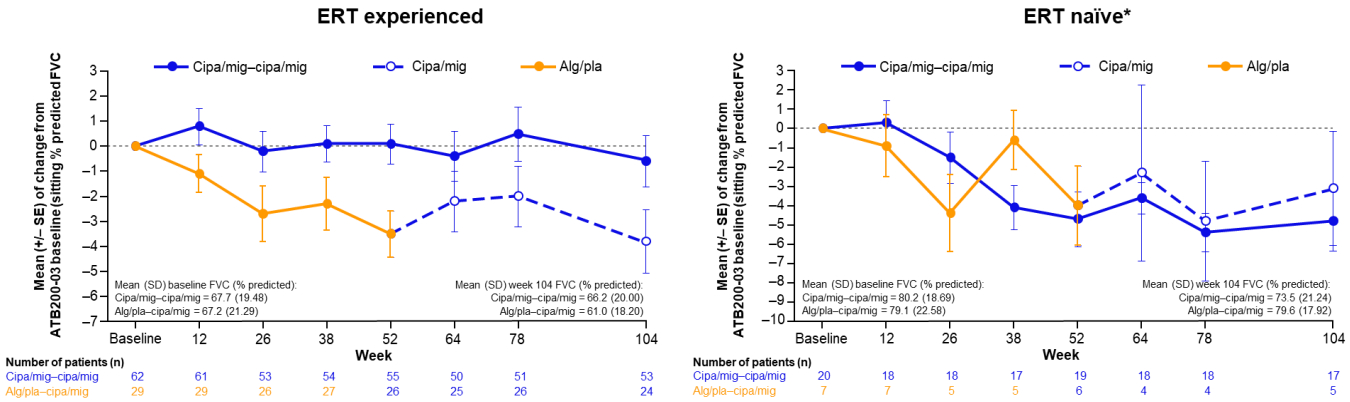
ERT-naïve patients in both treatment groups experienced some decline in PROPEL that stabilized in the OLE with no further decline in FVC to week 104.



Overall, data demonstrate that treatment with cipaglucosidase alfa/miglustat up to 104 weeks was associated with a durable effect and was well-tolerated, supporting the long-term benefits of cipaglucosidase alfa /miglustat treatment for patients with LOPD.
Data were analyzed descriptively, with no statistical comparisons made.

In addition, the 4 year data from the Ph I /II trial (included in appendix Q of the dossier) confirms the durability of effectiveness of cipaglucosidase alfa/ miglustat. This data has now been published Byrne et al., Journal of Neurology Dec 2023 https://doi.org/10.1007/s00415-023-12096-0.
This data confirms the preservation of muscle function and respiratory function assessed by 6MWD, manual muscle test (MMT) and FVC respectively.

References:

Van der Ploeg et al. Eur J Neurol. 2017 https://pubmed.ncbi.nlm.nih.gov/28477382/
Parenti et al Mol Ther. 2014 22 11 https://doi.org/10.1038/mt.2014.138
Xu et al JCI Insight. 2019;4(5):e125358. https://doi.org/10.1172/jci.insight.125358.
Schoser et al. Presented at the 19th Annual WORLD Symposium, Orlando, FL, USA; February 22–26, 2023.
Byrne et al., Journal of Neurology Dec 2023 https://doi.org/10.1007/s00415-023-12096-0