NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating late-onset Pompe disease [ID3771]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cipaglucosidase alfa with miglustat for treating late-onset Pompe disease [ID3771]

Contents:

The following documents are made available to stakeholders:

The **final scope** and **final stakeholder list** are available on the NICE website.

9. **External Assessment Report critique of company response to technical engagement** prepared by CRD and CHE Technology Assessment Group, University of York

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cipaglucosidase alfa in combination with miglustat for treating Pompe disease (ID3771)

Document B

Company evidence submission

December 2022

File name	Version	Contains confidential information	Date
ID3771_Cipaglucosidase alfa with miglustat_Document B_02Dec22_redacted	1.1	Yes	02Dec22

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission covers the full anticipated marketing authorisations for cipaglucosidase in combination with miglustat [redacted]". The decision problem addressed within this submission is broadly consistent with the NICE final scope for this appraisal with respect to the population, intervention, outcomes, comparators and the NICE reference case. The differences between the decision problem addressed within this submission and the NICE final scope are outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with Pompe disease.	Adults with a confirmed diagnosis of LOPD (GAA deficiency).	Only adults with LOPD aged 18 years and older are considered in this submission. This aligns with the population in the pivotal trial (PROPEL), data from which support this appraisal [redacted].
Intervention	Cipaglucosidase alfa in combination with miglustat.	As per NICE final scope.	NA
Comparator(s)	• Alglucosidase alfa • Avalglucosidase alfa	• Primary comparator: Alglucosidase alfa • Secondary comparator: Avalglucosidase alfa	Avalglucosidase alfa (Nexviadyme®) received Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation in July 2022[1] and NICE guidance in August 2022 (TA821; with a 30-day implementation period)[2] for the treatment of Pompe disease of all ages. However, at the time of this submission, Amicus understands that avalglucosidase alfa is not commercially available in the United Kingdom (UK) for the treatment of adults with LOPD,[2, 3] and, as agreed in the decision problem meeting, that it would be unlikely to be widely used in clinical practice for some time even after it were to become commercially available. Therefore, avalglucosidase alfa has been included as a secondary comparator and therefore has only been included in scenario analyses in this submission.
Outcomes	The outcome measures to be considered include: • change in motor function • change in respiratory function • change in muscular function	The outcome measures to be considered include: • change in motor function (assessed using the six-minute walk test [6MWT]) • change in respiratory function	In line with the NICE final scope, except that mortality was not assessed as part of the Phase III PROPEL study. This was due to the low number of expected events over the one-year timeframe of the clinical trial. Assessment of mortality in Pompe disease is inherently difficult due to rate of disease

	• mortality • health-related quality of life (HRQoL) • immunogenicity response • adverse effects of treatment	(assessed using sitting forced vital capacity [FVC] % predicted) • change in muscular function (assessed using manual muscle testing and the Gait, Stairs, Gowers' manoeuvre, and Chair [GSGC] assessments) • HRQoL • immunogenicity response • adverse effects of treatment	progression and wide range of ages and stages of progression within the population. Given the lack of long-term data available, it was assumed that cipaglucosidase alfa in combination with miglustat would not impact mortality until adults with LOPD transitioned into a health state where they required ventilation or mobility support, which is reflected in the model.
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • people who have received prior treatment with alglucosidase alfa • people who have not received prior treatment with alglucosidase alfa	The population considered in this submission is the total population in the PROPEL trial, adults with LOPD.	[redacted], and as discussed and agreed in the decision problem meeting, this submission focuses on the total population of adults with LOPD, which is comprised of treatment-naïve and treatment-experienced people. During an advisory board, clinicians noted that they would not treat enzyme replacement therapy (ERT)-experienced and ERT-naïve adults with LOPD differently.[4] Therefore, Amicus believes that prior ERT status should not be a factor in accessing treatment with cipaglucosidase alfa in combination with miglustat in the interests of fair and equitable access. Therefore, clinical and economic results are presented for the total population of adults with LOPD. ERT-experienced and ERT-naïve data from the PROPEL clinical trial are presented in Appendix E for completeness, in line with the study design. These data are impacted by the small participant numbers for the ERT-naïve arm (ERT-naïve: n=28; ERT-

			experienced: n=95),[5] as is expected in a rare disease with low incidence. Thus, as discussed and agreed in the decision problem meeting, the total cohort is the most reliable and meaningful source of data in PROPEL and for the cost-effectiveness analysis.
Special considerations including issues related to equity or equality	-	-	As described above, at the time of this submission, Amicus understands that there currently are no commercially available treatments for people with LOPD who are unable to receive alglucosidase alfa treatment, or for those who do not respond to, or whose response declines with, alglucosidase alfa, meaning that they are left without a satisfactory treatment option. The company strongly believes in equity of access which also means ensuring that people with Pompe disease who are eligible within the regulatory label are not restricted in access to Pompe disease medicines (including cipaglucosidase alfa in combination with miglustat) due to their previous ERT status, ambulation, disability status or level of progression. Although cipaglucosidase alfa in combination with miglustat is undergoing a single technology appraisal (STA), its assessment is anticipated to have several features that are commonly seen in the highly specialised technology (HST) programme: the condition is very rare (Section B.1.3.1), with few people potentially eligible for treatment, and the disease severely impairs the quality of life of an individual with LOPD (Section B.1.3.2). Therefore, in light of the difficulties in evidence generation in a condition such as LOPD, NICE are asked to apply flexibility in

			the STA process to enable timely and equitable access for people with a rare disease of this nature, when compared to products being assessed through the STA process for conditions with a much higher prevalence.

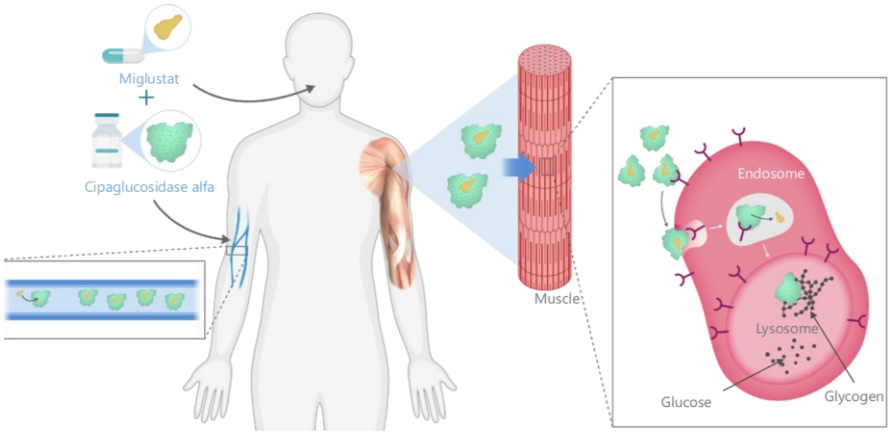
Abbreviations: 6MWT: six-minute walk test; EMA: European Medicines Agency; ERT: enzyme replacement therapy; FVC: forced vital capacity; GAA: acid α-glucosidase; GSGC: Gait, Stairs, Gowers' manoeuvre, and Chair; HST: highly specialised technology; LOPD: late-onset Pompe Disease; MHRA: Medicines and Healthcare products Regulatory Agency; NICE: National Institute for Health and Care Excellence; STA: single technology appraisal; UK: United Kingdom.
Source: NICE final scope document [ID3771].

B.1.2 Description of the technology being appraised

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements of cipaglucosidase alfa in combination with miglustat in the treatment of adults with LOPD is presented in Table 2. The innovative nature of cipaglucosidase alfa in combination with miglustat is reflected by its incorporation into the [redacted] and its Promising Innovative Medicine (PIM) designation,[6, 7] through which Amicus has frequently engaged with NICE and other system partners to ensure the most robust submission possible as well as providing feedback on the [redacted] itself,[6] as discussed further in Section Appendix M.

Table 2: Technology being appraised

UK approved name and brand name	Cipaglucosidase alfa [redacted] in combination with miglustat [redacted]
Mechanism of action	Cipaglucosidase alfa in combination with miglustat consists of the co-administration of a next-generation intravenous enzyme replacement, cipaglucosidase alfa, with an orally administered enzyme stabiliser, miglustat. Cipaglucosidase alfa is a recombinant human acid alpha-glucosidase (rhGAA) enzyme replacement therapy which compensates for the lack of natural GAA enzyme in adults living with LOPD.[8] Cipaglucosidase alfa has higher levels of mono- (M6P) and bis-mannose 6-phosphate (bis-M6P) than alglucosidase alfa.[8, 9] The bis-M6P N-glycans located on cipaglucosidase alfa enable the enzyme to bind cation-independent mannose 6-phosphate receptors (CI-MPR; a receptor which is located on target cells), with higher affinity than alglucosidase alfa and at the low nanomolar concentrations expected in the interstitium (a contiguous, fluid filled space existing between the skin and organs) following dosing.[8, 10-12] Cipaglucosidase alfa reaches peak (saturable) enzyme activity for CI-MPR at concentrations approximately 1000-fold lower than alglucosidase alfa.[8, 11, 12] Uptake of cipaglucosidase alfa into fibroblasts in people with Pompe disease resulted in greater internalised GAA activity than with alglucosidase alfa at concentrations that can be achieved in the interstitium.[8 12] In the blood (pH 7.4), cipaglucosidase alfa is significantly less stable than in the lysosome (pH 5.2), due to the difference in pH between the two environments. Miglustat is a small molecule enzyme stabiliser that 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.[9] This gives the enzyme longer to reach and bind to the CI-MPR prior to uptake into the muscle.[9] The innovative design of cipaglucosidase alfa in combination with miglustat has been demonstrated in a murine model to allow rhGAA to be fully processed by the body to maximise cellular and muscular uptake, enabling the efficacy outcomes seen compared with alglucosidase alfa.[13] As a result of this innovative design, evidence from a model in GAA knockout mice

	predicted that cipaglucosidase alfa 20 mg/kg administered with miglustat 10 mg/kg (comparable to 260 mg in humans) provides enhanced glycogen reduction compared with alglucosidase alfa 20 mg/kg.[9] **Figure 1: Mechanism of action of cipaglucosidase alfa in combination with miglustat**  The innovative nature of cipaglucosidase alfa in combination with miglustat is reflected by its incorporation into the [redacted] and PIM designation.[7]
Marketing authorisation/CE mark status	An application for the marketing authorisations for cipaglucosidase in combination with miglustat in the indication of interest was submitted directly to the EMA in [redacted]. Marketing authorisations for cipaglucosidase in combination with miglustat in this indication are expected in [redacted]. Cipaglucosidase alfa in combination with miglustat also received a positive scientific opinion on 4th June 2021 to begin an Early Access to Medicines Scheme (EAMS) in the UK. [redacted] This demonstrates a clear demand to seek an alternative to established care.

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	[redacted]
Method of administration and dosage	**Cipaglucosidase alfa:**[8] Intravenous infusion of 20 mg/kg over approximately four hours, administered every other week. **Miglustat:**[14] Oral capsules administered every other week alongside cipaglucosidase alfa. For [redacted] weighing ≥50 kg, the recommended dose is 4 capsules of 65 mg (260 mg total). For [redacted] weighing ≥40 kg to <50 kg, the recommended dose is 3 capsules of 65 mg (195 mg total). Full details of the method of administration are located in each product's respective SmPC (see Appendix C).
Additional tests or investigations	No additional tests or investigations are required to identify [redacted] eligible for treatment with cipaglucosidase alfa in combination with miglustat.
List price and average cost of a course of treatment	The proposed list price of cipaglucosidase alfa is [redacted] per vial. The proposed list price of miglustat is [redacted] per bottle of 4 capsules ([redacted]).
Patient access scheme (PAS) (if applicable)	[redacted]

Abbreviations: CHMP: Committee for Medicinal Products for Human Use; CI-MPR: cation-independent mannose 6-phosphate receptor; EAMS: Early Access to Medicines Scheme; EMA: European Medicines Agency; [redacted] LOPD: late-onset Pompe disease; MHRA: Medicines and Healthcare products Regulatory Agency; M6P: mannose 6-phosphate; PAS: patient access scheme; PIM: Promising Innovative Medicine; rhGAA: recombinant human acid α-glucosidase; SmPC: Summary of Product Characteristics; UK: United Kingdom.
Source: Cipaglucosidase alfa draft SmPC;[14] Miglustat draft SmPC.[8]

B.1.3 Health condition and position of the technology in the treatment pathway

Summary of the health condition

- LOPD is a rare, autosomal recessive, lysosomal storage disorder characterised by a deficiency in the lysosomal enzyme GAA, leading to accumulation of glycogen in muscle cells.[15]
- Excess glycogen leads to irreversible muscle damage, particularly affecting the musculoskeletal and respiratory systems and leading to severely impaired mobility and respiratory failure.[16]
- The severe muscle damage and respiratory failure observed in adults with LOPD, and the need for ambulatory and ventilatory support, carries substantial impact on their quality of life across multiple domains, with this impact increasing as the disease progresses.[17-20]
- LOPD carries a substantial economic burden for society in terms of direct treatment costs, healthcare cost and resource use (HCRU), and indirect costs such as loss of work-related productivity and non-medical resource usage.[21]

Summary of the treatment pathway and limitations of alglucosidase alfa

- Avalglucosidase alfa (Nexviadyme®) received MHRA marketing authorisation in July 2022[1] and NICE guidance in August 2022 (TA821; with a 30-day implementation period)[2] for the treatment of Pompe disease of all ages. However, at the time of this submission, Amicus understands that avalglucosidase alfa is not commercially available in the UK for the treatment of adults with LOPD.[2, 3] It would be unlikely to be widely used in clinical practice for some time even after it were to become commercially available. Therefore, currently, the only commercially available, established care for adults with LOPD in the UK is treatment with alglucosidase alfa (Myozyme®).[22]
- There is substantial heterogeneity in response to alglucosidase alfa, with some people not gaining any initial benefit.[23] Furthermore, for those people with LOPD who do respond to alglucosidase alfa, benefits are not typically sustained and decline in motor and respiratory function is typically observed within 2–3 years of ERT treatment.[4, 20, 23-25]
- There is a substantial unmet need for an effective treatment for individuals who do not gain any benefit from alglucosidase alfa and those experiencing the well-established declining effectiveness of alglucosidase alfa. For these individuals, it is crucial that further decline is avoided, in order to improve clinical and quality of life outcomes. There is also an unmet need for individuals who are unable to receive alglucosidase alfa.

Position of cipaglucosidase alfa in combination with miglustat

- In line with the limitations of alglucosidase alfa, cipaglucosidase alfa in combination with miglustat will provide a treatment option for people who do not gain any benefit and those experiencing declining therapeutic efficacy while receiving this treatment.
- Cipaglucosidase alfa in combination with miglustat is anticipated to be [redacted]. Cipaglucosidase alfa in combination with miglustat is intended for use in individuals with LOPD [redacted]

[redacted], in line with clinical opinion.[4]

B.1.3.1 Disease overview and epidemiology

Pathophysiology

Pompe disease is a rare, autosomal recessive, lysosomal storage disorder characterised by a deficiency in the lysosomal enzyme acid α-glucosidase (GAA).[15] The physiological function of GAA is to break down glycogen into glucose through cleavage of the α-1,4- and α-1,6-glycosidic bonds.[26] Deficiency of GAA in Pompe disease leads to progressive accumulation of lysosomal glycogen, particularly in muscle cells which are a major site of glycogen storage.[26, 27] This process of glycogen accumulation causes rupture of lysosomes and displacement of the contractile elements of muscle fibres, leading to fibrosis, weakness and irreversible muscle damage (primarily to skeletal, smooth and cardiac muscles).[26, 28] Muscle weakness particularly affects muscles in the limbs and those required for breathing, leading to severely impaired mobility and respiratory failure, the most common cause of death in Pompe disease.[16]

Pompe disease sub-types

There are two main sub-types of Pompe disease, infantile-onset (IOPD) and late-onset (LOPD), broadly characterised by the age of symptom onset and the extent of cardiac involvement.[27] The focus of this submission is adults with LOPD (aged ≥18 years).

Diagnosis and assessment

Individuals with Pompe disease frequently experience delays in diagnosis and subsequently treatment initiation, owing to the rarity of the condition, lack of awareness among healthcare professionals, relatively non-specific phenotypic features, gradual onset and variable availability of genetic testing.[16, 29, 30] While the average age of symptom onset in adults with Pompe disease has been reported as [redacted] years,[31] one survey of 23 adults with LOPD in Europe identified diagnostic delays of 12–480 months (median: 144 months), with disease progression frequently occurring during this time.[32]

International expert consensus guidelines state that Pompe disease is diagnosed through measurement of GAA activity assays in dried blood spots, leukocytes or fibroblasts.[16, 33] Additionally, genetic testing for GAA mutations is available and can be used to confirm a diagnosis of Pompe disease.[16] These diagnosis methods can be performed at any age.[16] A complete diagnostic assessment should also include: pulmonary function tests, muscle strength tests and functional assessments, electrophysiology, hearing assessments, blood testing (routine blood testing including liver function tests, creatine kinase [CK] and, if the person has abnormal pulse oximetry and capnography, an arterial blood gas), chest x-ray, electrocardiogram, echocardiogram, and polysomnography.[16]

Epidemiology

To date, there are no published studies accurately describing the epidemiology of Pompe disease in the UK. Historically, the prevalence of Pompe disease has been estimated globally at approximately 1 in 40,000.[34, 35] However, the two key studies informing this estimate assessed carrier frequency in small, local samples of neonates in the United States (US)[35] and the Netherlands.[34] Therefore, these studies are unlikely to provide robust extrapolations to inform UK estimates for the epidemiology of LOPD in adults.

In the absence of published England-specific epidemiology data following a targeted review, [redacted]. The Association for Glycogen Storage Disease UK (AGSD-UK), an England-based patient advocacy organisation, state on their website that approximately 200 people are currently diagnosed with Pompe disease in the UK [redacted][38] This estimate was verified through expert opinion of clinicians, who approximated there are [redacted] treated adults with Pompe disease in England who could be eligible for treatment with cipaglucosidase alfa in combination with miglustat.

B.1.3.2 Disease burden

Symptoms

LOPD is a chronically debilitating condition in which people experience progressive loss of muscle function leading to severely disabling multi-system dysfunction. The core two domains of morbidity in adults with LOPD are:[16]

- Musculoskeletal (limb girdle weakness, back pain, gait abnormalities, fatigue and exercise intolerance, difficulties with speech);
- Respiratory (respiratory insufficiency progressing into respiratory failure, frequent and recurrent pulmonary infections, sleep apnoea).

However, there are a wide range of other symptoms and complications that can have detrimental effects on the day-to-day lives of adults with Pompe disease and their families. Other organ systems may also be adversely affected, such as the heart (cardiomegaly, arrythmias), gastrointestinal tract (weight loss, diminished gag reflex leading to risk of aspiration, difficulty chewing), and the brain and cerebrovascular system (aneurysms, microbleeds).[16, 39] The systemic effect of LOPD is depicted in Figure 2.

In a study of 54 Dutch adults with confirmed Pompe disease, performed prior to the advent of ERT, only a single person was able to climb a flight of stairs without any difficulty, with 41% indicating that they could not ascend or descend stairs at all. With regards to respiratory issues, 37% of respondents required ventilatory support, with a median duration of 11.5 hours per day. Of these, 20% required an invasive tracheal cannula. Thus, without treatment, the natural course of Pompe disease carries substantial symptomatic burden for people with LOPD.[40]

In a study of 27 adults with LOPD, it was reported that of Pompe-specific symptoms, walking difficulties (n=15; 55.6%), fatigue (n=10; 37.0%), breathing problems (n=10; 37.0%), balance issues (n=6; 22.2%), continence issues (n=6; 22.2%) and muscle pain (n=5; 18.5%) were the most important symptoms to treat.[41]

Figure 2: Systemic effect of LOPD

Abbreviations: LOPD: late-onset Pompe Disease

Impact on health-related quality of life (HRQoL)

LOPD symptoms have a substantial negative impact on individuals' HRQoL across the domains of physical functioning, general health, vitality, and social functioning, leading to an increased risk of depression and anxiety.[17-20] This effect is established in the literature, as demonstrated in individuals with LOPD in the Netherlands who had a health utility score that was on average 0.15 (17%) lower than that of the country's general population. This statistically significant outcome was attributed predominantly to limitations in the domains of mobility, usual activities and pain. Furthermore, the authors noted that within their analysis, individuals with severe limitations contributed to only a small

number of cases and therefore, the impact of Pompe disease on health utilities across the spectrum of disease severity may be underestimated.[19] More severe disease progression also correlates to a lower HRQoL.[19, 27, 42]

Interviews with people with LOPD have described an archetypal emotional journey for those living with the disease.[41] Initially, people with LOPD experience a lengthy and distressing diagnostic process prior to referral to a specialist healthcare professional. Diagnosis and commencement of established care bring some initial relief and improvement, followed by progressive physical decline and multifactorial impact on HRQoL.[41] Poor physical outcomes in adults with LOPD have been observed to translate into decreased HRQoL.[43] When compared with the general population, adults with untreated LOPD report significantly worsened HRQoL outcomes in terms of physical functioning, general health, vitality, fatigue, pain and social functioning, with these outcomes deteriorating further as the disease progresses.[17-20] Furthermore, people with LOPD who rely on mobility devices reported significantly lower perceived health across all domains surveyed, underscoring the impact of mobility decline on their lives.[17]

In a 2021 survey of adults in the UK with LOPD (n=27), most participants felt that LOPD severely affected their lives. On a scale of 0–10 (with 0 being no impact at all and 10 being a severe impact), the mean score was 8.5.[41] Amongst adults with LOPD, being physically active prior to diagnosis or of younger age, and experiencing financial hardship were all associated with a greater perceived impact on HRQoL. The majority of participants faced increasing challenges as their condition deteriorated, experiencing a negative impact on their daily activities, social life, employment and their relationships with family members and carers alongside an increasing sense of dependency on others.[41]

These results were further supported by a 2022 survey of adults with LOPD in the UK ([redacted]), [redacted] of whom were receiving ERT ([redacted] received alglucosidase alfa and [redacted] received an ERT currently in clinical trials).[31] The vast majority ([redacted]) required mobility aids and over half ([redacted]) required respiratory assistance. When asked to consider their lives over the past three months, only [redacted] ([redacted]) reported that they did not require any assistance with day-to-day living, with most people with LOPD relying on help from their families and friends.[31] Thus, LOPD poses a significant burden and impacts their daily lives, predominantly through the need for ambulatory and ventilatory support, as well as increasing requirements for assistance with daily living.

[redacted]

[redacted]

Caring for a person with LOPD can also have a substantial impact on the carer's quality of life. In a survey of [redacted] people with caring responsibilities for people living with Pompe disease, [redacted] reported an effect on their finances, [redacted] reported an impact on their social activities and an overwhelming [redacted] reported an impact on their mental health.[44]

[redacted]

[redacted]

Disease progression

Pompe disease is progressive in nature, with severity and morbidity increasing with time.[25] As muscle function deteriorates, people with LOPD suffer from organ failure and the need for ambulatory and ventilatory support, ultimately leading to premature death.[25, 27, 42] Disease progression is typically captured using outcome measures assessing mobility decline (6MWT) and respiratory decline (FVC). However, given the systemic nature of the pathology of LOPD, resulting symptoms can also progressively impact upon a range of everyday activities (e.g. losing the ability to climb stairs or to walk), as well as fundamental physiological processes (e.g. impaired breathing, eating and drinking).[45] In a 2020 prospective analysis of adults with Pompe disease in France, 10–15 years after diagnosis, 50% were either wheelchair-bound or ventilator dependent.[25, 46]

Mortality

Respiratory failure is the most common cause of death in people with Pompe disease.[16] In an international prospective observational study of adults with Pompe disease (n=268), the largest published to date, the life expectancy for ERT-naïve adults with Pompe disease ranged from 23–77 years.[46] Another study reported that median survival for ERT-naïve adults with LOPD was 27 years following diagnosis; the estimated 10-, 20- and 30-year survival was 83%, 65% and 40%, respectively.[47] However, assessment of mortality in Pompe disease is inherently difficult due to rate of disease progression and the wide range of ages and stages of progression within the population. It has been established in the literature that people with Pompe disease who required wheelchair or respiratory support had a shorter life expectancy at any age than those who did not.[25, 46]

B.1.3.3 Current treatment pathway of people with LOPD

The first guidelines on the diagnosis and treatment of Pompe disease were created by Kishnani *et al.* 2006, with the American College of Medical Genetics and Genomics (ACMG), and are largely based on experiences in the US.[16] European consensus recommendations were published in 2017, advocating the use of ERT alongside supportive care in adults and children with a confirmed diagnosis of Pompe disease.[15] At present, there are no UK-specific guidelines for LOPD.

Current commercially available, established care for adults with LOPD is alglucosidase alfa (Myozyme®).[22] Alglucosidase alfa is approved for use in people with Pompe disease of all ages, and was commissioned directly by the National Health Service (NHS) Highly Specialised Services in 2006.[22, 48] Alglucosidase alfa works through direct replacement of the deficient GAA enzyme in people with Pompe disease, stabilising cardiac and skeletal muscle through breakdown of excessive lysosomal glycogen stores, hence limiting muscle fibre damage.[14] Alglucosidase alfa is currently given as a first-line treatment and nearly all people with Pompe disease have been treated with alglucosidase alfa,[4] as evidenced in a UK study of 62 people with LOPD in which only three had not been treated with alglucosidase alfa.[21] The limitations of alglucosidase alfa are described in Section B.1.3.4.

Avalglucosidase alfa (Nexviadyme®) received MHRA marketing authorisation in July 2022[1] and NICE guidance in August 2022 (TA821; with a 30-day implementation period)[2] for the treatment of Pompe disease of all ages. However, at the time of this submission, Amicus understands that avalglucosidase alfa is not commercially available in the UK for the treatment of adults with LOPD.[2, 3] It would be unlikely to be widely used in clinical practice for some time even after it were to become commercially available.

Alongside alglucosidase alfa, supportive care is a fundamental feature of the treatment plan for an adult with LOPD, owing to the limited and non-curative nature of therapies currently available for Pompe disease.[16] A person with LOPD may require input from medical specialists in areas such as respiratory (e.g., in management of chronic respiratory insufficiency and the role of non-invasive ventilation) and neurology (e.g., in the detection neuropathies).[16] In addition, allied health professional input can be beneficial in terms of physiotherapy (e.g. for muscular strengthening and orthotic intervention to aid with muscle weakness).[16] However, the aforementioned UK study[21] and clinical advice indicate that it would be very rare for adults with LOPD within the UK, that are eligible for treatment with alglucosidase alfa, to receive only supportive care (i.e., without ERT).[4] Therefore, supportive care is not formally included as a comparator in this submission.

B.1.3.4 Limitations of alglucosidase alfa and unmet medical need

The effectiveness of alglucosidase alfa is primarily limited by its lack of stability in circulation, inefficient uptake into muscle cells, heterogeneity in clinical response and waning long-term treatment effect.[23, 25, 49]

Alglucosidase alfa, as with all lysosomal enzymes, is unstable at neutral pH and can be denatured and inactivated in the bloodstream.[49] Limited molecular phosphorylation on the structure of alglucosidase alfa also leads to inefficient entry into muscle cells.[49] Through a combination of these factors, the vast majority of alglucosidase alfa is cleared from circulation by non-muscle tissues and cells including the liver, spleen and fibroblasts, leading to poor distribution of ERT in muscle cells.[49] Without sufficient distribution in muscle cells, alglucosidase alfa cannot break down excess glycogen accumulating there and thus cannot adequately mitigate the damage to muscle that occurs in Pompe disease, leading to ongoing disease progression.[26, 28] There is subsequently an unmet need for new therapies in LOPD that can overcome these pharmacological challenges of stability and

uptake in order to effectively address the underlying pathophysiology of Pompe disease and improve outcomes for people with LOPD.

There is also substantial heterogeneity in clinical response to alglucosidase alfa, with many people with LOPD who have received this treatment failing to achieve any benefit or stabilisation in their disease course.[23] In a real-world analysis of adults treated with alglucosidase alfa in the Netherlands and France (n=30), no initial improvement or even stabilisation was observed in terms of six-minute walk distance (6MWD) and upright forced vital capacity (FVC) for 17% and 31% of participants, respectively; 7% of participants experienced an initial decline in both outcomes despite treatment.[23] This initial decline in efficacy can be observed as early as 18 months after starting treatment, according to consensus from clinicians.[50] For those who do respond, a secondary decline in mobility and respiratory function (evidenced by reducing FVC and increasing requirements for ventilation after initial response) has been observed as a trend in people with Pompe disease after approximately 2–3 years of alglucosidase alfa treatment.[4, 20, 23-25]

There is therefore a substantial unmet need for an effective treatment for individuals who do not gain any benefit from alglucosidase alfa and those experiencing the well-established declining effectiveness of alglucosidase alfa. For these individuals, it is crucial that further decline is avoided, in order to improve clinical and quality of life outcomes. There is also an unmet need for individuals who are unable to receive alglucosidase alfa. Currently, adults living with LOPD represent a population with substantial unmet need for effective treatments,[39, 51] as supported by demand seen for the EAMS for cipaglucosidase alfa in combination with miglustat (Section B.2.11).[52] [redacted]

Anticipated positioning of cipaglucosidase alfa in combination with miglustat

In line with the limitations of alglucosidase alfa described above, cipaglucosidase alfa in combination with miglustat will provide a treatment option for people who do not gain any benefit and those experiencing declining therapeutic efficacy while receiving this treatment.

Cipaglucosidase alfa in combination with miglustat consists of the co-administration of a next-generation intravenous enzyme replacement, cipaglucosidase alfa, with an orally administered enzyme stabiliser, miglustat. The innovative design of cipaglucosidase alfa in combination with miglustat allows rhGAA to be fully processed by the body to maximise cellular and muscular uptake (Section B.1.2), enabling the efficacy outcomes seen compared with alglucosidase alfa (Section B.2).[13]

Cipaglucosidase alfa in combination with miglustat is anticipated to be [redacted]. Cipaglucosidase alfa in combination with miglustat is intended for use in individuals with LOPD [redacted], in line with clinical opinion.[4] Clinicians anticipate switching from alglucosidase alfa to cipaglucosidase alfa in combination with miglustat in individuals who have

experienced a decline in therapeutic benefit with existing ERT or for whom alternative ERT is not appropriate, or in line with preferences of individuals receiving ERT when clinically appropriate.[4]

B.1.4 Equality considerations

Avalglucosidase alfa (Nexviadyme®) received MHRA marketing authorisation in July 2022[1] and NICE guidance in August 2022 (TA821; with a 30-day implementation period)[2] for the treatment of Pompe disease of all ages. However, at the time of this submission, Amicus understands that avalglucosidase alfa is not commercially available in the UK for the treatment of adults with LOPD.[2, 3] It would be unlikely to be widely used in clinical practice for some time even after it were to become commercially available. Therefore, there are currently no commercially available treatments for people with LOPD who are unable to receive alglucosidase alfa treatment, or for those who do not respond to, or whose response declines with, alglucosidase alfa, meaning that they are left without a satisfactory treatment option.

Although cipaglucosidase alfa in combination with miglustat is undergoing appraisal through an STA, its assessment has several features that are commonly seen in the HST programme: the condition is very rare, with few people potentially eligible for treatment and the disease severely impairs the quality of life of an individual with LOPD. Therefore, in light of the difficulties associated with evidence generation commonly experienced in a condition such as LOPD, NICE are asked to apply flexibility in the STA process to enable timely and equitable access for people with a rare disease of this nature, when compared to products being assessed through the STA process for conditions with a much higher prevalence.

There may be considerations relating to inequitable access to treatment for adults with LOPD, due to regional variation in density of specialist treatment centres. Adults with LOPD residing in rural communities may have to overcome a significant travel burden in order to access specialist services, an issue compounded by the impact on mobility that Pompe disease is known to have. This issue is not expected to be a considered within this submission but does highlight a consideration for NHS England and Integrated Care Systems when planning services for adults with LOPD.

Amicus strongly believes in equity of access, which also means ensuring that adults with LOPD who are eligible within the regulatory label are not restricted from access to Pompe disease medicines (including cipaglucosidase alfa in combination with miglustat) due to their previous ERT status, ambulation or disability status or level of progression.

B.2 Clinical effectiveness

Clinical evidence base

- The clinical evidence to support the efficacy and safety of cipaglucosidase alfa in combination with miglustat in this submission primarily derives from PROPEL, a pivotal Phase III, head-to-head, international, prospective, double-blind randomised controlled trial (RCT) with a superiority study design. The trial compared cipaglucosidase alfa in combination with miglustat against alglucosidase alfa in combination with placebo in late-onset Pompe disease (LOPD), in line with the decision problem.
- Long-term clinical evidence through 48 months of cipaglucosidase alfa in combination with miglustat treatment derives from ATB200-02, a Phase I/II open-label, fixed-sequence, ascending-dose study. Input was incorporated from UK clinical experts, adults with Pompe disease, and NICE to ensure that both studies investigated patient-centric and clinically meaningful endpoints, while remaining scientifically robust and highly relevant for cost-effectiveness decision making.

Efficacy

- 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.

Indirect comparative effectiveness

- In the absence of direct clinical trial evidence between cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa in adults with LOPD regardless of prior treatment status, a multi-level network meta-regression (ML-NMR) has been conducted to establish the comparative effectiveness of the two treatments in LOPD, in line with the NICE final scope.
- [redacted].

Adverse reactions

- Co-administration of cipaglucosidase alfa and miglustat was well-tolerated. The overall safety profile of cipaglucosidase alfa in combination with miglustat was similar to alglucosidase alfa, with no new safety signals identified and no deaths reported.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in June 2022 to identify relevant clinical evidence on the efficacy and safety data of treatment for adults with Pompe disease. The searches identified novel records that were considered relevant for the review, of these, 55 publications reporting on 27 unique studies were included in the SLR. Full details of the SLR search strategy, methodology and results can be found in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

Of the included studies in the SLR, one study, the pivotal PROPEL trial, presented relevant data to inform the direct evidence for the comparison of cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa in adults with LOPD. PROPEL is a Phase III, international, prospective, double-blind, randomised controlled trial (RCT), data from which have been published in *The Lancet Neurology* by Schoser *et al.* (2021).[53] PROPEL is the first trial in LOPD to include adults who have previously been treated with alglucosidase alfa at the licensed dose, reflective of clinical practice in the UK,[21, 54] with a median of 7.4 years of prior enzyme replacement therapy (ERT), as well as ERT-naïve participants.[53] The trial captured a number of disease-relevant endpoints including motor function, respiratory function, muscle function and PROs, and was conducted in 24 countries, including the UK. Of all the included studies in the SLR, PROPEL therefore provides data that are most relevant to adults with LOPD and generalisable to UK clinical practice. Additionally, as PROPEL is the only trial that provides direct, head-to-head evidence against alglucosidase alfa (the primary comparator in this submission), the clinical evidence to support the efficacy and safety of cipaglucosidase alfa in combination with miglustat in this submission primarily derives from the PROPEL Clinical Study Report (CSR).[55] The CSR is the reference source used for all studies in this submission, including PROPEL, as these represent the most comprehensive set of data (please note that values in the PROPEL CSR may differ slightly from those in the Schoser et al publication).

The SLR also identified the Phase II, open-label, fixed-sequence, ascending-dose, single-arm study (ATB200-02; NCT02675465) reported on the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of cipaglucosidase alfa in combination with miglustat in adults with LOPD.[56] The data from ATB200-02 supported the PIM designation and ultimately the early access to medicines scheme (EAMS). As with PROPEL, the participant population in ATB200-02 is aligned with the population of relevance for this submission.

A summary of PROPEL and ATB200-02 is presented below in Table 3.

Table 3: Clinical effectiveness evidence

	PROPEL (NCT03729362, ATB200-03) Schoser *et al.* (2021)	**ATB200-02 (NCT02675465) Byrne *et al.* (2022)**
Study design	Phase III, international, prospective, double-blind, RCT	Phase I/II open-label, fixed-sequence, ascending-dose study
Population	Adults with LOPD	Adults with LOPD

Intervention(s)	Cipaglucosidase alfa in combination with miglustat	Cipaglucosidase alfa in combination with miglustat
Comparator(s)	Alglucosidase alfa in combination with placebo	None
Indicate if trial supports application for marketing authorisation	Yes	No
Indicate if trial used in the economic model	Yes	Yes
Rationale if study not used in the model	NA	48-month efficacy and safety data became available in the weeks leading up to the submission and has been presented in this section. However, due to the time constraints, 36-month data from this study were utilised in the model.
Reported outcomes specified in the decision problem[a]	• **Change in motor function (6MWD assessed using the 6MWT)** • **Change in respiratory function (assessed using sitting FVC % predicted)** • Change in muscular function (assessed using manual muscle testing [MMT] and the Gait, Stairs, Gowers' manoeuvre, and Chair [GSGC] assessments) • HRQoL • Immunogenicity response • Adverse effects of treatment	• **Change in motor function 6MWD assessed using the 6MWT)** • **Change in respiratory function (assessed using sitting FVC % predicted)** • Change in muscular function (MMT and the GSGC assessments) • HRQoL • Immunogenicity response • Adverse effects of treatment
All other reported outcomes	Whilst not specified in the decision problem, data on changes in serum CK and urinary hexose tetrasaccharide (Hex4) levels are presented in this submission.	Whilst not specified in the decision problem, data on changes in serum CK and urinary Hex4 levels are presented in this submission.

[a]Outcomes marked in **bold** represent outcomes considered within the economic model.
Abbreviations: 6MWD: six-minute walk distance; 6MWT: six-minute walk test; CK: creatine kinase; EAMS: early access to medicines scheme; ERT: enzyme-replacement therapy; FVC: forced vital capacity; GSGC: Gait, Stairs, Gowers' manoeuvre, and Chair; Hex4: hexose tetrasaccharide; HRQo: health-related quality of life; LOPD: late-onset Pompe disease; MMT: manual muscle testing; PIM: Promising Innovative Medicine; RCT: randomised controlled trial.
Source: Schoser *et al*. (2021);[53] Byrne *et al*. (2022);[57] Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[55]

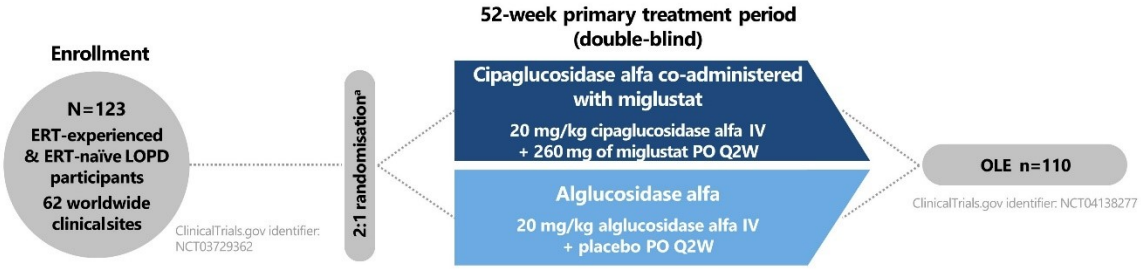
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial designs

PROPEL trial design

An overview of the study design of PROPEL is presented in Figure 3. PROPEL had an active-controlled (head-to-head), superiority design, comparing the safety and efficacy of cipaglucosidase alfa in combination with miglustat with alglucosidase alfa in combination with placebo. PROPEL is the first and only randomised control trial in LOPD to include participants who have previously been treated with alglucosidase alfa at the licensed dose.

Figure 3: Overview of the study design for PROPEL



[a]Two participants were randomised but not dosed; randomisation was stratified by prior ERT status and baseline 6MWD
Abbreviations: ERT: enzyme-replacement therapy; IV: intravenous; LOPD, late-onset Pompe disease; OLE, open-label extension; PO: oral; qow, every other week.

Participants were initially selected based on the eligibility criteria described below (Table 5).[53] Eligible participants were randomly assigned in a 2:1 ratio to receive either the interventional arm (cipaglucosidase alfa in combination with miglustat) or the control arm (alglucosidase in combination with placebo). Randomisation was stratified by 6MWD, i.e. the distance at Baseline (75 to <150 m, 150 to <400 m, or ≥400 m) and ERT status (ERT-naïve or ERT-experienced).[53] Participants continued treatment in both arms of the trial for 52 weeks at which point they were given the option to continue in the open-label extension (OLE; NCT 04138277) to be treated with cipaglucosidase alfa in combination with miglustat, regardless of the treatment received in PROPEL.

ATB200-02 trial design

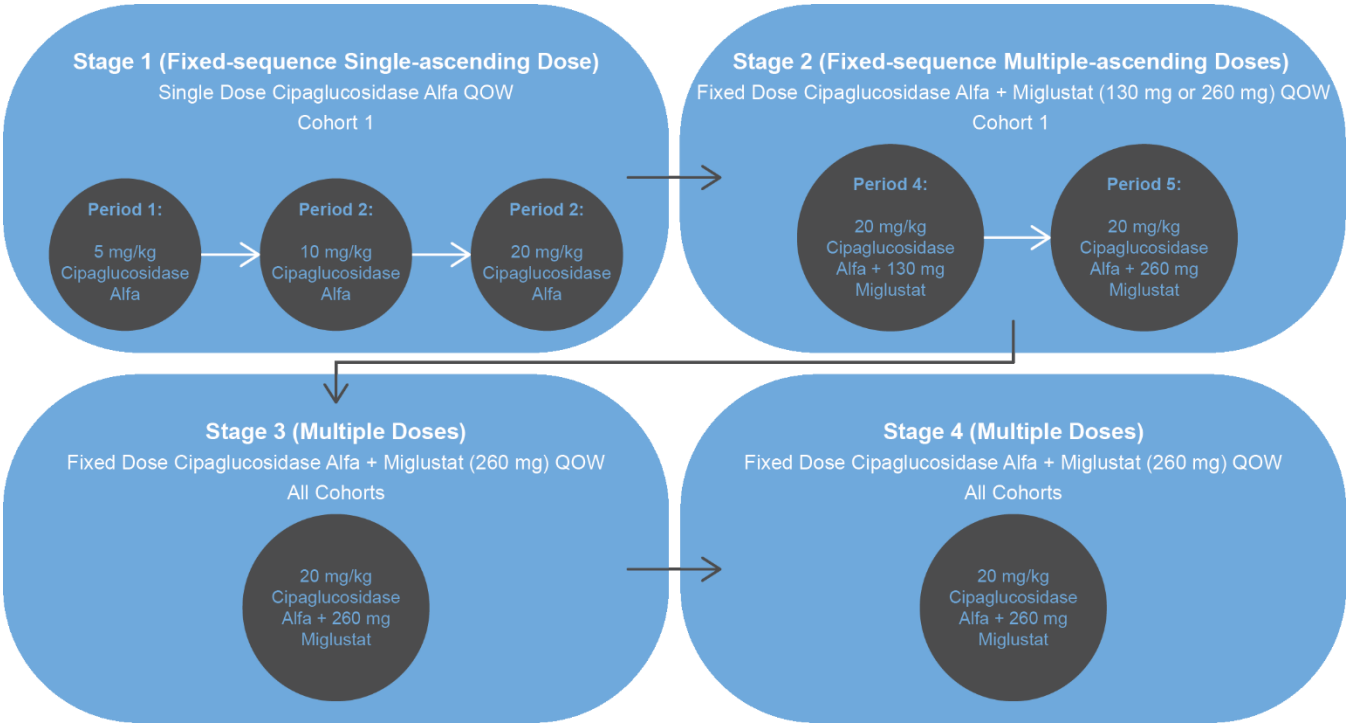
ATB200-02 was conducted in four stages and four cohorts, with Stages 1 and 2 only for Cohort 1 and Stages 3 and 4 for all four cohorts (see Figure 4 and Table 4). All cohorts enrolled adults with Pompe disease. This enrolled population was deemed to be representative of the total LOPD population, and therefore relevant to the decision problem.[58, 59] The four cohorts in the study were as follows:

- Cohort 1: This cohort enrolled ERT-experienced ambulatory participants, defined as adults with Pompe disease who had been on ERT for two to six years prior to enrolment and were able to walk at least 200 m in the 6MWT.
- Cohort 2: This cohort enrolled ERT-experienced non-ambulatory participants, defined as adults with Pompe disease who used a wheelchair, were unable to walk unassisted and had been on ERT for at least two years prior to enrolment.
- Cohort 3: This cohort enrolled ERT-naïve ambulatory participants, defined as adults with Pompe disease who had never received treatment with ERT, or who had received no more than one dose of ERT more than six months before the baseline visit in this study (in Australian study centres only), and who were able to walk at least 200 m in the 6MWT.
- Cohort 4: This cohort enrolled ERT-experienced ambulatory participants, defined as adults with Pompe disease who had been on ERT for at least seven years prior to enrolment and were able to walk at least 75 m in the 6MWT. This cohort was added after the first three cohorts, starting February 2018.

The four study stages were as follows (Figure 4):

- Stage 1: A 3-period, fixed-sequence, single ascending-dose pharmacokinetics (PK) study of cipaglucosidase alfa alone. Safety, tolerability, and PK were evaluated following sequential single ascending doses of 5 mg/kg, 10 mg/kg, and 20 mg/kg of intravenous (IV)-infused cipaglucosidase alfa administered two weeks apart. Only participants in Cohort 1 participated in Stage 1.
- Stage 2: A 2-period, fixed-sequence, single- and multiple-dose PK study of cipaglucosidase alfa 20 mg/kg in combination with multiple ascending doses of miglustat. In Stage 2, safety, tolerability, and PK were evaluated following single and multiple ascending-dose combinations: 20 mg/kg of IV-infused cipaglucosidase alfa in combination with 130 mg of miglustat administered orally every 14 days (± 3 days) for 3 doses, followed by 20 mg/kg of IV-infused cipaglucosidase alfa in combination with 260 mg of miglustat administered orally for three doses. Only participants in Cohort 1 participated in Stage 2.
- Stage 3: Cohort 1 participants who completed Stages 1 and 2 entered into a 2-year treatment period of the study, during which they continued on extended treatment with 20 mg/kg of IV-infused cipaglucosidase alfa in combination with 260 mg of miglustat administered orally every two weeks. During Stage 3, three new cohorts (Cohorts 2, 3, and 4) were enrolled. Participants from Cohorts 2, 3, and 4 were treated with 20 mg/kg of IV-infused cipaglucosidase alfa in combination with 260 mg of miglustat administered orally every 2 weeks.
- The Stage 4 treatment period began at the end of Stage 3 and continued as a long-term extension to provide additional safety and efficacy data until participant withdrawal, regulatory approval, or marketing authorisation and/or commercialisation in the participant's country, or study termination by the sponsor, Amicus. Data for 48 months of treatment are presented in Section B.2.6. However, it should be noted that data for 36 months of treatment are included in the economic model as there was insufficient time between the data being published and the submission to implement them in the model (Section B.3).

Figure 4: Overview of the study design for ATB200-02



Abbreviations: QOW: every other week
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[55]

Table 4: Treatment assignment and outcomes for Stages 1, 2, 3, and 4 (ATB-200-02)

	Time →						
Cohorts	**Stage 1 (fixed-sequence single ascending dose) (6 weeks)**			**Stage 2 (fixed-sequence multiple ascending dose) (12 weeks)**		**Stage 3 (multiple dose) (2 years)**	**Stage 4 (multiple dose) (until approval)**
	Period 1 single-dose	**Period 2 single-dose**	**Period 3 single-dose**	**Period 4 3 doses, co-administration**	**Period 5 3 doses, co-administration**	**24 months extension, co-administration**	**Long-term extension, co-administration**
Cohort 1 [redacted]	Cipaglucosidase alfa 5 mg/kg	Cipaglucosidase alfa 10 mg/kg	Cipaglucosidase alfa 20 mg/kg	Cipaglucosidase alfa 20 mg/kg + miglustat 130 mg	Cipaglucosidase alfa 20 mg/kg + miglustat 260 mg	Cipaglucosidase alfa 20 mg/kg + miglustat 260 mg	Cipaglucosidase alfa 20 mg/kg + miglustat 260 mg
Cohort 2 [redacted]	NA					Cipaglucosidase alfa 20 mg/kg + miglustat 260 mg	Cipaglucosidase alfa 20 mg/kg + miglustat 260 mg
Cohort 3 [redacted]	NA					Cipaglucosidase alfa 20 mg/kg + miglustat 260 mg	Cipaglucosidase alfa 20 mg/kg + miglustat 260 mg
Cohort 4 [redacted]	NA					Cipaglucosidase alfa 20 mg/kg + miglustat 260 mg	Cipaglucosidase alfa 20 mg/kg + miglustat 260 mg
Outcomes							
All cohorts	Plasma GAA activity and total GAA protein PK; safety/tolerability			Plasma GAA activity, total GAA protein and miglustat PK; safety/tolerability; PD		Plasma GAA activity, total GAA protein and miglustat PK; safety/tolerability; efficacy	Safety/tolerability; efficacy

The draft SmPC for cipaglucosidase alfa specifies a dose of 20 mg/kg. The draft SmPC for miglustat specifies a dose of 260 mg of migalastat for people weighing ≥ 50 kg. Therefore, the dose administered in Stage 2 Period 5 and all subsequent stages align with the draft SmPCs.

When at least one of the 2 sentinel participants (participants dosed ahead of the whole cohort) completed Period 5, Stage 2 dosing, the safety data were reviewed by the SSC before any newly enrolled participants in Cohorts 2 and 3 were dosed. The first 2 participants in Cohorts 2 and 3 also served as sentinel participants for their respective cohorts.
Cohorts 1, 2, 4: ERT-experienced participants; Cohort 3: ERT-naïve participants; Cohorts 1, 3, 4: ambulatory participants; Cohort 2: non-ambulatory participants.
Abbreviations: ERT: enzyme replacement therapy; GAA: human acid α-glucosidase; NA: not applicable; PD: pharmacodynamics; PK: pharmacokinetics; SSC: Safety Steering Committee.
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[55]

B.2.3.2 Trial methodology

A summary of the methodology of PROPEL and ATB200-02 is presented in Table 5. Full details of the methodology can be found in the CSRs for each trial.[5, 55] Both trials were designed to include a broad range of international sites and to involve both ERT-experienced and ERT-naïve participants with LOPD, to ensure the broadest access to the Pompe community and generalisability to UK clinical practice.[5] Input was incorporated from clinical experts, adults with Pompe disease and NICE 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.

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.[55] 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.[60, 61] 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.[62] 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:

[redacted]

Amicus also solicited advice on trial endpoints, population and methodology directly from NICE through Scientific Advice in June 2018 and through the NICE Office for Market Access (OMA) in September 2020.

Table 5: Summary of the PROPEL and ATB200-02 trial design and methodology

Trial name and number	PROPEL; ATB200-03; NCT03729362	ATB200-02; NCT02675465
Overview	Phase III, prospective, double-blind, international, head-to-head superiority RCT	Phase I/II open-label, fixed-sequence, ascending-dose study

Eligibility criteria for participants	**Key inclusion criteria:**
	• Aged ≥18 years old and weighed ≥40 kg at screening
	• Diagnosis of LOPD based on documentation of one of the following:
	  ○ Deficiency of GAA enzyme
	  ○ GAA genotyping
	• Sitting FVC ≥ 30% of the predicted value for healthy adults at screening.
	• Performed two 6MWTs at screening that were valid, as determined by the clinical evaluator, and that met all of the following criteria:
	  ○ both screening values of 6MWD were ≥ 75 m
	  ○ both screening values of 6MWD were ≤ 90% of the predicted value for healthy adults
	  ○ the lower value of 6MWD was within 20% of the higher value of 6MWD
	
	Key exclusion criteria:
	• Receipt of 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 was longer, before Day 1 or was anticipated to do so during the study
	• Receipt of gene therapy for Pompe disease
	• Taking any of the following prohibited medications within 30 days before Day 1:
	  ○ miglitol (e.g. Glyset®)
	  ○ miglustat (e.g. Zavesca®)
	  ○ acarbose (e.g. Precose® or Glucobay®)
		Key inclusion criteria (total population):
		• Aged ≥18 years old
		• Diagnosis of Pompe disease based on documentation of one of the following:
		  ○ Deficiency of *GAA* enzyme
		  ○ *GAA* genotyping
		• 6MWD between 200 and 500 m
		• Upright FVC must have been 30% to 80% of predicted value for healthy adults
		
		Key inclusion criteria (cohort-specific):
		• Cohort 1: Received ERT for two to six years prior to enrolment and had 6MWD of at least 200 m
		• Cohort 2: Received ERT for at least two years prior to enrolment, required use of a wheelchair and unable to walk unassisted
		• Cohort 3: Never received treatment with ERT, or received no more than one dose of ERT more than six months before the baseline visit in this study (in Australian study centres only) and had 6MWD of at least 200 m
		• Cohort 4: Received ERT for at least seven years prior to enrolment and had 6WMD of at least 75 m
		
		Key exclusion criteria (total population):
		• Receipt of 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 was longer, before Day 1 or was anticipated to do so during the study

	○ voglibose (e.g. Volix®, Vocarb®, or Volibo®) • Required invasive or non-invasive ventilation support for >6 hours per day while awake • Hypersensitivity to any of the excipients in cipaglucosidase alfa, alglucosidase alfa, or miglustat • Had a medical condition or any other extenuating circumstance that may have, in the opinion of the investigator or medical monitor, posed an undue safety risk to the participant or may have compromised his/her ability to comply with or adversely impacted protocol requirements. This included clinical depression (as diagnosed by a psychiatrist or other mental health professional) with uncontrolled or poorly controlled symptoms. • If female, was pregnant or breastfeeding at screening • Whether male or female, was planning to conceive a child during the study • Refusal to undergo genetic testing	• Taking any of the following prohibited medications within 30 days before Day 1: ○ miglitol (e.g. Glyset®) ○ miglustat (e.g. Zavesca®) ○ acarbose (e.g. Precose® or Glucobay®) ○ voglibose (e.g. Volix®, Vocarb®, or Volibo®) ○ oral β2-receptor agonists and non-selective β-blockers (eg, propranolol, nadalol and carvedilol). • Hypersensitivity to any of the excipients in cipaglucosidase alfa, alglucosidase alfa, or miglustat • Had a medical condition or any other extenuating circumstance that may have, in the opinion of the investigator or medical monitor, posed an undue safety risk to the participant or may have compromised his/her ability to comply with or adversely impacted protocol requirements. • If female, was pregnant or breastfeeding at screening • Whether male or female, was planning to conceive a child during the study
Randomisation	Participants were randomly allocated on a 2:1 basis using proprietary and validated interactive response technology software (Almac Clinical Technologies, Craigavon, UK) to receive cipaglucosidase alfa in combination with miglustat or alglucosidase alfa in combination with placebo. Randomisation was stratified by: ○ 6MWD at Baseline (75 to <150 m, 150 to <400 m, or ≥400 m) ○ Previous ERT status (ERT-naïve or ERT-experienced)	This was an open-label study, and no randomisation procedures were used.
Blinding	• Participants, the study sponsor, investigators, site personnel, and contracted research organisations involved in monitoring, data management, data analysis, or other aspects of the study were masked to treatment assignment. • Study drug codes were available for data analysis after completion of the study, verification of data files, determination of protocol violations, and locking of the database.	This was an open-label study, and no blinding procedures were used.

Assessments	• Efficacy assessments were done at Baseline and at weeks 12, 26, 38, and 52 (or End of Study)[a]
	• Serum CK levels were measured using the standard laboratory test
	• Urinary Hex4 levels were quantified at the Duke Biochemical Genetics Laboratory, Durham, NC, USA, by stable isotope dilution following ultraperformance liquid chromatography
	• Clinical laboratory tests and physical examinations were done at weeks 2, 4, 6, 12, 26, 38, and 52
	• Immunogenicity testing was performed on day 1 and at weeks 2, 4, 6, 12, 26, 38, and 52, and 30 days or longer after the last dose.
	• Adverse events were assessed at all infusion visits (every 2 weeks) and follow-up visits
	• The site investigator determined whether an adverse event was deemed related to study drug
	• Exploratory PROs were assessed from Baseline to Week 52, including:
	  ○ Patient-Reported Outcomes Measurement Information System (PROMIS)–Dyspnea
	  ○ PROMIS–Upper Extremities
	  ○ Rasch-built Pompe-specific Activity (R-PAct) Scale
	  ○ EuroQol 5 Dimensions-5 Levels instrument (EQ-5D-5L) based on the EuroQol visual analogue scale quantitative score
		• Efficacy assessments were performed at Baseline, every 3 months in Stage 3, and every 6 months in Stage 4. For ambulatory participants (Cohorts 1, 3 and 4) these included:
		  ○ FVC, maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), and Sniff Nasal Inspiratory Pressure (SNIP)
		  ○ MMT using the Medical Research Council grading scale
		  ○ Quantitative muscle testing (QMT) using hand held dynamometer for both upper and lower limbs
		  ○ 6MWT
		  ○ 10-metre walk test (10MWT)
		  ○ Gait, Stairs, Gowers' manoeuvre, and Chair (GSGC)
		  ○ Timed Up and Go (TUG)
		• For non-ambulatory (Cohort 2) participants these included:
		  ○ FVC, MIP, MEP, and SNIP
		  ○ MMT using the Medical Research Council grading scale
		  ○ QMT using handheld dynamometer for upper limbs only
		  ○ The Subject Global Impression of Change (SGIC) and Physician Global Impression of Change (PGIC) were only be administered in Stage 3 and 4
		  ○ Adverse events were assessed during all stages of the study
		• Exploratory PROs were also assessed after protocol Amendment 7, including:
		  ○ PROMIS–Dyspnea
		  ○ PROMIS–Upper Extremities
		  ○ Rasch-built Pompe-specific Activity (R-PAct) Scale
		  ○ EQ-5D-5L based on the EuroQol visual analogue scale quantitative score

Location and study setting	International multicentre trial conducted across 62 neuromuscular and metabolic medical centres in 24 countries: Argentina, Austria, Australia, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Denmark, France, Germany, Greece, Hungary, Italy, Japan, the Netherlands, New Zealand, Poland, Slovenia, Spain, South Korea, Sweden, Taiwan, UK, and US	International multicentre trial conducted across 16 neuromuscular and metabolic medical centres in five countries: Australia, Germany, the Netherlands, UK, and US
Trial design	Phase III, prospective, double-blind, international, head-to-head superiority RCT	Phase I/II open-label, fixed-sequence, ascending-dose study
Method of study drug administration	The study drugs used in this study were co-administration of cipaglucosidase alfa with miglustat (investigational product) or co-administration of alglucosidase alfa with placebo (active comparator). **Cipaglucosidase alfa and alglucosidase alfa** • The doses of cipaglucosidase alfa and alglucosidase alfa were 20 mg/kg of body weight. • Cipaglucosidase alfa or alglucosidase alfa was administered every 2 weeks as a 4 hour IV infusion. **Miglustat and placebo** • The dose of miglustat was 195 mg (3 × 65 mg oral capsules) for participants weighing ≥ 40 kg to < 50 kg and 260 mg (4 × 65 mg oral capsules) for participants weighing ≥ 50 kg. • The dose of placebo was 195 mg (3 x 65 mg oral capsules) for participants weighing 40 kg to < 50 kg and 260 mg (4 x 65 mg oral capsules) for participants weighing ≥ 50 kg, designed to match the miglustat doses. • Participants fasted for at least 2 hours before and 2 hours after administration of miglustat.	**Cipaglucosidase alfa** In all stages, cipaglucosidase alfa was to be administered every 2 weeks as an approximate 4-hour IV infusion (± 15 minutes). **Miglustat** In Stages 2, 3, and 4, the administration of miglustat oral capsule(s) occurred one hour before the IV infusion of cipaglucosidase alfa and was supervised by the investigator or a qualified designee. Participants fasted for at least 2 hours before and 2 hours after administration of miglustat. The doses of cipaglucosidase alfa and miglustat varied depending on the study stage (see Trial designs).
Permitted and disallowed concomitant medication	**Permitted concomitant medications** • Prior medications and non-drug therapies (e.g., procedures, surgery, physical therapy, occupational therapy, mobility aids, and respiratory support) were those taken or administered before the first dose of study drug	**Permitted concomitant medications** Concomitant medications were allowed as long as they were reported to the study investigator. **Disallowed concomitant medication**

	were considered concomitant if they were taken or administered on or after the first dose of study drug, had onset dates prior to first dose of study drug without a stop date, or had a stop date after first dose of study drug.
	• Use of the following were recorded:
	  ○ Non-drug therapies (including physiotherapy and occupational therapy)
	  ○ Ambulatory aids, such as a cane, walker, or rollator, and respiratory support (e.g. continuous positive airway pressure or bi-level positive airway pressure).
	
	Disallowed concomitant medication
	No specific medications were disallowed, besides those listed under 'Exclusion criteria' for trial eligibility**.**
		No specific medications were disallowed, besides those listed under 'Exclusion criteria' for trial eligibility.

Duration of study and follow-up	The PROPEL study consisted of a screening period of up to 30 days, a 52-week double-blind treatment period, and a 30-day follow-up period.	Stage 4 of the trial is ongoing at the time of submission and will continue until participant withdrawal, regulatory approval, or marketing authorisation and/or commercialisation in the participating participant's country, or study termination by the sponsor, Amicus.
Pre-planned subgroups	Subgroup analyses by age group, gender, and race using all available categories were performed for the primary endpoint and the change in FVC % predicted at Week 52. In addition, the following subgroups were analysed for the primary endpoint and the change in FVC % predicted from Baseline to Week 52, unless otherwise specified: • ERT status (ERT-experienced vs. ERT-naïve) • Baseline 6MWD (75 to < 150 m, 150 to < 400 m, or ≥ 400 m) • Baseline 6MWD < median value, baseline 6MWD ≥ median value • Baseline FVC < median value, baseline FVC ≥ median value • Regions (North/South America, Europe, Asia Pacific) • ERT duration (2 to < 3, 3 to < 5, and ≥ 5 years) • History of infusion-associated reactions (IARs) (yes, no)	NA

[a]Participants who missed study visits due to COVID-19 pandemic-related reasons were allowed to participate in the study beyond 52 weeks
Abbreviations: 6MWT: six-minute walk test; ERT: enzyme-replacement therapy; FVC: forced vital capacity; GAA: acid α-glucosidase IV: intravenous; LOPD: late-onset Pompe disease; RCT: randomised controlled trial.
Sources: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report);[55] Amicus Therapeutics Data on File (PROPEL Clinical Study Report);[5] ClinicalTrials.gov.[63]

Efficacy and safety measurements were selected to reflect clinically meaningful endpoints which demonstrate the impact of the disease on adults with LOPD, including pulmonary function, muscle strength, and motor function as well as PROs and participant and physician impression of changes. Definitions for efficacy outcome measures used in PROPEL and ATB200-02 are presented in Table 6.

Table 6: Definitions for key outcome measures from PROPEL and ATB200-02 relevant to the submission

Outcome measure[a]	Definition
Efficacy assessments	
6MWD	The 6MWD, measured in m, is the distance walked in the 6MWT.
Sitting FVC % predicted	Sitting FVC, measured in litres (L), as the percentage of predicted FVC.
MMT score	Each MMT is evaluated on a scoring scale from 0 to 5, as follows: 0: no muscle movement; 1: visible muscle movement, but no movement at the joint; 2: movement at the joint, but not against gravity; 3: movement against gravity, but not against added resistance; 4: movement against resistance, but less than normal; 5: normal strength. MMT Lower Extremity score: The total score for MMT lower extremity strength is obtained by summing the test scores across the following 8 body parts: right/left hip flexion, right/left hip abduction, right/left knee flexion, and right/left knee extension. The total score ranges from 0 to 40, with lower combined hip and knee scores indicating lower muscle strength.
PROMIS – Physical Function	PROMIS – Physical Function Short Form 20a (v2.0) consists of 20 questions. The first 14 questions are each scored on a scale from 1 to 5 as follows: 1: unable to do; 2: with much difficulty; 3: with some difficulty; 4: with a little difficulty; 5: without any difficulty; the next 6 questions are each scored on a scale from 1 to 5 as follows: 1: cannot do; 2: quite a lot; 3: somewhat; 4: very little; 5: not at all.
PROMIS – Fatigue	PROMIS – Fatigue Short Form 8a consists of 8 questions, each scored on a scale from 1 to 5 as follows: 1: not at all; 2: a little bit; 3: somewhat; 4: quite a bit; 5: very much; and 2 questions, each scored on a scale from 1 to 5 as follows: 1: never; 2: rarely; 3: sometimes; 4: often; 5: always.
GSGC	GSGC total score is the sum of the component scores from the following 4 functional tests: • 10-metre walk test (10MWT) is the time in seconds (s) it takes for the participant to walk 10 m. The test is scored as: 1: normal; 2: mild waddling, lordosis and/or toe walking; 3: moderate waddling, lordosis and/or toe walking; 4: severe waddling, lordosis and/or toe walking; 5: walks only with assistance (ie, braces, cane, crutches); 6: stands, but unable to walk; 7: confined to wheelchair. The score from this test is used as the Gait score in GSGC. • Stairs score (based on the participant climbing 4 stairs). This is

	scored as: 1: climbs four stairs without assistance; 2: supports one hand on thigh; 3: supports both hands on thighs; 4: climb stairs in upright position but with aid of railing; 5: climbs while clinging to the railing with both hands; 6: manages to climb only a few steps; 7: unable to climb steps. • Gowers' manoeuvre score (based on the participant lying down on the floor, then rising from the floor to get to a standing position). This is scored as: 1: normal; 2: butt first manoeuvre, one hand on floor; 3: butt first manoeuvre, two hands on floor; 4: unilateral hand support on thigh; 5: bilateral hand support on thighs; 6: arises only with aid of an object (table, chair, cane, etc); 7: unable to rise. • Chair score (based on the participant arising from a sitting position in a chair to a standing position). This is scored as: 1: normal; 2: with wide base and/or difficulty but without support; 3: with support on one thigh; 4: with support on both thighs; 5: with support on arms of chair or on a table; 6: not possible. For each of the above motor function tests, the actual time (in seconds [s]) that the participant takes to perform the test is also recorded for analysis. The total GSGC score ranges from 4 (normal performance) to 27 (worst performance).
Safety endpoints	
Adverse event (AE)	Any untoward medical occurrence in a participant administered a pharmaceutical product, biologic (at any dose), or medical device, that did not necessarily have a causal relationship with the treatment For all participants, AEs and SAEs were reported from the time of ICF signing until 30 days after the last dose of study drug.
Treatment-emergent AE (TEAE)	Any AE that began after the first dose of study drug. Participants experiencing AEs were followed up until their health returned to baseline status or stabilised.
Serious AE (SAE)	Any AE that resulted in death, was life threatening, required inpatient hospitalisation or prolonged existing hospitalisation, resulted in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, as decided by the investigator, or was a congenital anomaly/birth defect.
IAR	A disorder characterised by one or more adverse reaction(s) to the infusion of pharmacological or biological substances.
Pharmacodynamic assessments	
CK	Change in serum CK level, a biomarker for muscle injury, from Baseline to Week 52.
Hex4	Change in urinary Hex4, a biomarker for disease substrate, level from Baseline to Week 52.

[a]All efficacy and pharmacodynamic endpoints are expressed in terms of 'Change from Baseline to X'
Abbreviations: 6MWD: six-minute walk distance; CK: creatine kinase; AE: adverse event; FVC: forced vital capacity; GSGC: Gait, Stairs, Gowers' manoeuvre and Chair; Hex4: hexose tetrasaccharide IAR: infusion-associated reaction; ICF: informed consent form; MMT: manual muscle test; PROMIS: Patient-reported Outcomes Measurement Information System; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report)[5]

In PROPEL, thresholds for clinically relevant changes in 6MWD and FVC were developed to ensure results could be meaningfully interpreted in terms of their impact for adults with LOPD. In Pompe disease, there are no well-established thresholds for clinically relevant changes in these outcomes. However, a large body of data exists from other neuromuscular and chronic respiratory diseases, especially interstitial pulmonary fibrosis (IPF). There, 6MWD increases greater than 6% (range 3 to 11%) and FVC changes greater than 3% (range 2 to 6%) are considered clinically relevant using both anchor-based and distribution-based methodologies.[64-67] Accordingly, these thresholds were applied to analyses of PROPEL trial results (Table 7).

Table 7: Pre-defined thresholds for clinically meaningful within-participant change in outcome measures

Clinical Outcome	Declining	Stable	Improving
6MWD[a]	< -6%	-6 to < +6%	≥ +6%
FVC % predicted[b]	< -3%	-3 to < +3%	≥ +3%
MMT lower extremity score	< -7%	-7 to < +7%	≥ +7%

The above thresholds are consistent with published MCID (minimal clinically important differences) values for comparable instruments in similar disease populations[64-67]
[a]Threshold was based on the percent change from Baseline.
[b]Threshold was based on the change from Baseline.
Abbreviations: 6MWD: six-minute walk distance; FVC: forced vital capacity; MMT: manual muscle testing
Source: Schrover *et al*. (2017);[67] Baschung Pfister *et al*. (2018);[64] Lachmann *et al*. 2013[66]

Thresholds for clinically relevant changes in 6MWD and FVC were not pre-specified in the statistical analysis plan (SAP) for ATB200-02. However, the same thresholds presented in Table 7 are relevant to ATB200-02 participants given the similarities in the population, although they were not used for analysis of 6MWD given the data are presented as change in m as opposed to % improvement. The threshold clinically meaningful within-participant change for FVC % predicted used in PROPEL was also used in the *post hoc* analysis for ATB200-02.

B.2.3.3 Baseline characteristics

Baseline characteristics in the included population of PROPEL

The participant demographics, baseline disease characteristics, and baseline mobility and respiratory function of participants in PROPEL are presented in Table 8, Table 9, and Table 10, respectively. Overall, participant characteristics were well-balanced between treatment arms,[5] with minor differences in relative percentages noted, reflective of RCTs performed in rare diseases with relatively low sample sizes. Expert opinion confirmed the baseline characteristics for participants in PROPEL are closely aligned to those of adults with Pompe disease in UK clinical practice, which provides validation that results from PROPEL are generalisable to UK clinical practice.[5, 53, 55]

Table 8: Participant demographics in PROPEL (Intention to Treat (ITT) Population, including outlier participant)[a]

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 38)	Total (N = 123)
Age at informed consent date (years)			
Mean (Standard deviation [SD])	47.6 (13.25)	45.1 (13.30)	[redacted]
Median (first quartile [Q1], third quartile [Q3])	48.0 [redacted]	46.0 [redacted]	[redacted]
Min, max	19, 74	22, 66	[redacted]
Gender, n (%)			
Male	36 (42.4)	20 (52.6)	[redacted]
Female	49 (57.6)	18 (47.4)	[redacted]
Race group[b]			
Asian	[redacted]	[redacted]	[redacted]
Japanese	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]
White	74 (87.1)	30 (78.9)	[redacted]
Other	[redacted]	[redacted]	[redacted]

[a]Data from an ERT-naïve outlier participant in the alglucosidase alfa in combination with placebo treatment arm are included in this table

Percentages were based on the number of participants in each treatment group for the ITT Population.

[b]Participants may have chosen more than 1 racial category.

Abbreviations: max: maximum; min: minimum; ITT: Intention to Treat; Q1: first quartile; Q3: third quartile; SD: standard deviation.

Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

Table 9: Baseline disease characteristics in PROPEL (ITT Population, including outlier participant)[a]

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 38)	Total (N = 123)
ERT status, n (%)			
ERT-naïve	20 (23.4)	8 (21.1)	28 [redacted]
ERT-experienced	65 (76.5)	30 (78.9)	95 [redacted]
ERT duration (years)[b]			
n	65	30	95

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 38)	Total (N = 123)
Mean (SD)	7.48 (3.378)	7.14 (3.635)	[redacted]
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Using assistive devices at Baseline, n (%)			
Yes	17 (20.0)	11 (28.9)	[redacted]
No	[redacted]	[redacted]	[redacted]
History of IARs, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]

[a]Data from an ERT-naïve outlier participant in the alglucosidase alfa in combination with placebo treatment arm are included in this table
Percentages were based on the number of participants in each treatment group for the ITT Population.
[b]Enzyme replacement therapy duration was calculated as (date of informed consent - date of first dose of ERT)/365.25, rounded to the nearest tenth (0.1).
Abbreviations: ERT: enzyme replacement therapy; max: maximum; min= minimum; IAR: infusion-associated reaction; ITT: Intention to Treat; Q1: first quartile; Q3: third quartile; SD: standard deviation.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

Table 10: Baseline mobility and respiratory function in PROPEL (ITT Population, including outlier participant)[a]

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 38)	Total (N = 123)
Baseline 6MWD (m)[a]			
n	85	38	[redacted]
Mean (SD)	357.931 (111.843)	350.142 (119.776)	[redacted]
Median (Q1, Q3)	359.500 [redacted]	358.450 [redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Baseline % predicted 6MWD(%)[b]			
n	85	38	[redacted]
Mean (SD)	57.819 (15.797)	[redacted]	[redacted]
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Baseline 6MWD category 1, n (%)[b]			
≥ 75 to < 150 m	[redacted]	[redacted]	[redacted]

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 38)	Total (N = 123)
≥ 150 to < 400 m	[redacted]	[redacted]	[redacted]
≥ 400 m	[redacted]	[redacted]	[redacted]
Sitting FVC % predicted[c]			
n	85	38	[redacted]
Mean (SD)	70.74 (19.573)	70.04 (21.301)	[redacted]
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]

[a]Data from an ERT-naïve outlier participant in the alglucosidase alfa in combination with placebo treatment arm are included in this table
Percentages were based on the number of participants in each treatment group for the ITT Population.
[b]Baseline was the average of the last 2 values obtained on or prior to the first dose date; predicated value calculated based on age, height, heart rate, weight, and gender.
[c]Baseline for FVC was the average of the last 2 values obtained on or prior to the first dose date for each parameter
Abbreviations: 6MWD: six-minute walk distance; FVC: forced vital capacity; ITT: Intention-to-Treat; max: maximum; min= minimum; Q1: first quartile; Q3: third quartile; SD: standard deviation.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report)[5]

Baseline characteristics in the included population of ATB200-02

The baseline demographics for ATB200-2 are presented in Table 11. The mean participant age was similar in the PROPEL trial and the ATB200-02 trial, [redacted] and [redacted], respectively. Participants in ATB200-02 had a higher mean 6MWD but lower FVC % predicted than in PROPEL.

Table 11: Participant demographics and clinical characteristics in ATB200-02 (All enrolled participants)

	Total (Cohorts 1 – 4) ([redacted])
Age (years)	
n	[redacted]
Mean (SD)	[redacted]
Median (Q1, Q3)	[redacted]
evalMin, Max	[redacted]
Gender, n (%)	
Male	[redacted]
Female	[redacted]
Race, n (%)[a]	
White	[redacted]

	Total (Cohorts 1 – 4) ([redacted])
Missing	[redacted]
Ethnicity, n (%)	
Not Hispanic or Latino	[redacted]
Missing	[redacted]
6MWD	
n	[redacted]
Mean (SD)	[redacted]
FVC % predicted	
n	[redacted]
Mean (SD)	[redacted]

[a]Race and ethnicity were only collected at United States sites.
[b]Cohorts 1, 3 and 4 only (ambulatory participants).
Cohorts 1, 2, 4: ERT-experienced participants; Cohort 3: ERT-naïve participants; Cohorts 1, 3, 4: ambulatory participants; Cohort 2: non-ambulatory participants.
[redacted]
Abbreviations: 6MWD: six-minute walk distance; BMI: body mass index; ERT: enzyme replacement therapy; FVC: forced vital capacity; iCSR: interim clinical study report; Max: maximum; Min: minimum; Q1: first quartile; Q3: third quartile; SD: standard deviation.
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[55]

B.2.3.4 Concomitant medications

Concomitant medications in PROPEL

Table 5 summarises permitted and disallowed concomitant medications in PROPEL. To reflect real-world practice and intended use of cipaglucosidase alfa in combination with miglustat, use of concomitant and prior medication was permitted. The most common concomitant medications ([redacted]) by anatomical therapeutic chemical (ATC) classification were anilides ([redacted]), vitamin D and analogues ([redacted]), influenza vaccines ([redacted]), propionic acid derivatives ([redacted]; most commonly ibuprofen [redacted]), uncoded medications ([redacted]), proton pump inhibitors ([redacted]), other antihistamines for systemic use ([redacted]), plain angiotensin-converting-enzyme (ACE) inhibitors ([redacted]), SSRIs ([redacted]), glucocorticoids ([redacted]), opioids in combination with nonopioid analgesics ([redacted]), and plain multivitamins ([redacted]).[5]

Concomitant medications in ATB200-02

Prior medication use was similar across cohorts and stages except for alglucosidase alfa, which was predominantly used by all participants in Cohorts 1, 2, and 4. The most common prior medications overall were alglucosidase alfa ([redacted]), paracetamol ([redacted]), plain multivitamins ([redacted]), omeprazole ([redacted]), ibuprofen ([redacted]), and vitamin D not otherwise specified ([redacted]).[55]

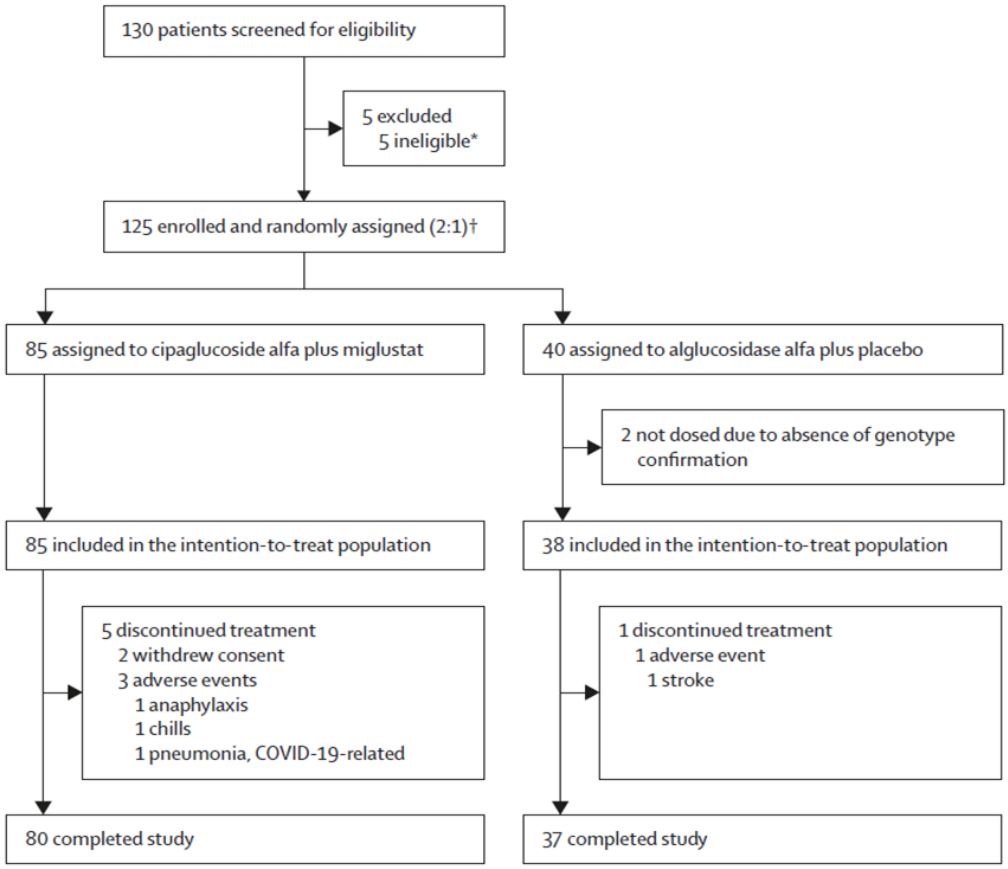
Concomitant medication use was similar across cohorts and stages. The most common concomitant medications for participants who received the dose of the study drug that is equivalent to that in PROPEL and the proposed indication for individuals ≥50 kg (cipaglucosidase alfa 20 mg/kg in combination with miglustat 260 mg; i.e., participants in Stage 2 Period 5, Stage 3, and Stage 4) were paracetamol ([redacted]), other viral vaccines ([redacted]), ibuprofen ([redacted]), colecalciferol ([redacted] and influenza vaccine ([redacted]). The commonly used medications were similar to those used in the PROPEL trial.[5, 55]

B.2.3.5 Participant flow

Participant flow in PROPEL

In PROPEL, 130 participants were initially screened for eligibility and 125[redacted] enrolled and underwent randomised 2:1 treatment assignment. Five[redacted] of the original 130 participants did not meet the inclusion criteria of PROPEL and were not randomised to treatment. 85 participants were assigned to the intervention arm (cipaglucosidase alfa in combination with miglustat) whilst 40 participants were assigned to the control arm (alglucosidase in combination with placebo). Two[redacted] participants randomised to treatment in the control arm subsequently did not receive treatment due to absence of LOPD genotype confirmation. Overall, five participants [redacted] in the intervention arm and one participant [redacted] in the control arm discontinued from the study. A full Consolidated Standards of Reporting Trials (CONSORT) diagram of participant flow in PROPEL is presented in Figure 5.[5]

Figure 5: CONSORT diagram showing participant flow in PROPEL



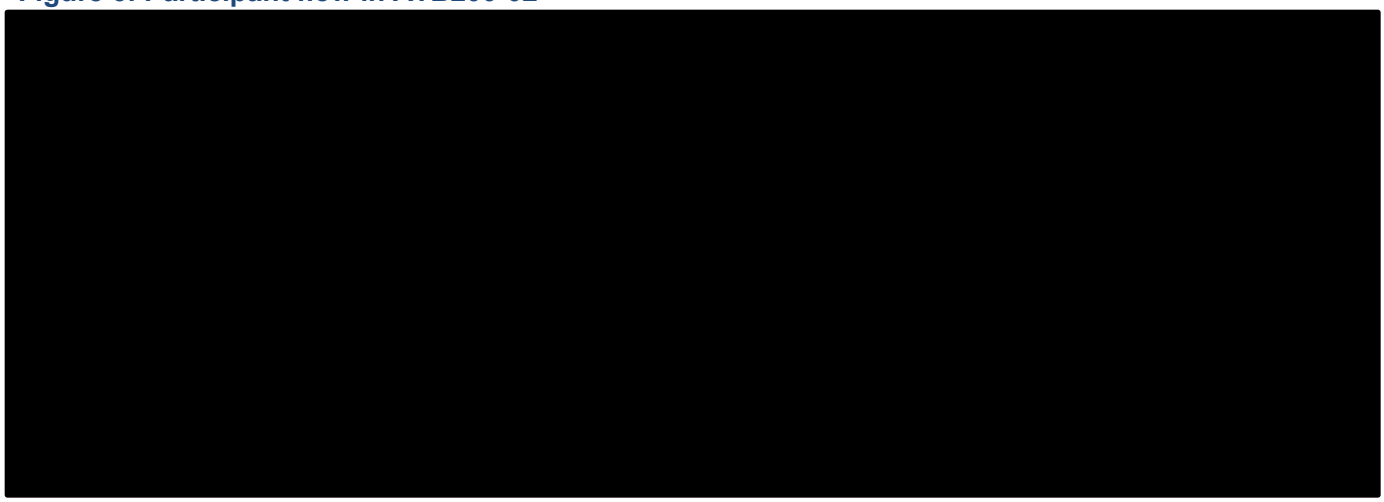
*Five participants signed an informed consent form but did not meet study inclusion criteria and were therefore not randomly assigned.
†Randomisation was stratified by previous enzyme replacement therapy status and 6MWD at Baseline.

Abbreviations: CONSORT: Consolidated Standards of Reporting Trials; COVID-19: coronavirus 2019.
Source: Schoser *et al*. (2021).[53]

Participant flow in ATB200-02

As of the interim data cut-off [redacted]. [redacted] had discontinued the study during Stage 3. Discontinuations were due to AEs in [redacted] and withdrawal of consent in [redacted]. Figure 6 summarises participant flow by stages of treatment for all enrolled participants.

Figure 6: Participant flow in ATB200-02



Abbreviations: AE: adverse event.
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[55]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Statistical analysis in PROPEL

Statistical hypothesis testing and assessment of efficacy in PROPEL

PROPEL had one primary efficacy endpoint (change from Baseline to Week 52 in 6MWD) and six key secondary endpoints assessed in a hierarchical order (Figure 7). The first and most important of these key secondary endpoints is the FVC (i.e., change from Baseline to Week 52 in sitting FVC % predicted). All p-values for primary and key secondary endpoints were calculated and tested for statistical significance. Statistical significance was interpreted as 'nominal' if a prior endpoint in the pre-specified hierarchy failed to meet statistical significance.

Figure 7. Pre-specified hierarchical testing procedure in PROPEL

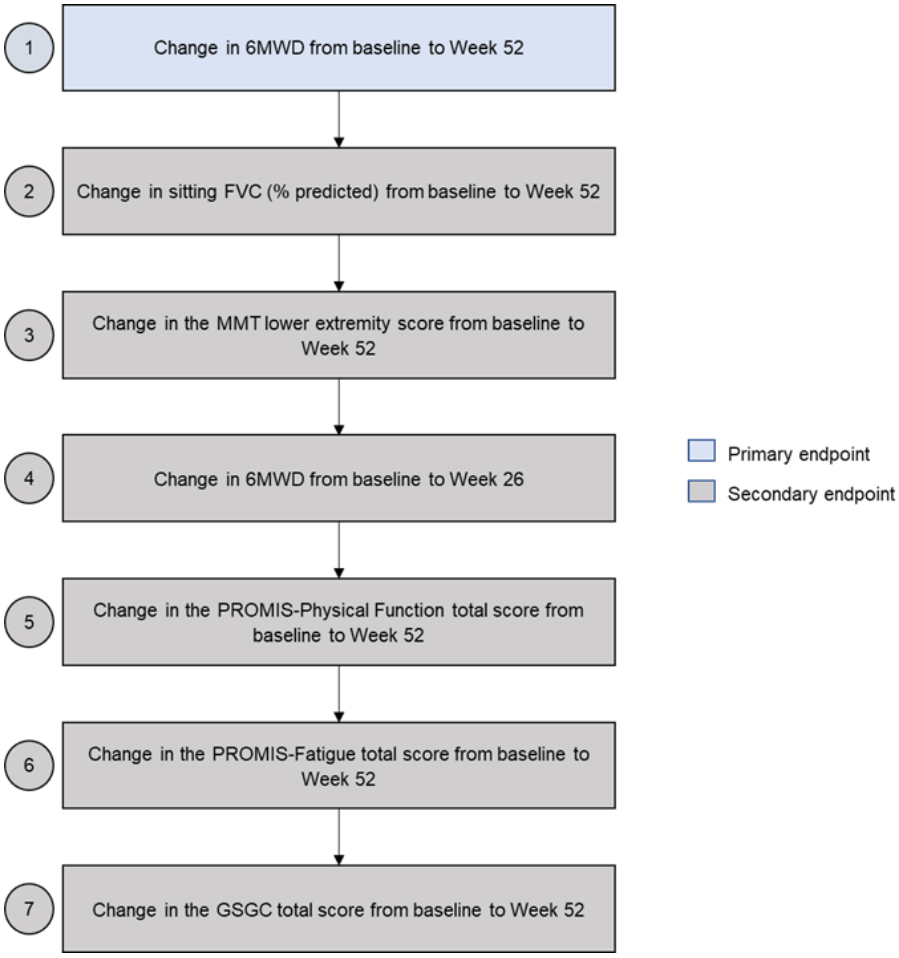


Figure shows the order of statistical testing in PROPEL. If any endpoint did not meet statistical significance, statistical significance of subsequent endpoints was interpreted as nominal significance.
Abbreviations: 6MWD: six-minute walk distance; FVC: forced vital capacity; MMT: manual muscle testing; PROMIS: Patient-Reported Outcomes Measurement Information System.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

All inferential statistical tests for the primary and key secondary efficacy endpoints were 1-sided and were performed at the alpha level of 0.025. For ease of interpretation, all results of statistical tests are presented as 2-sided p values (which can be more easily interpreted with an alpha level of 0.05). All 1-sided p-values are available in the PROPEL CSR.[5] Where basic summary statistics were used, continuous variables were summarised using descriptive statistics (n, mean, standard deviation [SD], median, first quartile, third quartile, minimum, and maximum); categorical variables were summarised using number and percentage. For basic summaries involving the change from Baseline, a 95% confidence interval (CI) for the mean difference was provided. Details of the pre-specified statistical analyses used in PROPEL are presented in Table 12.

Table 12: Statistical methods for the analysis of PROPEL

	Primary efficacy analysis (6MWD)	Secondary analysis (FVC % predicted and other secondary endpoints)
Hypothesis objective	• The null hypothesis for the primary efficacy analysis was that the intervention treatment is less effective than the control, with respect to the primary efficacy endpoint • The alternative hypothesis for the primary efficacy analysis was that the intervention treatment is more effective than the control, with respect to the primary efficacy endpoint	• The null hypothesis for the key secondary efficacy analyses was that the intervention treatment is less effective than the control, with respect to the key efficacy endpoint being tested • The alternative hypothesis for the key secondary efficacy analyses was that the intervention treatment is more effective than the control, with respect to the key efficacy endpoint being tested
Statistical analysis	• The primary efficacy endpoint (change from Baseline to Week 52 in 6MWD) was analysed using an mixed effect model for repeated measures (MMRM) model to compare between treatment and control on the ITT Population. • For this analysis, the dependent variable was the change from Baseline to all post-Baseline visits. Independent variables in the model were the fixed, categorical effects of treatment, time (i.e., visit), treatment-by-time interaction, ERT status and gender, as well as the fixed, continuous covariates of baseline 6MWD, baseline age, baseline weight and baseline height • The main variable estimated in the primary comparison was the difference between cipaglucosidase alfa in combination with miglustat and alglucosidase alfa in combination with placebo in mean change in 6MWD from Baseline to Week 52, regardless of whether intercurrent events had occurred. The significance test was based on the treatment comparison of LS means at Week 52 and a p-value was presented for this time point only • The MMRM analysis was used as the primary efficacy analysis for the 6MWD regardless of the results of the normality checks. The non-parametric randomisation-based covariance analysis was performed as a sensitivity analysis only if the normality assumption was notably violated with the Shapiro-Wilk test p-value <0.01.	• Statistical significance of key secondary endpoints was interpreted following a hierarchical testing order: ○ change from Baseline to Week 52 in sitting FVC % predicted ○ change from Baseline to Week 52 in the MMT score for the lower extremities ○ change from Baseline to Week 26 in 6MWD ○ change from Baseline to Week 52 in the total score for the PROMIS – Physical Function ○ change from Baseline to Week 52 in the total score for the PROMIS – Fatigue ○ change from Baseline to Week 52 in GSGC total score • Each key secondary endpoint was analysed using an analysis of covariance (ANCOVA) model on the ITT-last observation carried forward (ITT-LOCF) Population. The model was adjusted for the baseline value (as a continuous covariate) and ERT status (ERT-naïve vs. ERT-experienced), as well as baseline age, gender, baseline height and baseline weight to compare between the 2 treatment groups. • Each interaction term was explored using a separate ANCOVA model that included the full set of covariates (i.e., treatment, baseline value (as a continuous variable), ERT status, baseline age, gender, height, and weight) as well as the interaction term.

	The MMRM analysis assumed that data were missing at random.	• Interaction terms with a 2-sided p<0.10 were further examined clinically. • As a supportive analysis, each of the key secondary endpoints were analysed using an MMRM analysis on the ITT Population.

Abbreviations: 6MWT: six-minute walk test; ANCOVA: analysis of covariance; ERT: enzyme-replacement therapy; FVC: forced vital capacity; GSGC: Gait, Stairs, Gowers' manoeuvre and Chair; ITT-LOCF: intention-to-treat-last observation carried forward; ITT: intention-to-treat; MMRM: mixed effect model for repeated measures; PROMIS: Patient-reported Outcomes Measurement Information System.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

Planned sample size

The required sample size of PROPEL was determined based on a 2-group t-test with a 1-sided significance level of 0.025. Using a 2:1 randomisation ratio, a total of 99 participants (66 participants in the cipaglucosidase alfa in combination with miglustat group and 33 participants in the alglucosidase alfa in combination with 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 randomisation), approximately 110 participants were planned to be randomised to ensure 99 evaluable participants.

Analysis populations

Analysis populations are described in Table 13. After the database was locked and treatment assignments were unblinded, it was noted that one participant (known as the "outlier participant") in the ITT Population showed a clinically implausible change in 6MWD from Baseline. Given this finding, the results for this participant were investigated and it was found that the participant took an investigational anabolic steroid 2–4 weeks prior to study entry and deliberately underperformed on baseline 6MWT and FVC assessments, in order to meet the inclusion criteria for the study. The participant confirmed that subsequent assessment efforts were performed with a full effort. A pre-specified sensitivity analysis excluding outlier data points was also performed, which excluded this participant's datapoints. Given the participant admitted underperformance on the screening test, the clinically implausible results, and most importantly the outlier sensitivity analysis, all efficacy analyses on the ITT population were performed with and without this outlier participant. To avoid bias, all efficacy results on the ITT Population presented in this submission (Section B.2.6) exclude this participant; this is stated clearly above each table of efficacy results. Adverse reactions presented in this submission include data from this participant (Section B.2.10). The baseline characteristics previously presented in Section B.2.3.3 also include this participant unless stated.

Table 13: Analysis populations used in the analysis of outcomes in PROPEL

Analysis set	Definition
ITT Population **ITT-observed (ITT-OBS) Population, including or excluding outlier participant**	• The ITT Population consisted of all randomised participants who received at least one dose of study drug. This population was analysed according to the planned treatment groups. • The ITT Population was used for baseline and demographic summaries. • The ITT Population was characterised further as the ITT-OBS and the ITT-LOCF Populations. • The ITT-OBS Population used all available, observed data without imputation for missing post-baseline data; missing data at Week 52 and at other visits were not replaced. The ITT-OBS Population was identical to the ITT Population and is therefore referred to as the ITT Population throughout. • Efficacy analyses presented on the ITT Population in this submission exclude the outlier participant unless otherwise stated.
ITT-LOCF Population, including or excluding outlier participant	• The ITT-LOCF Population used the LOCF method to replace missing data. • The LOCF method replaced missing data at Weeks 26, 38, and 52 with the last available endpoint value. • A missing value at Week 52 was replaced with the last available value from the participant in the study, including the value from early termination or end of study visits, if available. If not available, the last available value from prior Post-Baseline Visits (Week 38, Week 26, or Week 12, whichever is available) was used to replace the missing value at Week 52. • Efficacy analyses presented on the ITT Population in this submission exclude the outlier participant unless otherwise stated.
Safety Population	• The Safety Population was defined as all participants who received at least one dose of study drug (cipaglucosidase alfa in combination with miglustat or alglucosidase alfa in combination with placebo). • This population was used in the assessment and reporting of safety data. Participants were analysed according to the actual treatment received. • The Safety Population included the outlier participant

Abbreviations: ITT: intention-to-treat; ITT-LOCF: intention-to-treat-last observation carried forward; ITT-OBS: intention-to-treat-observed; MMRM: mixed effect model for repeated measures.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

B.2.4.2 Statistical analysis in ATB200-02

Statistical assessment of efficacy in ATB200-02

No inferential statistics were utilised in this study. In general, continuous variables were summarised using descriptive statistics, including the number of participants (n), mean, SD, median, the first quartile, third quartile, minimum, and maximum. Unless otherwise stated, these summaries were provided for the raw values, absolute change from Baseline, and the percent change from Baseline values. Where appropriate, a 95% CI for the mean change from Baseline (and/or the median of

change from Baseline) was provided for summary purposes. Categorical variables were summarised using frequencies (counts) and percentages. All efficacy analyses were conducted on the Efficacy population using summary statistics.

Planned sample size

No formal sample size calculation was performed. A sample size between 18 to 34 participants was considered adequate for the purpose of this study.

Analysis populations

Table 14: Analysis populations used in the analysis of outcomes in ATB200-02

Analysis set	Definition
Efficacy Population	• The Efficacy population consisted of all enrolled participants who took at least one dose of cipaglucosidase alfa 20 mg/kg in combination with miglustat 260 mg in Stage 3 and had both a baseline and at least one post-baseline assessment for any efficacy endpoint. • For Cohort 1 participants, this included those who entered Stage 2 Period 5 and received at least 1 dose of cipaglucosidase alfa 20 mg/kg in combination with miglustat 260 mg. • All efficacy analyses were based on this population, unless otherwise specified.
Safety Population	• The Safety population consisted of all enrolled participants who were exposed to at least 1 dose of cipaglucosidase alfa 20 mg/kg in combination with miglustat 260 mg. • This includes all Cohort 1 participants who entered Stage 2 Period 5 and received at least 1 dose of cipaglucosidase alfa 20 mg/kg in combination with miglustat 260 mg, as well as all the participants who were later enrolled into Cohorts 2, 3, and 4 in Stage 3. • All safety analyses were conducted on this population, unless otherwise specified.

Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[55]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Full details of the SLR performed to assess clinical effectiveness evidence for interventions in adult participants with Pompe disease, including methods, results, and quality assessments, can be found in Appendix D.

Quality assessment of PROPEL was performed using the University of York's Centre for Reviews and Dissemination (CRD) checklist for RCTs (as per recommendations from NICE).[68] Randomisation and blinding were adequate, and there were no unexpected imbalances between treatment groups and analysis of the ITT population. Overall, PROPEL is considered to be of high quality with low risk of bias (Table 15).

Quality assessment of ATB200-02 was performed using the Critical Appraisal Skills Programme (CASP) checklist (also per recommendations from NICE). Exposures and outcomes were accurately measured to minimise bias, authors identified and took confounding factors into account and precise reports were reported. Overall, ATB200-02 is also considered to be high quality with a low risk of bias (Table 16).

Table 15: Critical appraisal of the PROPEL trial

	PROPEL
Was randomisation carried out appropriately?	
Yes/no/unclear	Yes
Justification	Eligible participants were randomly assigned in a 2:1 ratio to receive cipaglucosidase alfa in combination with miglustat or alglucosidase alfa in combination with placebo. Randomisation was stratified by ERT status (ERT-experienced and ERT-naïve) and baseline 6MWD (75 to < 150 m, 150 to < 400 m, or ≥ 400 m).
Was the concealment of treatment allocation adequate?	
Yes/no/unclear	Yes
Justification	An on-site computer-based randomisation system that was not readable until the time of allocation was used for concealment of treatment allocation. Patients, the study sponsor, investigators, site personnel, and contracted research organisations involved in monitoring, data management, data analysis or other aspects of the study were masked to treatment assignment.
Were the groups similar at outset of the study in terms of prognostic factors?	
Yes/no/unclear	Yes
Justification	The characteristics of the participants were well-balanced in both groups (see Section B.2.3.3 for further details).
Were the care providers, participants and outcome assessors blind to treatment allocation?	
Yes/no/unclear	Yes
Justification	This was a double-blind study. Participants, the study sponsor, investigators, site personnel, and contracted research organisations involved in monitoring, data management, data analysis, or other aspects of the study were masked to treatment assignment.
Were there any unexpected imbalances in dropouts between groups?	
Yes/no/unclear	No
Justification	Numbers of withdrawals have been reported in Section B.2.3.5. Dropouts between the treatment groups were not dissimilar.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	
Yes/no/unclear	No
Justification	There was no evidence to suggest the authors measured more outcomes than they reported.

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	
Yes/no/unclear	Yes
Justification	ITT Population results are reported (exclusion of the outlier participant is discussed in Section B.2.4.1). Methods to account for missing data are also summarised in Section B.2.4.1.

Abbreviations: 6MWD: six-minute walk distance; ERT: enzyme replacement therapy; ITT: intention to treat.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

Table 16: Critical appraisal of the ATB200-02 trial

	ATB200-02
Was the cohort recruited in an acceptable way?	
Yes/no/unclear	Yes
Justification	During the recruitment process, IEC and IRB approvals were obtained, signed informed consent was obtained and the study was performed in accordance with the declaration of Helsinki and Good Clinical Practice.
Was the exposure accurately measured to minimise bias?	
Yes/no/unclear	Yes
Justification	Exposure to cipaglucosidase alfa in combination with miglustat was measured for each cohort of the study and reported to minimise bias.
Was the outcome accurately measured to minimise bias?	
Yes/no/unclear	Yes
Justification	The outcomes measured in this analysis were done so according to standardised procedures to minimise bias.
Have the authors identified all important confounding factors?	
Yes/no/unclear	Yes
Justification	The CSR noted that previous ERT experience and ambulatory status would be confounding factors.
Have the authors taken account of the confounding factors in the design and/or analysis?	
Yes/no/unclear	Yes
Justification	Subgroup analyses were conducted based on ERT experience and ambulatory status to account for the possibility of confounding.
Was the follow-up of participants complete?	
Yes/no/unclear	No
Justification	Follow-up is ongoing until participant withdrawal, regulatory approval, or marketing authorisation and/or commercialisation in the participating participant's country.
How precise (for example, in terms of CI and p values) are the results?	
Yes/no/unclear	Yes, the results are considered to be precise
Justification	The results are presented with a 95% CI.

Abbreviations: CI: confidence interval; CSR: Clinical Study Protocol, ERT: enzyme replacement therapy.
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[55]

B.2.6 Clinical effectiveness results of the relevant trials

- Results from PROPEL demonstrate the improved efficacy of cipaglucosidase alfa in combination with miglustat over alglucosidase alfa across motor function, respiratory function and other endpoints relevant to LOPD.[5]
- In the total population, 6MWD (the primary efficacy endpoint) showed greater improvement with cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa but did not demonstrate statistical superiority.[5]
- Improvement in FVC % predicted (first key secondary endpoint) with cipaglucosidase alfa in combination with miglustat was clinically and nominally significantly greater than with alglucosidase alfa.[5]
- The treatment effects observed in the primary and first key secondary analyses were supported by other secondary endpoints, as nearly all assessed outcomes were either numerically or nominally statistically significant in favour of cipaglucosidase alfa in combination with miglustat over alglucosidase alfa.[5]
- Results from the 48-month data cut-off of ATB200-02 support the results from PROPEL and demonstrate the durability of efficacy benefit with cipaglucosidase alfa in combination with miglustat.[55]

Efficacy results presented here include motor function, respiratory function, muscle strength and HRQoL endpoints from:

- PROPEL, the pivotal Phase III trial investigating the clinical efficacy and safety of cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa in combination with placebo in participants with LOPD over 52 weeks;
- The 48-month data-cut of ATB200-02, the Phase I/II open-label, fixed-sequence, ascending-dose study of cipaglucosidase alfa in combination with miglustat treatment, derives from ATB200-02.

B.2.6.1 Change in motor and respiratory function

PROPEL primary efficacy endpoint: Change in 6MWD from Baseline to Week 52

The 6MWT was used to assess ambulatory function involving the skeletal muscle, pulmonary and cardiac systems, and motor function. A numerically higher improvement from Baseline to Week 52 in 6MWD (the distance measured in the 6MWT) was observed with cipaglucosidase alfa in combination with miglustat [redacted] than alglucosidase alfa [redacted] in the total population. The MMRM analysis using restricted maximum likelihood found the LS mean treatment difference was [redacted] (95% CI: [redacted]), with a 2-sided p-value of 0.097, and therefore not statistically superior (Table 17).[5]

Because the 6MWD data were not normally distributed (Shapiro-Wilk test p<0.01), a prespecified non-parametric ANCOVA analysis was also employed to compare the two treatment groups (p=0.071).[5]

The numerical improvement from Baseline in 6MWD with cipaglucosidase alfa in combination with miglustat treatment was observed from the first assessment at Week 12, and continued to Week 52, indicating a rapid and sustained treatment effect (Figure 3). 6MWD did not plateau up to 52 weeks.

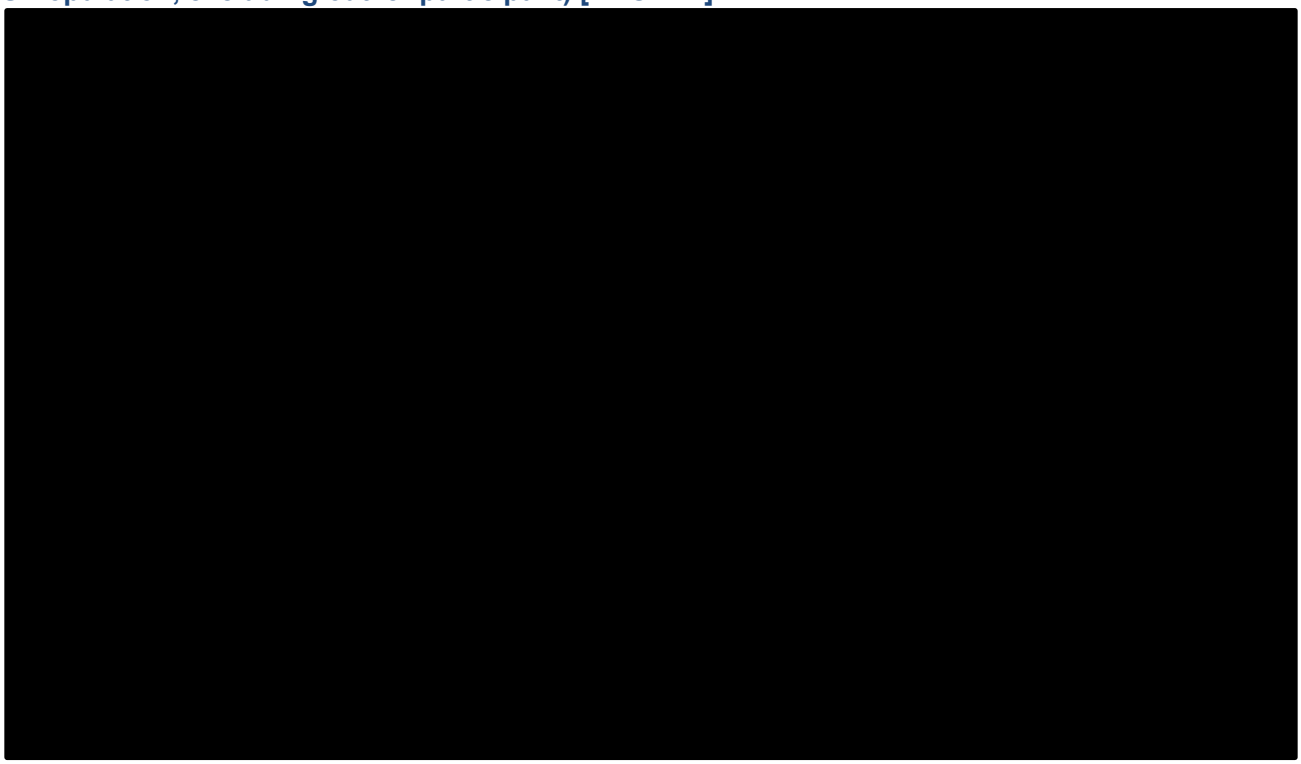
As the primary endpoint did not meet statistical significance, subsequent analyses of key secondary endpoints were interpreted as nominal statistical assessments of superiority.

Table 17: Summary of change in 6MWD (m) by visit from Baseline to Week 52 (ITT-LOCF Population) and MMRM Analysis (ITT-OBS Population, excluding outlier participant) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 37)
Baseline,[a] mean (SD)	357.93 (111.843)	350.95 (121.322)
Change from Baseline at Week 52 (LOCF), mean (SD)	20.79 (42.773)	7.24 (40.277)
MMRM parameter estimation and comparison at Week 52[b]		
LS mean difference (SE)	[redacted]	
95% CI	[redacted]	
2-sided p-value	[redacted]	
Parameter estimation and comparison from non-parametric ANCOVA[c]		
2-sided p-value	0.071	

[a]Baseline was the average of the last 2 values obtained on or prior to the first dose date.
[b]The MMRM approach (using restricted maximum likelihood estimation) was used for analysis. The model included terms for treatment, baseline 6MWD, age, height, weight (all as continuous covariates), ERT status (ERT-naïve vs. ERT-experienced), gender, time, and treatment-by-time interaction. Time was used as a repeated measure, and an unstructured covariance approach was applied.
[c]Non-parametric ANCOVA compared between the treatment groups, adjusting for baseline 6MWD, age, height, weight (all as continuous covariates), ERT status (ERT-naïve vs. ERT-experienced) as strata, and gender.
Abbreviations: 6MWD: six-minute walk distance; ANCOVA: analysis of covariance; CI: confidence interval; ITT: Intention-to-Treat; LOCF: last observation carried forward; LS: least squares; MMRM: mixed-effect model for repeated measures; SE: standard error.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

Figure 8: Line Chart for LS Mean (SE) of Change in 6MWD (m) from Baseline to Week 52 (ITT-OBS Population, excluding outlier participant) [PROPEL]



LS mean and SE were obtained from the MMRM model.

Abbreviations: 6MWD: six-minute walk distance; ITT: Intention-to-Treat; LS: least squares; MMRM: mixed-effect model for repeated measures; SE: standard error.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

ATB200-02 endpoint: Change in 6MWD from Baseline to Month 48

Motor function was evaluated in all ambulatory participants in this study (i.e., Cohorts 1, 3, and 4). With cipaglucosidase alfa in combination with miglustat (i.e., in Stage 2 Period 5, Stage 3, and Stage 4), improvements were observed in 6MWD (Table 18). Initial improvement was observed over the first 1-2 years of treatment and then stabilised through follow-up to Month 48 (see Appendix E.2).

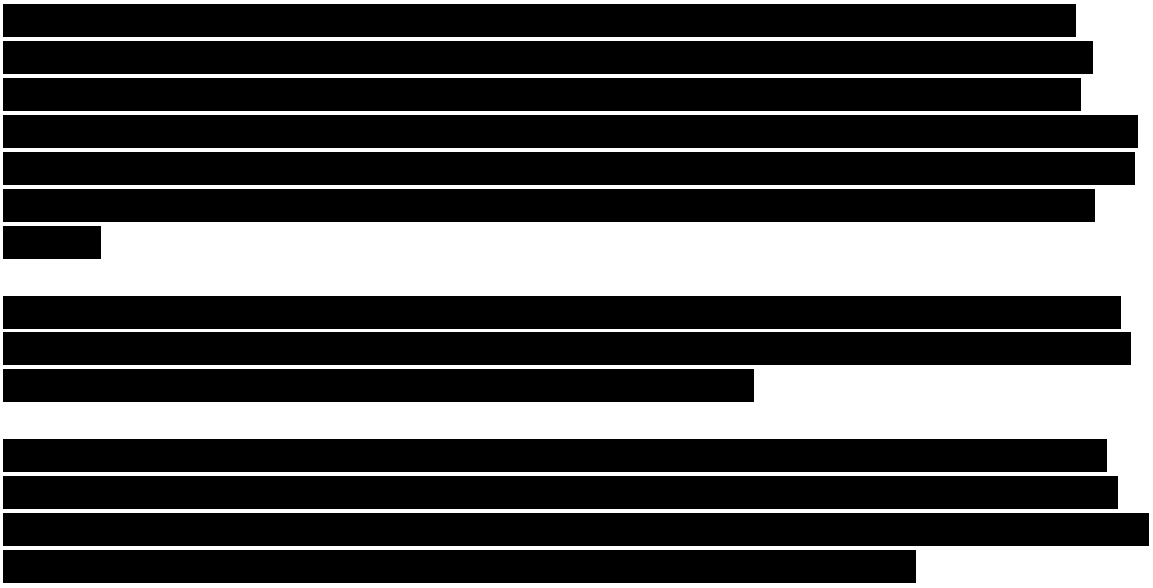
Table 18: Summary of 6MWD (m) from Baseline to Month 48 (Efficacy Population: Ambulatory Cohorts 1 + 3 + 4 [redacted]) [ATB200-02]

	Month 36	Month 48
Baseline, mean (SD)	[redacted]	
n	[redacted]	[redacted]
Change from Baseline to Month 48, mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median (Q1, Q3)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Cohorts 1, 4: ERT-experienced participants; Cohort 3: ERT-naïve participants; Cohorts 1, 3, 4: ambulatory participants. 6MWT was performed by only ambulatory participants.
Abbreviations: 6MWD: six-minute walk distance; CI: confidence interval; ERT: enzyme replacement therapy; max: maximum; min: minimum; Q1: first quartile; Q3: third quartile; SAP: statistical analysis plan; SD: standard deviation
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[55]

Clinical relevance of 6MWT results

Considering the effect of impaired mobility on daily living and HRQoL of people with LOPD (Section B.1.3.2),[41] participants receiving cipaglucosidase alfa in combination with miglustat, their carers and HCPs have expressed the important benefits of increased mobility to wellbeing and independence.[69]



Literature from diseases with neuromuscular symptoms consider increases greater than 6% (range: 3 to 11%) in 6MWD to be clinically relevant.[64, 66, 67] The mean improvement of 21 m in 6MWD with cipaglucosidase alfa in combination with miglustat in PROPEL represented approximately a [redacted] increase from Baseline, which indicates a clinically meaningful group-level improvement. The mean improvement relative to alglucosidase alfa in combination with placebo did not reach this threshold.[5]

Further analysis on PROPEL data demonstrated that improved walking distance in participants with LOPD is correlated and significantly associated with quality-of-life gains and with improvement in many patient-reported measures (Section B.2.6.3). This correlation and association analysis further supports the suggestion that improved walking ability in LOPD may have a meaningful impact on the patient experience, as measured by PRO measures and quality-of-life instruments.[70]

The clinical relevance of this group level analysis in PROPEL is further supported by a *post hoc* composite participant-level responder analysis using a clinically meaningful response threshold of ±6% for 6MWD. A greater proportion of participants in the total population treated with cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa demonstrated clinically meaningful improvement and a smaller proportion demonstrated clinically meaningful worsening in

6MWD, overall favouring cipaglucosidase alfa in combination with miglustat (2-sided p=[redacted] Figure 9).[5]

Figure 9: Proportion of participants with change from Baseline at Week 52 in 6MWD (m) grouped by consolidated ranges (ITT-LOCF Population, excluding outlier participant) [PROPEL]

Cipaglucosidase alfa in combination with miglustat: n=85; Alglucosidase alfa in combination with placebo: n=37

Abbreviations: 6MWD: six-minute walk distance; ITT-LOCF: intention to treat – last observation caried forward.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report)[5]

PROPEL key secondary efficacy endpoint: Change in sitting FVC % predicted from Baseline to Week 52

Due to the impact of Pompe disease on respiratory function, sitting FVC % predicted was the first key secondary endpoint (ordered by importance). This endpoint was normally distributed and analysed by prespecified ANCOVA.

A clinically meaningful and nominally significant improvement with cipaglucosidase alfa in combination with miglustat over alglucosidase alfa was observed in the total population at Week 52. Using last observation carried forward (LOCF), the mean change with cipaglucosidase alfa in combination with miglustat was -0.93% (SD: 6.231) vs. -3.95% (SD: 4.892) with alglucosidase alfa (Table 19). The LS mean treatment difference was 2.66% (95% CI: 0.37, 4.95), with a nominal 2-sided p-value of 0.023. This difference vs. alglucosidase alfa was sustained through to Week 52 (Figure 10).

Table 19: Summary of change in sitting FVC % predicted by visit from Baseline to Week 52 (ITT Population) and ANCOVA Model (ITT-LOCF Population, excluding outlier participant) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 37)
Baseline[a] mean (SD)	70.74 (19.573)	69.68 (21.475)
Change from Baseline at Week 52, mean (SD)	-0.93 (6.231)	-3.95 (4.892)
Parameter estimation and comparison from ANCOVA[b]		
LS mean difference (SE)	2.66 ([redacted])	
95% CI	(0.37, 4.95)	
2-sided p-value	0.023	

All estimates were obtained from the ANCOVA model including terms for treatment, baseline sitting FVC % predicted, age, height, weight (all as continuous covariates), ERT status (ERT-naïve vs. ERT-experienced), and gender.
[a]Baseline was the average of the last 2 values obtained on or prior to the first dose date.
[b]All estimates were obtained from the ANCOVA model based on the observed data including terms for treatment, baseline sitting FVC % predicted, age, height, weight (all as continuous covariates), ERT status (ERT-naïve vs. ERT-experienced), and gender.
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; FVC: forced vital capacity; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LOCF: last observation carried forward; LS: least squares; SE: standard error
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

Figure 10: Line chart for LS mean (SE) of change from Baseline in sitting FVC % predicted over time (ITT-LOCF Population, excluding outlier participant) [PROPEL]

LS mean and SE were obtained from the analysis of covariance model.
Abbreviations: FVC: forced vital capacity; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LS: least squares; SE: standard error
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

ATB200-02 endpoint: change in FVC % predicted from Baseline to Month 48

Respiratory function was evaluated in all ambulatory participants in this study (i.e., Cohorts 1, 3, and 4). With cipaglucosidase alfa in combination with miglustat, stable respiratory function was generally observed from Baseline through to Month 48 (Table 20; Appendix E.2).

Table 20: Summary of sitting FVC % predicted from Baseline to Month 48 (Efficacy Population: Ambulatory Cohorts 1 + 3 + 4 [redacted]) [ATB200-02]

	Month 36	Month 48
Baseline, mean (SD)	[redacted]	
n	[redacted]	[redacted]
Change from Baseline to Month 48, mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median (Q1, Q3)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Cohorts 1, 4: ERT-experienced participants; Cohort 3: ERT-naïve participants; Cohorts 1, 3, 4: ambulatory participants.
Abbreviations: CI: confidence interval; ERT: enzyme replacement therapy; FVC: forced vital capacity Max: maximum; Min: minimum; Q1: first quartile; Q3: third quartile; SAP: statistical analysis plan; SD: standard deviation
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[55]

Clinical relevance of FVC % predicted results

With respiratory failure being the most common cause of death in Pompe disease and the need for ventilator support causing a significant disease burden (Section B.1.3.2), the results presented above are of crucial importance. Stability of or improvement of respiratory function represent important clinical endpoints for adults with LOPD, as noted by participants treated with cipaglucosidase alfa in combination with miglustat, as well as their carers and HCPs (see ATB200-02 endpoint: Change in 6MWD from Baseline to Month 48 above). Adults living with LOPD also express concerns around their respiratory symptoms and future respiratory decline.[71]

[redacted]

FVC changes greater than 3% (range 2 to 6%) are considered clinically relevant in chronic respiratory diseases.[65, 66] The approximate 3% (2.66 [SE: [redacted]]) improvement in FVC participants treated with cipaglucosidase alfa in combination with miglustat experienced relative to those treated alglucosidase alfa in PROPEL indicates a clinically meaningful group-level improvement relative to standard of care.

Additional *post hoc* participant-level analyses of PROPEL data using the ±3% threshold for FVC showed that a greater proportion of participants treated with cipaglucosidase alfa in combination with miglustat demonstrated clinically meaningful improvement, and a smaller proportion demonstrated clinically meaningful worsening, than participants treated with alglucosidase alfa (p=[redacted]; Figure 11).

Figure 11: Proportion of participants with change from Baseline at Week 52 in sitting FVC % predicted grouped by consolidated ranges (ITT-LOCF Population, excluding outlier participant) [PROPEL]

Cipaglucosidase alfa in combination with miglustat: n=85; Alglucosidase alfa in combination with placebo: n=37
Abbreviations: ITT-LOCF: intention to treat – last observation caried forward; FVC: forced vital capacity.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report)[5]

Consistency across 6MWD and FVC % predicted

Results from PROPEL for both 6MWT and sitting FVC % predicted showed improvement with cipaglucosidase alfa in combination with miglustat over alglucosidase alfa, with this improvement being clinically and nominally significant for FVC % predicted.[5]

Results from additional *post hoc* participant-level analyses of data from PROPEL support this conclusion; using thresholds of both ±6% for 6MWD and ±3% for FVC, a greater proportion of participants treated with cipaglucosidase alfa in combination with miglustat demonstrated clinically meaningful improvement, and a smaller proportion demonstrated clinically meaningful worsening, than participants treated with alglucosidase alfa for both 6MWD and FVC (p=[redacted]).[5]

A *post hoc* global test was performed on individual participant response for 6MWT and FVC % predicted (i.e. changes from Baseline to Week 52 using LOCF). This test was conducted by ranking

individual participant responses (i.e. change from Baseline to Week 52 using LOCF) separately for each endpoint from least improvement to greatest improvement, summing the two ranks for each participant, and analysing the summed ranks using the Wilcoxon rank sum test to assess superiority of cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa. This test found superiority of cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa (2-sided p=[redacted]). Results from this *post hoc* test further support the significance and consistency of the treatment effect of cipaglucosidase alfa in combination with miglustat in the total ITT Population.[5]

B.2.6.2 Other efficacy endpoints

PROPEL key secondary efficacy endpoint: Change in the manual muscle test (MMT) lower extremity score from Baseline to Week 52

As described in Section B.1, Pompe disease results in a progressive loss of muscle function due to accumulation of glycogen in muscle cells. In addition, as explained in Section B.2.3.2, people with Pompe disease have expressed the importance of improving muscle strength and its impact on ability to perform daily activities. Therefore, the MMT evaluated muscle strength in the PROPEL trial.

Using an ANCOVA model with LOCF, the mean numerical improvement from Baseline with cipaglucosidase alfa in combination with miglustat was 1.56 (SD: 3.783) vs. 0.88 (SD: 2.579) with alglucosidase alfa in combination with placebo, with a LS mean treatment difference of 0.96 (95% CI: -0.48, 2.40)[5] and a nominal 2-sided p-value of [redacted] (Table 21).[5] This improvement from Baseline was observed from the first assessment at Week 12 and sustained to Week 52 (Figure 12).[5]

Table 21: Summary of change in MMT lower extremity score by visit from Baseline to Week 52 (ITT Population) and ANCOVA model (ITT-LOCF Population, excluding outlier participant) [PROPEL]

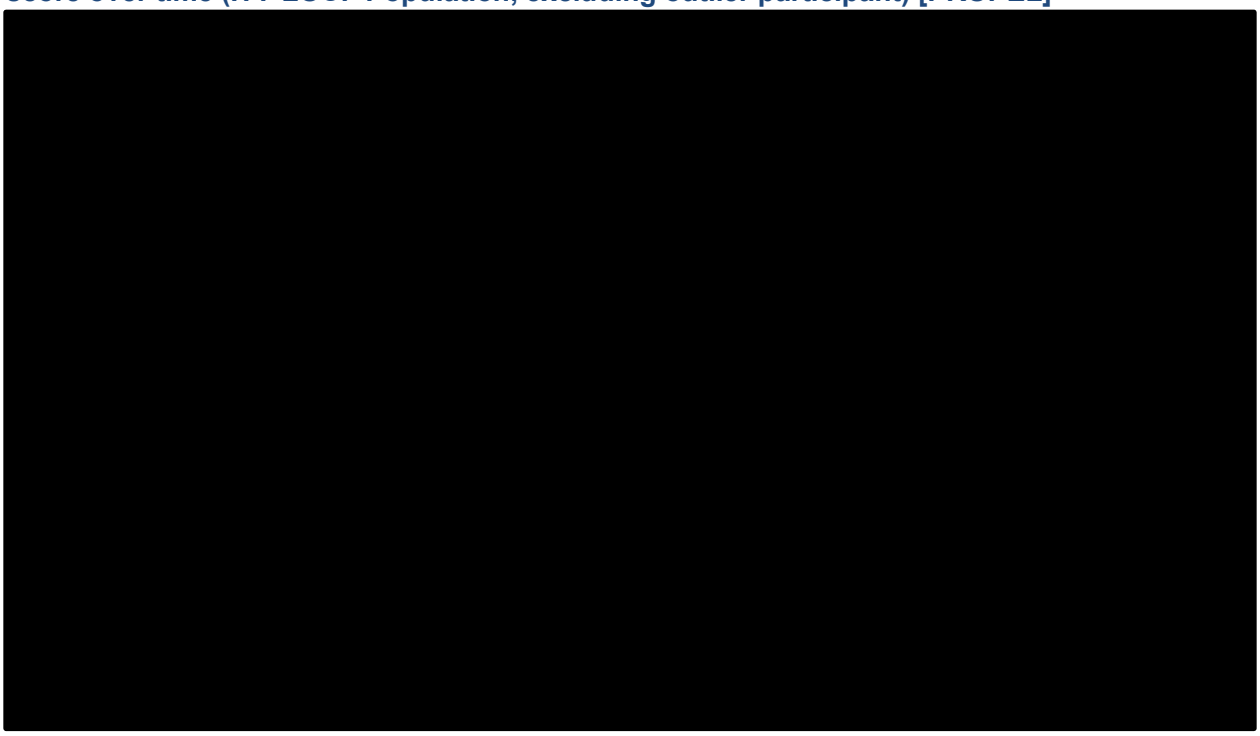
	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 37)
Baseline[a] mean (SD)	27.96 (5.757)	27.65 (6.169)
Change from Baseline at Week 52, mean (SD)	1.56 (3.783)	0.88 (2.579)
Parameter estimation and comparison from ANCOVA[b]		
n	80	[redacted]
LS mean difference (SE)	0.96 ([redacted])	
95% CI	(-0.48, 2.40)	
2-sided p-value	[redacted]	

The total score for the MMT lower extremity strength includes the following 8 body parts: right/left hip flexion, right/left hip abduction, right/left knee flexion, and right/left knee extension. The MMT score ranges from 0 to 40, with lower scores indicating weaker muscle strength.

[a]Baseline was the last non-missing value prior to the administration of the first dose of study drug.

[b]All estimates were obtained from the ANCOVA model including terms for treatment, baseline MMT lower extremity score, age, height, weight (all as continuous covariates), ERT status (ERT-naïve vs. ERT-experienced), and gender.
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; ITT: Intention-to-Treat; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LOCF: last observation carried forward; LS: least squares; MMT: manual muscle testing; SD: standard deviation.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report)[5]

Figure 12: Line chart for LS mean (SE) of actual change from Baseline in MMT lower extremity score over time (ITT-LOCF Population, excluding outlier participant) [PROPEL]



The total score for the MMT lower extremity includes the following 8 body parts: right/left hip flexion, right/left hip abduction, right/left knee flexion, and right/left knee extension. The total score ranges from 0 to 40, with lower scores indicating weaker muscle strength.
LS mean and SE were obtained from the analysis of covariance model.
Abbreviations: ITT-LOCF; Intention-to-Treat-Last Observation Carried Forward; LS; least squares; MMT; manual muscle testing; SE; standard error
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

ATB200-02 endpoint: Change in MMT from Baseline to Month 48

MMT was evaluated in all ambulatory participants in this study (i.e., Cohorts 1, 3, and 4). Cipaglucosidase alfa in combination with miglustat resulted in improvements and generally stable MMT scores from Baseline to Month 48 (Table 22; Appendix E.2).

Table 22: Summary of sitting MMT from Baseline to Month 48 (Efficacy Population: Ambulatory Cohorts 1 + 3 + 4 [redacted]) [ATB200-02]

	Month 36	Month 48
Baseline, mean (SD)	[redacted]	
n	[redacted]	[redacted]

Change from Baseline at Month 48, mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median (Q1, Q3)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Cohorts 1, 4: ERT-experienced participants; Cohort 3: ERT-naïve participants; Cohorts 1, 3, 4: ambulatory participants.
Abbreviations: CI: confidence interval; ERT: enzyme replacement therapy; FVC: forced vital capacity; max: maximum; min: minimum; Q1: first quartile; Q3: third quartile; SAP: statistical analysis plan; SD: standard deviation
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report)[55]

PROPEL key secondary efficacy endpoint: Change in the GSGC total score from Baseline to Week 52

The GSGC test evaluates four key motor performances and has been validated in participants with LOPD. A lower GSGC score indicates an improvement in motor function.[72]

Results for GSGC total score support the improvement in motor function using the 6MWT in PROPEL. Treatment with cipaglucosidase alfa in combination with miglustat was associated with a nominally significant improvement in GSGC vs. alglucosidase alfa in combination with placebo at Week 52 in the total ITT Population. Using LOCF values, a mean change from Baseline of -0.53 (SD: 2.542) was observed with cipaglucosidase alfa in combination with miglustat, compared with 0.77 (SD: 1.813) for the alglucosidase alfa in combination with placebo group (Table 23). For the ANCOVA model, the LS mean treatment difference was -1.414 (SE: [redacted]),[5] with a nominal 2-sided p-value of [redacted].[5] Thus, treatment with cipaglucosidase alfa in combination with miglustat represents a significant improvement vs. alglucosidase alfa in combination with placebo in participants' ability to perform key motor functions, including walking 10 m, climbing stairs, rising from the floor and arising from a sitting position. This improvement in motor function was observed from the first assessment at Week 12 and sustained to Week 52.[5]

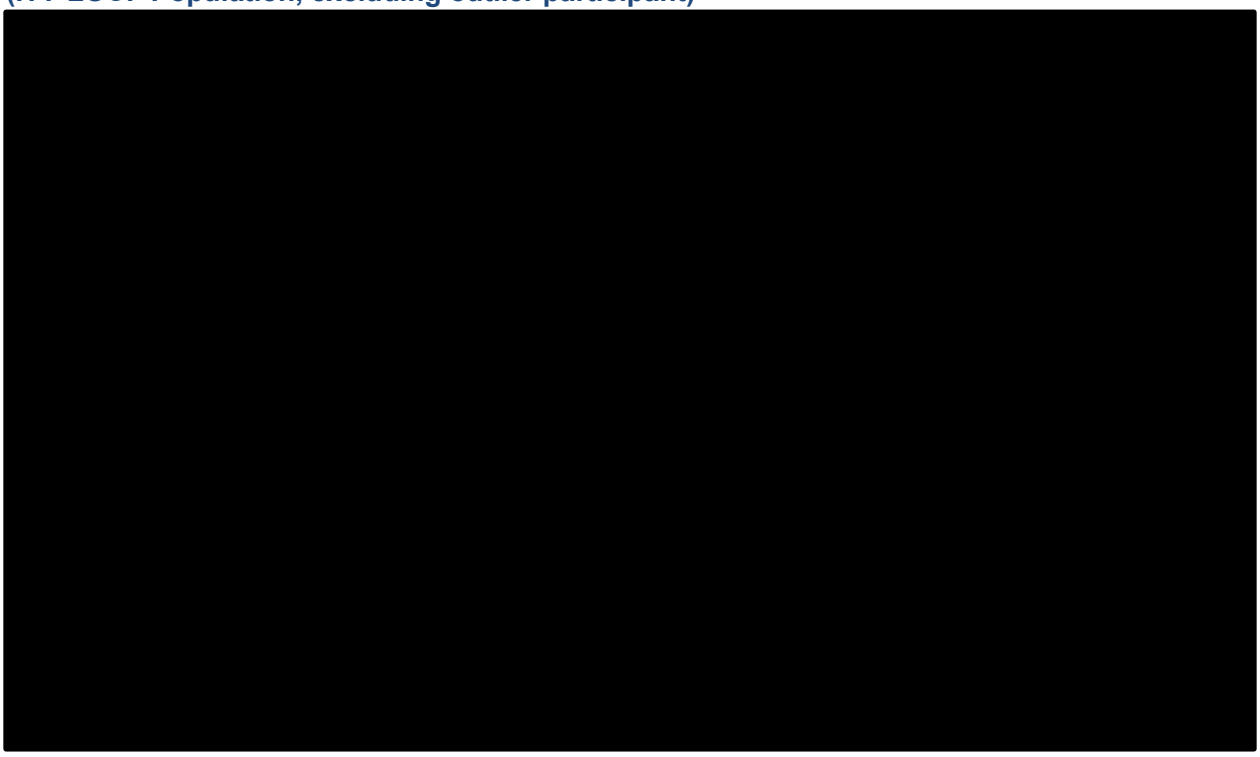
Table 23: Summary of change in GSGC total score by visit from Baseline to Week 52 (ITT Population) and ANCOVA model (ITT-LOCF Population, excluding outlier participant) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 37)
Baseline[a] mean (SD)	14.51 (5.171)	14.50 (4.718)
Change from Baseline at Week 52, mean (SD)	-0.53 (2.542)	0.77 (1.813)
Parameter estimation and comparison from ANCOVA[b]		
n	72	30
LS mean difference (SE)	-1.414 ([redacted])	
95% CI	(-2.463, -0.364)	

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 37)
2-sided p-value	[redacted]	

Gait score is based on the 10-metre walk test; stairs score was based on the participant climbing stairs; Gowers' manoeuvre score was based on the participant lying down on the floor, then rising from the floor to get to a standing position; chair score was based on the participant arising from a sitting position in a chair to a standing position. GSGC total score was the sum of 4 tests and ranges from a minimum of 4 points (normal performance) to a maximum of 27 points (worst score).
[a]Baseline was the last non-missing value prior to the administration of the first dose of study drug.
[b]All estimates were obtained from the ANCOVA model including terms for treatment, baseline GSGC total score, age, height, weight (all as continuous covariates), ERT status (ERT-naïve vs. ERT-experienced), and gender.
Abbreviations: ANCOVA; analysis of covariance; CI; confidence interval; GSGC; Gait, Stairs, Gowers' manoeuvre, and Chair; ITT; Intention-to-Treat; LOCF; last observation carried forward; LS; least squares; SD; standard deviation
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report)[5]

Figure 13: Line chart for LS mean (SE) of change from Baseline over time in GSGC total score (ITT-LOCF Population, excluding outlier participant)



Gait score was based on the 10-metre walk test; stairs score is based on the participant climbing stairs; Gowers' manoeuvre score was based on the participant lying down on the floor, then rising from the floor to get to a standing position; chair score was based on the participant arising from a sitting position in a chair to a standing position. GSGC total score was the sum of 4 tests and ranges from a minimum of 4 points (normal performance) to a maximum of 27 points (worst score). LS mean and SE were obtained directly from the ANCOVA model.
Abbreviations: ANCOVA: analysis of covariance; GSGC: Gait, Stairs, Gowers' manoeuvre, and Chair; ITT-LOCF: Intention-to-Treat–last observation carried forward; LS: least squares; SE: standard error
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report)[5]

ATB200-02 efficacy endpoint: Change in GSGC total score from Baseline to Month 48

Participants treated with cipaglucosidase alfa in combination with miglustat also demonstrated improvement in GSGC in the one to two years after initiation, which was maintained above the baseline value up to Month 48 of treatment (see ATB200-02 CSR for further details).[55]

B.2.6.3 Health-related quality of life

PROPEL secondary efficacy endpoint: Change in the PROMIS-Physical Function total score from Baseline to Week 52

PROMIS-physical function measures important aspects of daily function. A numerically greater improvement in PROMIS-Physical function total score from Baseline to Week 52 was observed with cipaglucosidase alfa in combination with miglustat (1.94; SD: 7.498) vs. alglucosidase alfa (0.19; SD: 10.819; Table 24). For the ANCOVA model, the LS mean treatment difference (SE) was 1.87 (SE: [redacted]), with a nominal [redacted] Numerical benefits in this participant-reported physical function outcome were sustained to Week 52 (Figure 14).[5]

Table 24: Summary of change in PROMIS-Physical Function Short Form 20a by visit from Baseline to Week 52 (ITT Population) and ANCOVA model (ITT-LOCF Population, excluding outlier participant) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 37)
Baseline[α] mean (SD)	66.86 (12.261)	67.97 (13.090)
Change from Baseline at Week 52, mean (SD)	1.94 (7.498)	0.19 (10.819)
ANCOVA parameter estimation and comparison at Week 52[b]		
n	84	37
LS mean difference (SE)	1.87 ([redacted])	
95% CI	-1.51, 5.25	
2-sided p-value	[redacted]	

The total score ranged from 20 to 100, with higher score indicating less impact on physical function.
[a]Baseline was the last non-missing value prior to the administration of the first dose of study drug.
[b]All estimates were obtained from the ANCOVA model including terms for treatment, baseline PROMIS-Physical Function total score, age, height, weight (all as continuous covariates), ERT status (ERT-naïve vs. ERT-experienced), and gender.
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; ITT: Intention-to-Treat; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LS: least squares; PROMIS: Patient-reported Outcomes Measurement Information System; SD: standard deviation
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

Figure 14: Line chart for LS mean (SE) of change from Baseline in PROMIS-Physical Function over time (ITT-LOCF Population, excluding outlier participant) [PROPEL]

LS mean and SE were obtained from the analysis of covariance model.
Abbreviations: ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LS: least squares; PROMIS: Patient-reported Outcomes Measurement Information System; SE: standard error.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

PROPEL key secondary efficacy endpoint: Change in the PROMIS-Fatigue total score from Baseline to Week 52

The PROMIS-Fatigue scores showed similar mean improvement from Baseline to Week 52 between participants treated with cipaglucosidase alfa in combination with miglustat (-2.02; SD: 5.763) and alglucosidase alfa (-1.67; SD: 6.623; Table 25). For the ANCOVA model, the LS mean treatment difference (95% CI) was 0.04 ([redacted]), with a nominal 2-sided p-value of [redacted].[5]

Table 25: Summary of change in PROMIS-Fatigue short form 8a by visit from Baseline to Week 52 (ITT Population) and ANCOVA model total score (ITT-LOCF Population, excluding outlier participant) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 37)
Baseline[a] mean (SD)	22.26 (8.304)	21.08 (6.098)
Change from Baseline at Week 52, mean (SD)	-2.02 (5.763)	-1.67 (6.623)

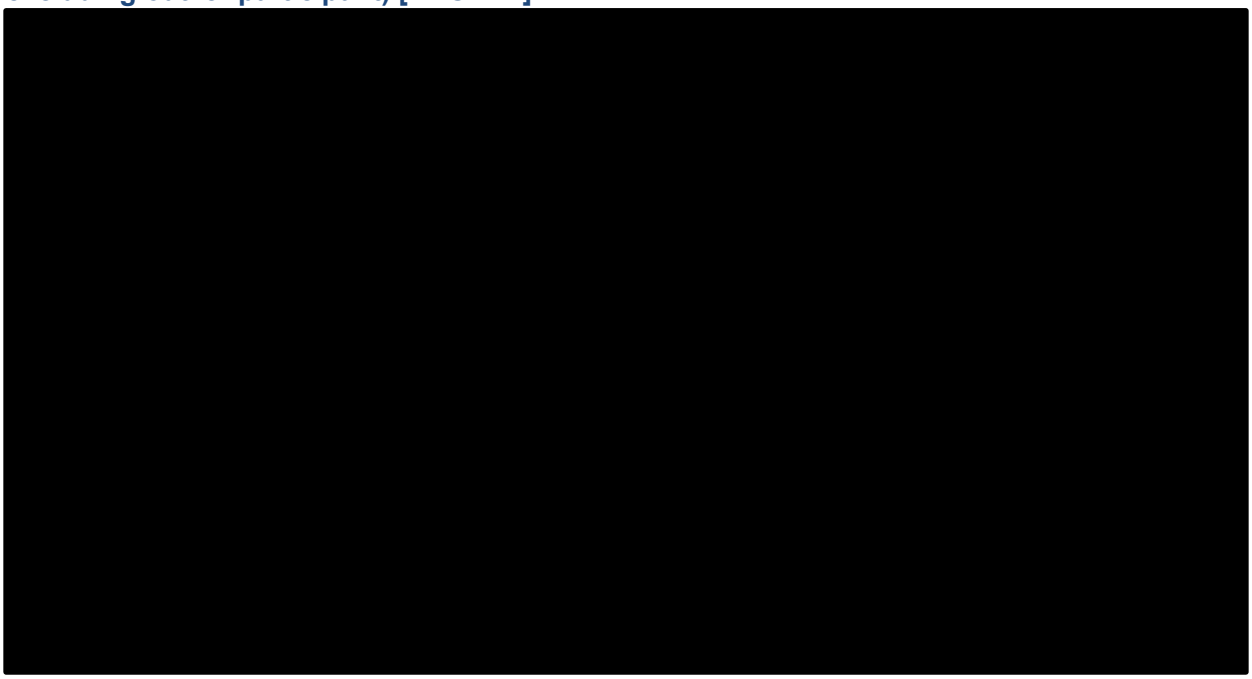
Parameter estimation and comparison from ANCOVA[b]		
n	85	37
LS mean difference (SE)	0.04 ([redacted])	
95% CI	(-2.12, 2.20)	
2-sided p-value	[redacted]	

If post-Baseline scores were partially missing but ≥ 50% of items were available, the total score was calculated as the average of non-missing items multiplied by the total number of items expected.
The total score ranged from 8 to 40, with lower score indicating less impact by fatigue, and it was calculated by summing scores (1 to 5) across all 8 items.
[a]Baseline was the last non-missing value prior to the administration of the first dose of study drug
[b]All estimates were obtained from the ANCOVA model including terms for treatment, baseline PROMIS-Fatigue total score, age, height, weight (all as continuous covariates), ERT status (ERT-naïve vs. ERT-experienced), and gender.
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; ITT: Intention-to-Treat; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LOCF: last observation carried forward; LS: least squares; PROMIS: Patient-reported Outcomes Measurement Information System; SD: standard deviation; SE: standard error
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

PROPEL secondary efficacy endpoint: Subject's Global Impression of Change (SGIC) at Week 52

SGIC gauges the patient-reported impact of treatment on a comprehensive set of eight endpoints: overall physical well-being, effort of breathing, muscle strength, muscle function, ability to move around, activities of daily living, energy level, and muscular pain. In all eight domains, a greater percentage of participants treated with cipaglucosidase alfa in combination with miglustat reported improvement and a lower percentage reported worsening, compared with participants treated with alglucosidase alfa. Results are shown in Figure 15 for the SGIC overall physical wellbeing-domain, which is representative of the benefits reported across these measures.[5]

Figure 15: SGIC overall physical wellbeing at Week 52 compared to Baseline (ITT Population, excluding outlier participant) [PROPEL]



Abbreviations: SGIC: Subject Global Impression of Change.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report)[5]

ATB200-02 secondary efficacy endpoints: Change in SGIC and Physician's Global Impression of Change (PGIC) at Month 48

Improvements in overall physical wellbeing the majority of participants in all cohorts were observed as early as 6 months after treatment initiation. At Month 48, the majority of participants in Cohorts 1 and 4 and all participants in Cohort 2 either had no change or reported improvement from Baseline in overall physical wellbeing. All participants in Cohort 3 reported improvement from Baseline at Month 48. PGIC results indicated improvement or stability in physician's impression of change for all cohorts and supported the results observed for other efficacy parameters (see ATB200-02 CSR for further details).[55]

Post hoc PROPEL responder analyses

In a *post hoc* responder analysis of PRO data from PROPEL, participants treated with cipaglucosidase alfa in combination with miglustat showed greater improvements in HRQoL in the majority of the PROs assessed in the trial, compared with participants treated with alglucosidase alfa.[73] The results of this analysis further demonstrate the HRQoL benefits of cipaglucosidase alfa in combination with miglustat.

B.2.6.4 Biomarkers and immunogenicity

Biomarker assessments in PROPEL

Creatine kinase (CK) is an enzyme that leaks into the bloodstream from injured muscle, thus marking muscle damage, and is often elevated in people with LOPD, whilst Hex4 is an indirect measure of glycogen clearance in Pompe disease.[74, 75]

Reductions in CK and Hex4 were significantly greater with cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa, with a nominal p<0.001 for both biomarkers (Table 26).[5] The improvements vs. alglucosidase alfa were observed from as early as Week 2 (CK; Figure 16) and Week 4 (Hex4; Figure 17), with biomarker levels continuing to decrease throughout 52 weeks of treatment,[5] biomarker results support the validity of efficacy results in the total population.[4]

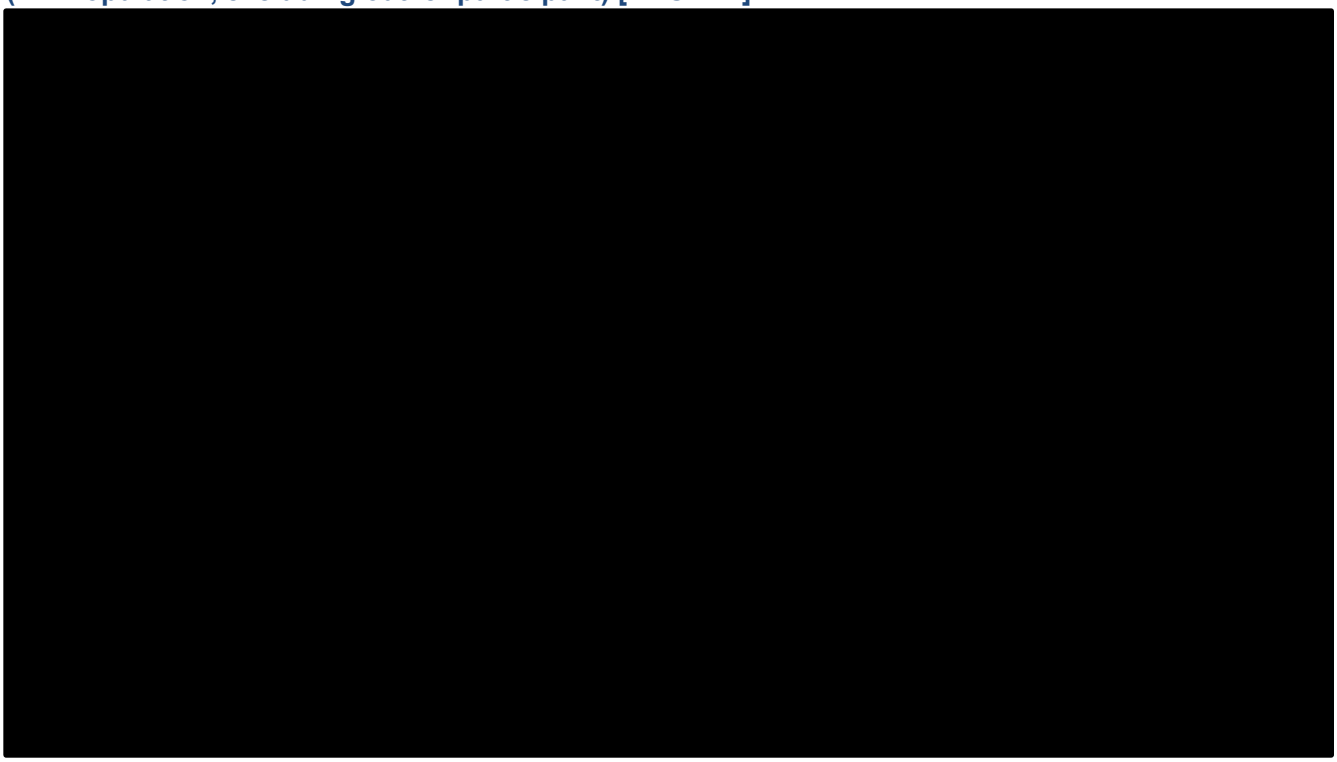
Table 26: Summary of absolute values for CK and Hex4 at Baseline and Week 52 (ITT Population, excluding outlier participant) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 37)
CK (U/L)		
Baseline[a] mean (SD)	447.0 (399.52)	527.8 (426.57)
Change from Baseline at Week 52, mean (SD)	-130.5 (231.18)	60.2 (159.49)
Parameter estimation and comparison from ANCOVA[b]		
n	85	37
LS mean difference (95% CI)	-176.0 (-244.4, -107.6)	
2-sided p-value	<0.001	
Hex4 (mmol/mol creatinine)		
Baseline[a] mean (SD)	4.61 (3.374)	6.92 (6.936)
Change from Baseline at Week 52, mean (SD)	-1.88 (2.380)	1.22 (4.432)
Parameter estimation and comparison from ANCOVA		
n	84	37
LS mean difference (95% CI)	-2.49 (-3.66, -1.32)	

2-sided p-value	<0.001

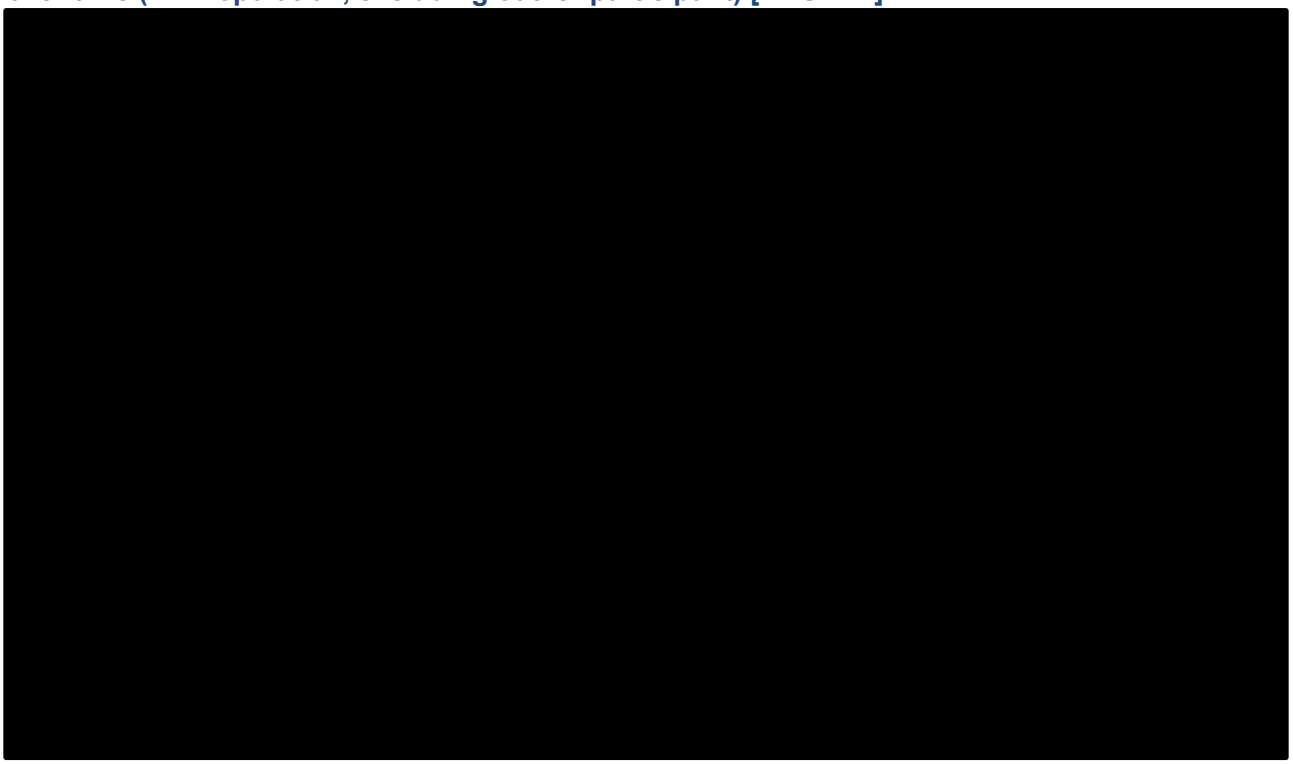
[a]Baseline was defined as the last available result on or prior to the first dose date.
Abbreviations: CHG: change from Baseline; CK: creatine kinase; Hex4: hexose tetrasaccharide; ITT: Intention-to-Treat; LOCF: last observation carried forward; max: maximum; min: minimum; Q1: first quartile; Q3: third quartile; SD: standard deviation; U: units.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report)[5]

Figure 16: Line chart for mean (± SE) of change from Baseline in CK (U/L) over time (ITT Population, excluding outlier participant) [PROPEL]



Baseline was defined as the last available result on or prior to the first dose date.
Abbreviations: CK: creatine kinase; ITT: Intention-to-Treat; SE: standard error
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report)[5]

Figure 17: Line chart for mean (± SE) of change from Baseline in Hex4 (mmol/mol creatinine) over time (ITT Population, excluding outlier participant) [PROPEL]



Baseline was defined as the last available result on or prior to the first dose date.

Abbreviations: Hex4: hexose tetrasaccharide; ITT: Intention-to-Treat; SE: standard error
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

Biomarker assessments in ATB200-02

Hex4 levels decreased from Baseline starting on the administration of the first dose of study drug in Stage 1 for participants given cipaglucosidase alfa 20 mg/kg and generally remained lower than Baseline in Stage 3 and Stage 4 for all cohorts. Similar to urine Hex4 levels, overall serum CK values decreased from Baseline in Stage 1 particularly over the first 3 months, and then remained generally stable at that decreased level in Stage 3 and Stage 4 through Month 48 with expected visit-to-visit variability. Please see the ATB200-02 CSR for further details.

Immunogenicity

Across PROPEL and ATB200-02, immunogenicity markers did not have a notable impact on the pharmacokinetic disposition, AEs (including IARs), biomarkers (Hex4 and CK) or efficacy (6MWT and FVC) associated with cipaglucosidase alfa in combination with miglustat.[5, 55]

B.2.7 Subgroup analysis

In line [redacted], the total population considered in the pre-invitation scope, and the NICE appraisal for avalglucosidase alfa,

the submission focuses on the total population of adults with LOPD without considering subgroups defined by prior treatment status (Section B.1.1).

During an advisory board, UK consultants from specialist Pompe treatment centres with years of experience treating people with Pompe disease, noted that there is no reason to expect different efficacy results between ERT-experienced and ERT-naïve adults with LOPD, as there is no biological difference between the people in these subgroups.[4] Furthermore, participants were not selected for PROPEL based on any known response to previous therapies. Therefore, Amicus considers that prior ERT status should not be a factor in accessing treatment with cipaglucosidase alfa in combination with miglustat in the interests of fair and equitable access.

Data from the ERT-experienced and ERT-naïve subgroups in the PROPEL and ATB200-02 clinical trial are presented in Appendix E.2 for completeness, in line with the study design and decision problem. In the ERT-experienced population, clinically and nominally significant improvements in 6MWD and FVC % predicted, in addition to stabilised respiratory function, were observed with treatment with cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa. In the ERT-naïve population, results did not clearly favour either treatment, with most endpoints showing improvement in both treatment groups. These data are impacted by the small participant numbers, particularly in the ERT-naïve arm in PROPEL (ERT-naïve: n=28; ERT-experienced: n=95), as is expected in a rare disease with low incidence. As noted by clinicians, these small participant numbers preclude drawing meaningful conclusions from the subgroup analyses; therefore, the overall cohort is considered to be the most reliable and meaningful source of data in PROPEL.[4]

B.2.8 Meta-analysis

As PROPEL represents the only study evaluating the safety and efficacy of cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa for the treatment of adults with LOPD (Section B.2.2), no meta-analysis was performed.

B.2.9 Indirect and mixed treatment comparisons

Rationale for an indirect treatment comparison (ITC)

- Although avalglucosidase alfa is not yet commercially available, it is included as a comparator in the NICE final scope.[2, 3] Therefore, for completeness, the economic analysis contains a scenario analysis with avalglucosidase alfa as a comparator (Section B.3.10.3).
- In the absence of direct, head-to-head evidence between cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa, an ITC has been conducted to establish the comparative effectiveness of the two treatments.

Methodology of the ITC

- An SLR and a feasibility assessment were performed to determined that seven trials (including a single-arm trial) of cipaglucosidase alfa in combination with miglustat, alglucosidase alfa and avalglucosidase alfa were suitable for inclusion in multi-level network

meta-regression ML-NMRs of change from Baseline in 6MWD and FVC % predicted in adults with LOPD, in line with the decision problem.

- The ML-NMR method provided relative effect estimates of the treatments in a population consisting of both ERT-naïve and ERT-experienced people whilst adjusting for baseline characteristics such as age, gender, ethnicity, previous ERT duration, baseline 6MWD and baseline FVC % predicted using individual patient data from the PROPEL trial, in order to minimise their modification of relative treatment effects.
- The ML-NMR was conducted in line with the framework described by Phillippo, 2020[76] and NICE Decision Support Unit (DSU) Technical Support Document (TSD) 3,[77] using a Bayesian framework applying both fixed effects (FE) and random effects (RE) models.

Results of the ITC

- [redacted]

Avalglucosidase alfa was recommended by NICE for the treatment of Pompe disease in August 2022 (TA821) and is listed as a comparator in the NICE final scope. However, there are no head-to-head, direct data comparing cipaglucosidase alfa in combination with miglustat with avalglucosidase alfa. Although the treatment is not yet commercially available, for completeness and in line with the NICE final scope, the economic analysis contains a scenario analysis with avalglucosidase alfa as a comparator (Section B.1.1). In order to provide indirect evidence on the relative efficacy of cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa in Pompe disease for this scenario, an ITC has been conducted. The ITC took the form of a ML-NMR in line with the NICE NICE DSU recommendations.[78] An overview of the methodology of the ML-NMR is presented in this section. Additional details are presented in Appendix D.

B.2.9.1 Identification of relevant studies

An SLR was conducted in line with the decision problem to identify studies for inclusion in the ITC, reporting on interventional studies of cipaglucosidase alfa in combination with miglustat, alglucosidase alfa and/or avalglucosidase alfa in adults with LOPD. Full details of this SLR, including the PRISMA diagram, are provided in Appendix D. This SLR was broadly aligned with the SLR described in Section B.2.1, with the exception of the following points:

- Study type was restricted to interventional studies only in the SLR conducted for the ITC to ensure high-quality evidence was used to reduce uncertainty;
- Any additional eligible abstracts that had not been indexed at the time of the original clinical SLR but had since been indexed were included in the SLR conducted for the ITC;
- Abstracts that did not mention efficacy outcomes of interest to the ITC (i.e., 6MWD and FVC % predicted were excluded;
- Abstracts which replicated information provided by other identified articles were not included.

B.2.9.2 Feasibility assessment

All interventional studies (RCTs or single-arm trials) identified in the SLR that reported on 6MWT, FVC and other motor/muscle function outcomes through treatment with cipaglucosidase alfa in combination with miglustat, avalglucosidase, alglucosidase alfa and placebo/supportive care in LOPD were considered for inclusion in the ITC (in line with the decision problem). Eight studies were therefore considered for inclusion in the ITC, a summary of which are presented in Table 27).

The rationale for the choice of ITC method (ML-NMR) is provided below. The feasibility of inclusion of each of the eight studies in ITC of change from baseline in 6MWD and change from baseline in FVC % predicted was assessed by evaluating data availability, heterogeneity and study quality, as detailed below.

Table 27: Summary of studies considered for inclusion in the ITC

Trial name/author	Design	Interventions	Prior ERT status	Countries	Data source	Included in the ITC?
PROPEL (NCT03729362)	RCT	Cipaglucosidase alfa in combination with miglustat Alglucosidase alfa in combination with placebo	ERT-naïve and -experienced	Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Republic of Korea, Netherlands, New Zealand, Poland, Slovenia, Spain, Sweden, Taiwan, United Kingdom, United States	• Byrne 2022[79] • Schoser 2021[53, 80, 81] • Kishnani 2022[82] • Mozaffar 2021[83] • Mozaffar 2022[84] • CCTR 2018[85] • CCTR 2019[86]	Yes
LOTS (NCT00158600)	RCT	Alglucosidase alfa Placebo	ERT-naïve	United States, France, Netherlands	• van der Ploeg 2010[87] • CCTR 2005[88] • CCTR 2009[89]	Yes
LOTS OLE (NCT00158600)	Open-label extension	Alglucosidase alfa	ERT-naïve	See LOTS main study	• van der Ploeg 2012[90] • CCTR 2007[91]	Yes
EMBASSY (NCT01288027)	Exploratory, open-label, multicentre	Alglucosidase alfa	ERT-naïve	United States, Germany, Netherlands, United Kingdom	• Van der Ploeg 2016[92]	No*
NEO-1 (NCT01898364) /-EXT (NCT02032524)	Single arm	Avalglucosidase alfa	ERT-naïve and -experienced	United States, Belgium, Denmark, France, Germany, Netherlands, United Kingdom	• CDER 2021[93] • Dimachkie 2020[94] • Dimachkie 2021[95] • Pena 2019[96] • Schoser 2020[97, 98]	Yes

					Dimachkie 2022[99]	
COMET (NCT02782741)	RCT	Avalglucosidase alfa Alglucosidase alfa	ERT-naïve	United States, Argentina, Australia, Austria, Brazil, Belgium, Canada, Czechia, Denmark, France, Germany, Hungary, Italy, Japan, Republic of Korea, Mexico, Netherlands, Poland, Portugal, Russian Federation, Sain, Switzerland, Taiwan, Turkey, United Kingdom	• Berger 2021[100] • CDER 2021[93] • Diaz-Manera 2021[101] • Kishnani 2021[102] • Kushlaf 2021[103] • Mozaffar 2022[104] • Schoser 2021[105]	Yes
COMET OLE (NCT02782741)	Open-label extension	Avalglucosidase alfa	ERT-experienced	See COMET main study	• CDER 2021[93] • Kishnani 2022[106] • Kushlaf 2022[107]	Yes
ATB200-02 (NCT02675465)	Single arm	Cipaglucosidase alfa in combination with miglustat	ERT-naïve and -experienced	Australia, Germany, Netherlands, New Zealand, United Kingdom, United States	• Byrne 2022[57]	Yes

The EMBASSY trial was not considered suitable for inclusion in the ML-NMRs because of the exploratory nature of the study (which is also limited by both a short follow-up [24 weeks] and a small sample size [N=16])

Abbreviations: CCTR: clinical trials regulation; CDER: Center for Drug Evaluation and Research; ERT: enzyme replacement therapy; RCT: randomised clinical trial
Source: SLR and ITC Report.[108]

B.2.9.3 Rationale for ML-NMR methodology

Standard network meta-analysis (NMA) collects aggregate data from multiple studies on multiple treatments in order to produce consistent estimates of relative treatment effects between each pair of treatments in the network.[109, 110] Network meta-regression (NMR) methods are an extension to the NMA that take into account the effect of study-level covariates which may modify treatment effect (baseline covariates are balanced within each trial by randomisation but may differ in distribution between trials).[111-113] ML-NMR is recommended by NICE as it optimally integrates all available evidence (aggregate and patient-level data).[76, 114] The ML-NMR method is a generalisation of the NMR method (which usually uses aggregate data), as well as methods using individual patient data (the matching adjusted indirect comparison and simulated treatment comparison).[115, 116] In addition, it provides relative effect estimates for any target population of interest, which is especially relevant in the context of Pompe disease, as key pivotal trials were conducted in ERT-naïve people, but relative effect estimates might be needed in the more general Pompe disease population which includes ERT-experienced people. Therefore, and given the availability of individual patient data for cipaglucosidase alfa in combination with miglustat from the PROPEL, an ML-NMR was conducted.

Data availability assessment

All eight studies considered for inclusion in the ML-NMRs provided change from baseline in 6MWD (m) and change from baseline in FVC (% predicted).

Assessment of heterogeneity

Heterogeneity in baseline characteristics across the eight trials considered for inclusion were assessed in order to determine the feasibility of conducting ML-NMRs for 6MWD and FVC % predicted, and any adjustments required in ML-NMR methodologies.

Baseline characteristics such as age, gender, ethnicity, previous ERT duration, baseline 6MWD and baseline FVC % predicted across studies are presented in Table 28. Some variation in baseline age, gender distribution, ERT duration and 6MWD and FVC % predicted were observed; most participants were White across the eight trials.

The ML-NMR methodology does not rely on an assumption of balanced effect modifiers. In this ML-NMR, the covariates of baseline age, gender, race, previous ERT duration, visit time, 6MWD and FVC % predicted were adjusted for using individual patient data from the PROPEL trial, in order to minimise the impact of these potential effect modifiers on relative treatment effects. However, as with any ITC, unobserved effect modifiers or effect modifiers not available in the data could not be accounted for.

Table 28: Baseline characteristics of trials included in the feasibility assessment

Trial name/author	Population	Treatment	N	Age, mean (SD)	% Male	% White	ERT duration in years, mean (SD)	6MWD in m, mean (SD)	Sitting FVC (% predicted), mean (SD)
LOTS/van der Ploeg, 2010[87]	ERT-naïve	Alglucosidase alfa	60	45.3 (12.4)	56.7	95.0	0 (0)	332.2 (126.69)	55.43 (14.44)
		Placebo	30	42.6 (11.6)	36.7	90.0	0 (0)	317.93 (132.29)	53.0 (15. 66)
LOTS OLE/van der Ploeg, 2012[90]	ERT-naïve	Alglucosidase alfa	26	NR	NR	NR	NR	312.7 (147.2)	51.1 (15.8)
EMBASSY/van der Ploeg, 2016[117]	ERT-naïve	Alglucosidase alfa	16	51.6 (13.69)	44.0	NR	0 (0)	449.9 (208.01)	76.4 (15.63)
NEO-1/-EXT/ 2022[99]	ERT-naïve	Avalglucosidase alfa	10	44.8 (20.3)	30.0	80.0	0 (0)	449.0 (118.0)	69.2 (19.3)
	ERT-experienced	Avalglucosidase alfa	14	46.7 (14.1)	64.3	92.9	4.0 (2.0)	440.0 (141.0)	77.3 (16.5)
COMET/Diaz-Manera, 2021[101]	ERT-naïve	Avalglucosidase alfa	51	46.0 (14.5)	52.9	92.2	0 (0)	399.3 (110.9)	62.5 (14.4)
		Alglucosidase alfa	49	50.3 (13.7)	51.0	95.9	0 (0)	378.1 (116.2)	61.6 (12.4)
COMET OLE/CDER, 2021[118]	ERT-experienced	Avalglucosidase alfa	44	51.24 (13.7)	51.0	95.9	0.94 (0)	383.6 (141.1)	61.2 (13.5)
ATB200-02/Byrne, 2022[57]	ERT-naïve	Cipaglucosidase alfa in combination with miglustat	6	46.10 (39.09)	17.0	70.	0 (0)	396.00 (75.20)	55.8 (19.1)
	ERT-experienced		17	45.73 (36.0)	65.0	80.8	6.4 (1.3)	393.08 (123.68)	-
PROPEL/Schoser, 2021[53]	ERT-naïve and -experienced	Cipaglucosidase alfa in combination with miglustat	85	47.6 (13.3)	42.4	87.1	7.5 (3.4)	357.9 (111.8)	70.7 (19.6)

		Alglucosidase alfa[a]	38	45.41 (13.3)	52.6	78.9	7.1 (3.6)	351.0 (121.3)	69.7 (21.5)

[a]Excludes the outlier participant discussed in Section B.2.4.1.
Abbreviations: 6MWD: six-minute walk distance; ERT: enzyme replacement therapy; FVC: forced vital capacity; SD: standard deviation.

Study quality assessment

Quality assessments for the included studies are provided in Appendix D. The risk of bias of the studies included in the feasibility assessment was considered to be low to moderate and were considered to be appropriate for inclusion into the ML-NMRs. However, this aspect of the feasibility assessment determined that the EMBASSY trial was not suitable for inclusion in the ML-NMRs because of the exploratory nature of the study (which is also limited by both a short follow-up [24 weeks] and a small sample size [N=16]), leaving a total of seven studies for final inclusion in the analysis.

B.2.9.4 Methodology

The ML-NMR was conducted in line with the framework described by Phillippo, 2020[76] and NICE DSU TSD 3,[77] with the aggregate level model formed from an integration of the individual level model over the population in each trial. Full details of the ML-NMR methodology are provided in Appendix D. In summary, a Bayesian framework was chosen in which the ML-NMR was implemented by using Markov chain Monte Carlo (MCMC) sampling in Stan.[119] The Bayesian framework is considered suitable for performing indirect treatment comparisons with a small number of trials and low sample sizes, as is the case in rare diseases, since informative priors, which reflect a prior belief of the possible values of the pooled relative effect and effects of covariates, can be chosen to alleviate the limitations of small networks and low sample sizes of the trials included in the network.

Both fixed effects (FE) and random effects (RE) ML-NMR models were applied. The fixed effects model assumed a common treatment effect across all study settings and any differences between observed effect sizes could be explained by the included effect modifiers or due to sampling error. The random effects model was fitted to check for any residual between-study heterogeneity remaining after adjusting for the included effect modifiers. Deviance information criteria (DIC) were used to assess goodness-of-fit of the models and to identify the appropriate model (FE or RE model) for the data. Significance was tested using a 2-tailed Z test with significance level 0.05.

Outcomes assessed in the ML-NMRs were change from baseline in 6MWD (m) and in FVC (% predicted) assessed at Week 52. For these continuous outcomes, mean treatment differences with associated 95% credible intervals (CrIs) were calculated. The following potential treatment effect modifiers were considered, with suitable marginal distributions chosen (Appendix D):

- Binary covariates: male (Y vs N) and White ethnicity (Y vs N);
- Continuous covariates: visit time in weeks, previous ERT duration at baseline, baseline 6MWD or FVC % predicted, baseline age.

Any residual between-study variability remaining after adjusting for the above potential treatment effect modifiers was checked through the random-effects model, with help of the residual heterogeneity standard deviation parameter.

Calculation of the surface under the cumulative ranking curve (SUCRA) score is presented in Appendix D.

Models were implemented in a Bayesian framework using Stan with help of the R package "multinma",[119] by using Markov chain Monte Carlo (MCMC) sampling in Stan. The Stan sampler was run within 3 parallel chains for 5,000 iterations with the first 1,000 iterations discarded as the "burn-in" period. Convergence of the chains was checked using the Gelman-Rubin (GR) statistic (i.e., the R-hat). A GR statistic ≤ 1.1 indicated that convergence had been reached.

Main analyses

In the main analyses for each endpoint, all trials selected in the feasibility assessment were included. Single-arm trials were included into the network by matching them to an appropriate comparator arm of the RCTs. The covariates were set to the mean values of the baseline characteristics from the PROPEL trial (Table 29).

Table 29: Base case scenario covariate setting

Age (years)	% male	% white	ERT duration (years)	6MWD (m)	FVC (% predicted)	Time (weeks)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

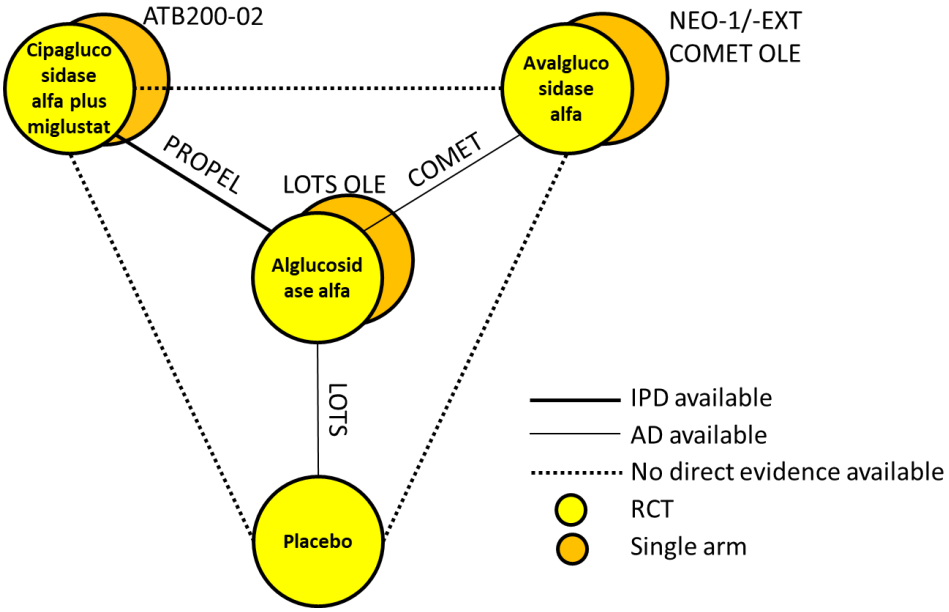
Abbreviations: 6MWD: six-minute walk distance; ERT: enzyme replacement therapy; FVC: forced vital capacity.
Sources: SLR and ITC Report[108]

Sensitivity and scenario analyses

In addition to the main analysis, two sensitivity analyses were conducted in which NEO-1/-EXT was removed (Sensitivity analysis 1) and all single arm trials were additionally removed (Sensitivity analysis 2). For each of the main analysis and sensitivity analyses, scenario analyses were conducted in which covariates were varied. Scenario analysis based on prior ERT experience are detailed and presented in Appendix D. All other scenario analyses are available in the SLR and ITC report.[108]

The evidence network for the ML-NMRs is presented in Figure 18.

Figure 18: Evidence network for the ML-NMRs



Abbreviations: AD: aggregated data; IPD: individual patient data, RCT: randomised controlled trial.

B.2.9.5 Results

Baseline characteristics in included studies are presented in Section B.2.9.2; since the ML-NMR methodology includes adjusting for baseline characteristics which may be treatment effect modifiers, the ITC was considered appropriate. Incorporation of single-arm studies into the network is detailed in Appendix D.

The full trial results that informed the ML-NMR, and full results of the ML-NMR (including the fit of fixed effects and random effects models, statistics of residual heterogeneity and SUCRA scores) are available in the SLR and ITC report.[108] A summary of key results is presented below.

6MWD: main analysis, base case

In the main analysis of 6MWD, both FE and RE ML-NMR models performed similarly (Appendix D). The RE ML-NMR model showed a better fit with a lower DIC; therefore, the results of the RE model are presented below.

[redacted]

The comparisons that include placebo show the largest variability (i.e., width of the 95% CrI), since the LOTS trial only included ERT-naïve participants, and the base case analysis has a relatively long previous ERT duration of 5.7 years.

Table 30: Relative effects for 6MWD change from baseline at Week 52 (main analysis, random effects ML-NMR model)

Comparison	Relative effect	p-value
Cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa	[redacted]	[redacted]
Cipaglucosidase alfa in combination with miglustat vs. avalglucosidase alfa	[redacted]	[redacted]
Cipaglucosidase alfa in combination with miglustat vs. placebo	[redacted]	[redacted]
Avalglucosidase alfa vs. alglucosidase alfa	[redacted]	[redacted]
Avalglucosidase alfa vs. placebo	[redacted]	[redacted]
Alglucosidase alfa vs. placebo	[redacted]	[redacted]

Abbreviations: 6MWD: six-minute walk distance; ML-NMR: multi-level network meta-regression model.
Sources: SLR and ITC Report[108]

Figure 19: Forest plot of relative effects for change from baseline in 6MWD at Week 52 (base case, random effects ML-NMR model)

Abbreviations: 6MWD: six-minute walk distance; Alglu: alglucosidase alfa; Aval: avalglucosidase alfa; Cipa: cipaglucosidase alfa in combination with miglustat; ML-NMR: multi-level network meta-regression model.
Sources: SLR and ITC Report[108]

FVC % predicted: main analysis, base case

The fixed effects ML-NMR model showed a better fit with a lower DIC than the RE ML-NMR model; therefore, the results of the fixed effects model are presented below.

[redacted]

As before, the comparisons that include placebo show the largest variability (i.e., width of the 95% CrI), since the LOTS trial only included ERT-naïve participants, and the base case analysis has a relatively long previous ERT duration of 5.7 years.

Table 31: Relative effects for FVC change from baseline at Week 52 (main analysis, fixed effects ML-NMR model)

Comparison	Relative effect	p-value
Cipaglucosidase alfa in combination with miglsustat vs. alglucosidase alfa	[redacted]	[redacted]
Cipaglucosidase alfa in combination with miglsustat vs. avalglucosidase alfa	[redacted]	[redacted]
Cipaglucosidase alfa in combination with miglsustat vs. placebo	[redacted]	[redacted]
Avalglucosidase alfa vs. alglucosidase alfa	[redacted]	[redacted]
Avalglucosidase alfa vs. placebo	[redacted]	[redacted]
Alglucosidase alfa vs. placebo	[redacted]	[redacted]

Abbreviations: FVC: forced vital capacity; ML-NMR: multi-level network meta-regression model.
Sources: SLR and ITC Report[108]

Figure 20: Forest plot on relative effects for FVC change from baseline at Week 52 (main analysis, fixed effects ML-NMR model)

Abbreviations: Alglu: alglucosidase alfa; Aval: avalglucosidase alfa; Cipa: cipaglucosidase alfa in combination with miglustat; FVC: forced vital capacity; ML-NMR: multi-level network meta-regression model.
Sources: SLR and ITC Report[108]

B.2.9.6 Interpretation of the indirect evidence

In the absence of head-to-head, direct data comparing new therapies cipaglucosidase alfa in combination with miglustat with avalglucosidase alfa, an ITC has been conducted to provide indirect evidence on the relative effect of cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa in LOPD on change from baseline in 6MWD and FVC % predicted. Whilst avalglucosidase alfa is not yet commercially available, [2, 3] this analysis aligns with the NICE final scope, and informs a scenario in the economic analysis with avalglucosidase alfa as a comparator (Section B.3.10.3).

An ITC was deemed feasible to assess change from baseline in 6MWD and FVC % predicted. The ITC took the form of a multi-level network meta-regression (ML-NMR) in line with the NICE guide to the methods of technology appraisal. The ML-NMR method was used to account for the heterogeneous study populations; single-arm evidence was incorporated into the network by matching the single arms to RCT comparator arms with similar previous ERT duration. Baseline characteristics such as age, gender, ethnicity, previous ERT duration, baseline 6MWD and baseline FVC % predicted were adjusted for using individual patient data from the PROPEL trial.

[redacted]

The evidence base for this ITC was limited, as is expected with a rare disease, with comparisons being informed by a small number of studies of which two (LOTS and COMET) only included ERT-naïve participants. Single-arm studies were not connected to the network through RCTs, and the links based on matching can result in biased relative effect estimates when there is high heterogeneity between the single- and the matched arm. Whilst the ML-NMR method adjusted the relative effect estimates for a number of baseline covariates, unobserved effect modifiers or effect modifiers not available in the data could not be accounted for. In the main base case analyses, comparisons of cipaglucosidase alfa in combination with miglustat vs. avalglucosidase alfa were associated with relatively little uncertainty owing to the inclusion of single-arm trials into the network. Overall, in the absence of direct RCT evidence, this analysis makes use of the ML-NMR method to provide robust efficacy comparisons of cipaglucosidase alfa in combination with miglustat vs. avalglucosidase alfa using limited evidence.

B.2.10 Adverse reactions

Results for the safety and tolerability of cipaglucosidase alfa in combination with miglustat and alglucosidase alfa from the PROPEL and ATB200-02 trials are presented below. Cipaglucosidase alfa in combination with miglustat generally was generally well-tolerated with a similar safety profile to alglucosidase alfa, with no new safety signals or deaths reported.[5, 55] In addition, results from ATB200-02 also indicated that there were no long-term safety concerns associated with cumulative study drug exposure for treatment duration of 48 months.

B.2.10.1 Treatment exposure

Treatment exposure in PROPEL

Treatment exposure was similar across both treatment arms, with [redacted] and [redacted] doses administered in the cipaglucosidase alfa in combination with miglustat and alglucosidase alfa in combination with placebo arms, respectively. Duration of treatment was [redacted] and [redacted], respectively.[5]

Treatment exposure in ATB200-02

Duration of exposure was similar for participants in Cohorts 1, 2 and 3. The mean duration of treatment exposure for these three cohorts were [redacted], [redacted] and [redacted], respectively. Exposure for participants in Cohort 4 was slightly lower because these participants joined the study later, with a mean treatment duration of [redacted].

B.2.10.2 Summary of treatment-emergent adverse events (TEAEs)

TEAEs in PROPEL

The overall incidence of TEAEs was similar between the cipaglucosidase alfa in combination with miglustat and alglucosidase alfa groups (95.3% and 97.4%, respectively; Table 32). The incidence of TEAEs leading to study drug discontinuation was low, and no TEAEs leading to death were reported. Most TEAEs were mild or moderate in severity, with 8 participants in the cipaglucosidase alfa in combination with miglustat group experiencing a serious TEAE. The incidence of serious TEAEs leading to study drug discontinuation was low across both treatment groups.[5]

Table 32: Overall summary of TEAEs in PROPEL (Safety Population)

	Cipaglucosidase alfa in combination with miglustat (n = 85)			Alglucosidase alfa in combination with placebo (n = 38)			Total (N = 123) n (%)
	Cipaglucosidase alfa n (%)	Miglustat n (%)	Total n (%)	Alglucosidase alfa n (%)	Placebo n (%)	Total n (%)	
Participants who had any TEAE			81 (95.3)			37 (97.4)	118 (95.9)
Participants who had any TEAE leading to study drug discontinuation (Section B.2.10.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related TEAE (Section B.2.10.4)	[redacted]	[redacted]	26 (30.6)	[redacted]	[redacted]	14 (36.8)	[redacted]
Participants who had any study drug-related TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any serious TEAE			8 (9.4)			1 (2.6)	[redacted]
Participants who had any serious TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related serious TEAE	[redacted]	[redacted]	1 (1.2)	[redacted]	[redacted]	0	[redacted]
Participants who had any study drug-related serious TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Cipaglucosidase alfa in combination with miglustat (n = 85)			Alglucosidase alfa in combination with placebo (n = 38)			Total (N = 123) n (%)
	Cipaglucosidase alfa n (%)	Miglustat n (%)	Total n (%)	Alglucosidase alfa n (%)	Placebo n (%)	Total n (%)	
Participants who had any TEAE leading to death	[redacted]	[redacted]	0	[redacted]	[redacted]	0	0

A TEAE was defined as any event that started or changed in intensity on or after the first dose of study drug.
A study drug-related TEAE was defined as a TEAE with the corresponding relationship to study drug marked as definite, probable, or possible. For the total column under each treatment, the participant was counted only once under the category according to the worst relationship for any component of the treatment. If relationship was missing, it was classified as related.
Percentages were based on the number of participants in each treatment group for the Safety Population.
Abbreviations: TEAE: treatment-emergent adverse event
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

TEAEs in ATB200-02

In Stage 1 of ATB200-02, at a dose of cipaglucosidase alfa 20 mg/kg, [redacted] experienced TEAEs, and [redacted] experienced TEAEs. In Stage 2, at a dose of IV-infused cipaglucosidase alfa 20 mg/kg in combination with miglustat 260 mg, [redacted] experienced TEAEs, and [redacted] experienced treatment-related TEAEs. [redacted] in Stage 1 or Stage 2.

In participants who received IV-infused cipaglucosidase alfa 20 mg/kg in combination with miglustat 260 mg co-administration (i.e., in Stage 2 Period 5, Stage 3, and Stage 4), [redacted] experienced TEAEs and [redacted] experienced treatment-related TEAEs (Table 33).

Table 33: Overview of TEAEs in ATB200-02 – Stage 2 Period 5 + Stage 3 + Stage 4 (Safety Population)

	Total ([redacted]) n (%)
Participants with TEAEs	[redacted]
Participants with treatment-related TEAEs	[redacted]
Participants with TEAEs leading to study drug discontinuation	[redacted]
Participants with treatment-related TEAEs leading to study drug discontinuation	[redacted]
Participants with TESAEs	[redacted]
Participants with treatment-related TESAEs	[redacted]
Participants with TESAEs leading to study drug discontinuation	[redacted]
Participants with treatment-related TESAEs leading to study drug discontinuation	[redacted]
Participants with adverse events leading to death	[redacted]

Adverse events are coded using MedDRA version 23.0.
Percentages are based on the Safety population.
For each category of a parameter, each participant was counted once, even if a participant experienced multiple events in that category. Treatment-emergent AEs are defined as AEs with an onset date on or after the first dose of study drug. Adverse events that occur more than 30 days after the last dose of study drug were not considered treatment emergent. An AE with missing or partial start date is considered treatment-emergent if it cannot be determined whether the AE started before or after the first dose of study drug.
Cohorts 1, 2, 4: ERT-experienced participants; Cohort 3: ERT-naïve participants; Cohorts 1, 3, 4: ambulatory participants; Cohort 2: non-ambulatory participants.
Abbreviations: AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse event.
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[55]

B.2.10.3 TEAEs occurring in at least 10% of participants

TEAEs occurring in at least 10% of participants in PROPEL

The most commonly reported TEAEs in the cipaglucosidase alfa in combination with miglustat group were falls, headache, nasopharyngitis, and myalgia. Commonly-reported TEAEs corresponded to the system organ classes (SOCs) of [redacted] Table 34).[5]

The most commonly reported TEAEs in the alglucosidase alfa group were falls, headache, nausea, and back pain.[5] Commonly-reported TEAEs corresponded to the SOCs of [redacted][5]

Table 34: Incidence of TEAEs ≥ 10% of participants in PROPEL by PT (Safety Population)

Preferred Term - n (%)	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 38)	Total (N = 123)
Participants with any TEAE	81 (95.3)	37 (97.4)	[redacted]
Fall	25 (29.4)	15 (39.5)	[redacted]
Headache	20 (23.5)	9 (23.7)	[redacted]
Nasopharyngitis	19 (22.4)	3 (7.9)	[redacted]
Myalgia	14 (16.5)	5 (13.2)	[redacted]
Arthralgia	13 (15.3)	5 (13.2)	[redacted]
Nausea	10 (11.8)	8 (21.1)	[redacted]
Back pain	9 (10.6)	7 (18.4)	[redacted]
Diarrhoea	11 (12.9)	4 (10.5)	[redacted]
Urinary tract infection	12 (14.1)	2 (5.3)	[redacted]
Fatigue	8 (9.4)	5 (13.2)	[redacted]
Pain in extremity	11 (12.9)	2 (5.3)	[redacted]
Oropharyngeal pain	10 (11.8)	2 (5.3)	[redacted]

A TEAE was defined as any event that started or changed in intensity on or after the first dose of study drug.
A participant who experienced the same TEAE multiple times was counted once for the corresponding SOC and preferred term.
SOCs and PTs were coded with MedDRA Version 23.0.
Percentages were based on the number of participants in each treatment group for the Safety Population.
TEAEs by preferred term are sorted by descending order of frequency in the total group.
Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SOC: system organ class; TEAE: treatment-emergent adverse event
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

TEAEs occurring [redacted] in ATB200-02

In participants who received IV-infused cipaglucosidase alfa 20 mg/kg in combination with miglustat 260 mg (i.e., in Stage 2 Period 5, Stage 3, and Stage 4), the SOCs with the highest frequency of drug related TEAEs were gastrointestinal disorders, general disorders and administrative site conditions, and nervous system disorders, and the most frequently reported drug-related TEAEs ([redacted]) were fatigue, headache, and diarrhoea (Table 36).

Table 34 : Incidence of TEAEs in ≥ 10% of participants in ATB200-02 by PT – Stage 2 Period 5 + Stage 3 + Stage 4 (Safety Population)

Preferred Term	Total ([redacted]) n (%)
Urinary tract infection	[redacted]
Abdominal pain upper	[redacted]
Contusion	[redacted]
Cough	[redacted]
Dizziness	[redacted]
Dyspnoea	[redacted]
Hypertension	[redacted]
Migraine	[redacted]
Nasal congestion	[redacted]
Pyrexia	[redacted]
Vertigo	[redacted]
Vomiting	[redacted]
Abdominal distension	[redacted]
Bronchitis	[redacted]
Influenza	[redacted]
Muscle strain	[redacted]
Pruritus	[redacted]
Rhinitis	[redacted]
Skin abrasion	[redacted]
Skin laceration	[redacted]
Vaccination complication	[redacted]
Chest discomfort	[redacted]
Constipation	[redacted]

Preferred Term	Total ([redacted]) n (%)
Dyspepsia	[redacted]
Dyspnoea exertional	[redacted]
Flatulence	[redacted]
Gait disturbance	[redacted]
Gastritis	[redacted]
Gastrooesophageal reflux disease	[redacted]
Haemorrhoids	[redacted]
Head injury	[redacted]
Hyperhidrosis	[redacted]
Iron deficiency	[redacted]
Large intestine polyp	[redacted]
Lower respiratory tract infection	[redacted]
Musculoskeletal pain	[redacted]
Non-cardiac chest pain	[redacted]
Pain	[redacted]
Thermal burn	[redacted]
Tremor	[redacted]
Viral infection	[redacted]

System organ class and preferred term coding not available, but AE term is displayed. Adverse events are coded using MedDRA version 23.0.
Percentages are based on the Safety population.
For each preferred term, each participant was counted once, even if a participant experienced multiple events in that preferred term.
Treatment-emergent AEs are defined as AEs with an onset date on or after the first dose of study drug. Adverse events that occur more than 30 days after the last dose of study drug were not considered treatment emergent. An AE with missing or partial start date is considered treatment-emergent if it cannot be determined whether the AE started before or after the first dose of study drug.
Abbreviations: AE: adverse event; ERT: enzyme replacement therapy; iCSR: interim clinical study report; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; TEAE: treatment-emergent adverse event.
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[55]

B.2.10.4 Drug-related TEAEs

Drug-related TEAEs in PROPEL

In the cipaglucosidase alfa in combination with miglustat group, the most frequently reported drug-related TEAEs (i.e. considered related to cipaglucosidase alfa or miglustat) were in the SOC of nervous system disorders, and the most frequently reported TEAEs were headache and diarrhoea

(Table 35). In the alglucosidase alfa in combination with placebo group, the most frequently reported drug-related TEAEs (i.e. considered related to alglucosidase alfa or placebo) were in the SOC of gastrointestinal disorders, and the most frequently reported TEAEs were nausea and fatigue.[5]

Table 35: Incidence of study drug-related TEAEs in [redacted] of participants in PROPEL by SOC and PT (based on pooled designation) (Safety Population)

System Organ Class Preferred Term – n (%)	Cipaglucosidase alfa in combination with miglustat (n = 85)			Alglucosidase alfa in combination with placebo (n = 38)		
	Cipaglucosidase alfa	Miglustat	Total	Alglucosidase alfa	Placebo	Total
Participants with any related TEAE	[redacted]	[redacted]	**26 (30.6)**	[redacted]	[redacted]	**14 (36.8)**
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal distension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flatulence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A TEAE was defined as any event that started or changed in intensity on or after the first dose of study drug.
"Related" included definite, probable, and possibly related; "not related" included unlikely and unrelated.
If a participant experienced more than 1 TEAE with different relationship categories within the same SOC/PT, only the worst case (related TEAE) was reported.

The pooled designation (in the total column) was considered “related” if the 2 categories of the individual relationships were discordant (ie, “related” to one and “not related” to the other); the pooled designation (in the total column) was concordant with the individual categories if the 2 categories of the individual relationships were concordant (i.e., “related” to both, or “not related” to both).
If relationship was missing, it was classified as “related.”
SOCs and PTs were coded with MedDRA Version 23.0.
Percentages were based on the number of participants in each treatment group for the Safety Population.
Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SOC: system organ class; TEAE: treatment-emergent adverse event
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

Drug-related TEAEs in ATB200-02

In Stages 1 and 2, the SOC with the highest frequency of drug-related TEAEs (ie, considered related to cipaglucosidase alfa, miglustat, or both) was Gastrointestinal Disorders, and the most frequently reported drug-related TEAEs were constipation and fatigue.

In participants who received IV-infused cipaglucosidase alfa 20 mg/kg in combination with miglustat 260 mg co-administration (i.e., in Stage 2 Period 5, Stage 3, and Stage 4), the SOCs with the highest frequency of drug-related TEAEs were Gastrointestinal Disorders, General Disorders and Administrative Site Conditions, and Nervous System Disorders, and the most frequently reported drug-related TEAEs ([redacted] of participants) were fatigue, headache, and diarrhoea (Table 36).[55]

Table 36: Incidence of treatment-related TEAEs in [redacted] of participants in ATB200-02 by SOC or PT – Stage 2 Period 5 + Stage 3 + Stage 4 (based on pooled designation; Safety Population)

	Total [redacted] n (%)
Subjects with any treatment-related TEAE	[redacted]
Gastrointestinal disorders	[redacted]
Abdominal pain	[redacted]
Diarrhoea	[redacted]
Flatulence	[redacted]
Nausea	[redacted]
Vomiting	[redacted]
General disorders and administration site conditions	[redacted]
Chills	[redacted]
Fatigue	[redacted]
Pyrexia	[redacted]
Nervous system disorders	[redacted]
Headache	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Dyspnoea	[redacted]
Skin and subcutaneous tissue disorders	[redacted]
Hyperhidrosis	[redacted]

System organ class and preferred term coding not available, but AE term is displayed. Adverse events are coded using MedDRA version 23.0.
Percentages are based on the Safety population.
If relationship is missing, it is classified as "Related." Related includes definite, probable, and possible related.
If a participant experienced more than 1 TEAE with different relationship categories within the same system organ class/preferred term, only the worst case (related TEAE) was reported, and the participant was counted only once under the highest relationship.
The pooled designation is considered "related" as long as one of the two individual relationships is "related."
Treatment-emergent AEs are defined as AEs with an onset date on or after the first dose of study drug. Adverse events that occurred more than 30 days after the last dose of study drug were not considered treatment emergent. An AE with missing or partial start date is considered treatment emergent if it cannot be determined whether the AE started before or after the first dose of study drug.
Cohorts 1, 2, 4: ERT-experienced participants; Cohort 3: ERT-naïve participants; Cohorts 1, 3, 4: ambulatory participants; Cohort 2: non-ambulatory participants.

Abbreviations: AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SOC: system organ class; TEAE: treatment-emergent adverse event.
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[55]

B.2.10.5 AEs leading to permanent discontinuation

AEs leading to permanent discontinuation in PROPEL

Overall, two participants in the cipaglucosidase alfa in combination with miglustat group and one participant in the alglucosidase alfa in combination with placebo group experienced TEAEs leading to study drug discontinuation. In the cipaglucosidase alfa in combination with miglustat group, both AEs were IARs: one was a serious TEAE (anaphylactic reaction) and the other was chills; both were related to the study drug. The one AE leading to withdrawal in the alglucosidase alfa in combination with placebo arm was a serious TEAE (cerebrovascular accident unrelated to study drug).[5]

AEs leading to permanent discontinuation in ATB200-02

In participants who received IV-infused cipaglucosidase alfa 20 mg/kg in combination with miglustat 260 mg co-administration (i.e., in Stage 2 Period 5, Stage 3, and Stage 4), [redacted] experienced TEAEs leading to study drug discontinuation: [redacted][55]

B.2.10.6 TEAEs of interest

TEAEs of interest in PROPEL

IARs are of interest as both ERTs were administered via IV infusion. Across both treatment groups, [redacted] (Table 37), and the incidence of IARs was similar between the cipaglucosidase alfa in combination with miglustat (24.7%) and alglucosidase alfa groups (26.3%).[5] All IAR-TEAEs were non-serious except one SAE of anaphylactic reaction in the cipaglucosidase alfa in combination with miglustat group.

Table 37: Overall summary of TEAEs reported to be IARs in PROPEL (Safety Population)

	Cipaglucosidase alfa in combination with miglustat (n = 85)			Alglucosidase alfa in combination with placebo (n = 38)			Total (N = 123) n (%)
	Cipaglucosidase alfa n (%)	Miglustat n (%)	Total[a] n (%)	Alglucosidase Alfa n (%)	Placebo n (%)	Total[a] n (%)	
Participants who had any IAR-TEAE			**21 (24.7)**			**10 (26.3)**	[redacted]
Participants who had any IAR-TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related IAR-TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related IAR-TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any serious IAR-TEAE			[redacted]			[redacted]	[redacted]
Participants who had any serious-TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related serious IAR-TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related serious IAR-TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any serious IAR-TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A study drug-related TEAE was defined as a TEAE with the corresponding relationship to study drug marked as definite, probable, or possible. For the total column under each treatment, the participant was counted only once under the category according to the worst relationship for any component of the treatment. If relationship was missing, it was classified as related.
A TEAE was defined as any event that started or changed in intensity on or after the first dose of study drug.
Percentages were based on the number of participants in each treatment group for the Safety Population.
Abbreviations: IAR: infusion-associated reaction; TEAE: treatment-emergent adverse event;
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

TEAEs of interest in ATB200-01

IARs were reported for Stage 2 Period 5, Stage 3, and Stage 4. A total of [redacted] were reported in [redacted] in this study. [redacted]y and experienced [redacted]. [redacted] had a history of IARs with no IARs in the study. Overall, infusion-associated reaction TEAEs were reported infrequently ([redacted] of infusions in participants with IARs and [redacted] of infusions for all participants).

All [redacted]IAR TEAEs were considered by the investigator to be related to cipaglucosidase alfa, and [redacted] were considered by the investigator to be related to both cipaglucosidase alfa and miglustat. The majority of IAR TEAEs were mild or moderate in severity. [redacted].[55]

Table 38: Overview of TEAEs reported to be IARs in ATB200-02 – Stage 2 Period 5 + Stage 3 + Stage 4 (Safety Population)

	Total ([redacted]) n (%)
Participants with IAR-TEAEs	[redacted]
Participants with IAR-treatment-related TEAEs	[redacted]
Participants with IAR-TEAEs leading to study drug discontinuation	[redacted]
Participants with IAR-treatment-related TEAEs leading to study drug discontinuation	[redacted]
Participants with IAR-TESAEs	[redacted]
Participants with IAR-treatment-related TESAEs	[redacted]
Participants with IAR-TESAEs leading to study drug discontinuation	[redacted]
Participants with IAR-treatment-related TESAEs leading to study drug discontinuation	[redacted]
Participants with IAR-adverse events leading to death	[redacted]

Adverse events are coded using MedDRA version 23.0.
Percentages are based on the Safety population.
For each category of a parameter, each participant was counted once, even if a participant experienced multiple events in that category.
Treatment-emergent AEs are defined as AEs with an onset date on or after the first dose of study drug. Adverse events that occur more than 30 days after the last dose of study drug were not considered treatment emergent. An AE with missing or partial start date was considered treatment-emergent if it cannot be determined whether the AE started before or after the first dose of study drug.
Cohorts 1, 2, 4: ERT-experienced participants; Cohort 3: ERT-naïve participants; Cohorts 1, 3, 4: ambulatory participants; Cohort 2: non-ambulatory participants.
Abbreviations: AE: adverse event; ERT: enzyme replacement therapy; IAR: infusion-associated reaction; MedDRA: Medical Dictionary for Regulatory Activities; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse event.
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report)[55]

B.2.11 Ongoing studies

Ongoing studies investigating the efficacy and safety of cipaglucosidase alfa in combination with miglustat in the indication relevant to this submission are presented in Table 39. None of the ongoing trial results are expected to become available during the NICE appraisal.

Table 39: Ongoing studies for cipaglucosidase alfa in combination with miglustat

UK EAMS (EAMS number: 50636/0001)	
Trial objective	To provide early access to cipaglucosidase alfa in combination with miglustat for UK adults with symptomatic LOPD who have received alglucosidase alfa for at least two years. As part of the EAMS, data will be collected on the efficacy and safety of cipaglucosidase alfa in combination with miglustat.
Anticipated results	Baseline results are expected to become available December 2023.
ATB200-02 OLE (NCT02675465)	
Trial objective	Data from the 48-month cut-off of this trial is presented in this submission (It should be noted data from the 36-month cut-off was used for the economic model).
Anticipated results	Additional results are expected to become available December 2023.
ATB200-07 (NCT04138277)	
Trial objective	This trial is a phase III open-label extension of PROPEL, aiming to assess the long-term efficacy of cipaglucosidase alfa in combination with miglustat in adults with LOPD.
Anticipated results	Results are expected to become available December 2023.

Abbreviations: EAMS: Early Access to Medicines Scheme; LOPD: late-onset Pompe disease; PD: pharmacodynamics; PK; pharmacokinetics.
Source: EAMS;[52] ATB200-04;[120] ATB200-07.[121]

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Clinical effectiveness

Cipaglucosidase alfa in combination with miglustat distinguishes itself from alglucosidase alfa through its improved pharmacological properties[122] that translate into improved outcomes for adults with LOPD. The innovative potential of cipaglucosidase alfa in combination with miglustat, as demonstrated in the PROPEL and ATB200-02 trials, is reflected in [redacted] its PIM designation.[6, 7]

Evidence on the efficacy and safety of cipaglucosidase alfa in combination with miglustat derive from a Phase III, head-to-head trial in participants with LOPD, in line with the decision problem. Results from PROPEL numerically favoured cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa across the primary and most key secondary endpoints including motor, respiratory and muscle function, as well as HRQoL. Furthermore, the improvement in FVC % predicted with cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa was clinically and nominally significant, representing an important result for people with LOPD. The significance and consistency of the treatment effect across endpoints

was supported by further *post hoc* analyses indicating nominally significantly higher 6MWT and FVC response rates (separately and combined) with cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa. Supporting the efficacy analyses, reductions in disease biomarkers were significantly greater with cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa.

Results from PROPEL are supported by a single-arm, Phase II study which provides long-term data on the efficacy and safety of cipaglucosidase alfa in combination with miglustat. In ATB200-02, treatment with cipaglucosidase alfa in combination with miglustat demonstrated numerical improvements over Baseline in 6MWD, FVC % predicted and MMT; these improvements were generally sustained above baseline values through 48 months of treatment and supported by PRO, SGIC, and PGIC results.

As described in Section B.1.3.2, LOPD causes progressive loss of muscle function, mobility impairment and respiratory impairment. Despite the availability of alglucosidase alfa, substantial unmet need remains, with response to alglucosidase alfa having been shown to decline as early as 18 months after treatment initiation.[50] This decline is supported by the preference expressed by adults with LOPD for new therapies:

[redacted]

Results from PROPEL and ATB200-02 together demonstrate the sustained benefits of cipaglucosidase alfa in combination with miglustat across motor function, respiratory function and other clinically meaningful endpoints relevant to adults with LOPD over 48 months. Thus, these results are expected to represent an improvement in the prognosis, quality of life and daily lives of adults with LOPD.

In conclusion, the PROPEL trial provides evidence that cipaglucosidase alfa in combination with miglustat is an effective treatment in adults with LOPD, providing a valuable alternative to alglucosidase alfa.

Indirect comparative evidence vs. avalglucosidase alfa

Although avalglucosidase alfa is not yet commercially available, it is included as a comparator in the NICE final scope.[2, 3] Therefore, for completeness, the economic analysis contains a scenario analysis with avalglucosidase alfa as a comparator (Section B.3.10.3). In the absence of direct, head-to-head evidence between cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa, an ITC was conducted to establish the comparative effectiveness of the two treatments. The ITC took the form of a ML-NMR in line with the NICE DSU TSD 3,[77]

[redacted]

B.2.12.2 Safety

Co-administration of cipaglucosidase alfa and miglustat was generally safe and well-tolerated. The overall safety profile of cipaglucosidase alfa in combination with miglustat was similar to alglucosidase alfa, with no new safety signals identified, and no deaths reported in the PROPEL trial. A similar safety profile was demonstrated in ATB200-02. Notably, there were a similar number of TEAEs in general and TEAEs that were designated to the IARs between those treated with cipaglucosidase alfa in combination with miglustat and those treated with alglucosidase alfa in combination with placebo.

Most TEAEs during the study were mild or moderate in severity, with low proportions of participants experiencing serious TEAEs across both studies. In PROPEL, the majority of serious TEAEs in the cipaglucosidase alfa in combination with miglustat group were considered by the investigator to be unrelated to study drug. The incidence of TEAEs leading to study drug discontinuation was also low across both treatment arms. Both ERTs studied were administered via IV infusion; the incidence of IARs was similar between the two treatment groups and were generally mild or moderate and resolvable.

B.2.12.3 Applicability to the decision problem

The clinical evidence presented within this submission has been derived from an SLR of clinical trials investigating the efficacy and safety of treatment options, including cipaglucosidase alfa in combination with miglustat, for treating Pompe disease. Whilst the scope of the SLR was broader than that of the decision problem (adults with LOPD), due to the expected low numbers of adults surviving to adulthood to date (Section B.1.3.1), the scope of the SLR aligns with the population described in the decision problem. The results of PROPEL and ATB200-02 are relevant to the decision problem specified in the NICE final scope, which proposes the use of cipaglucosidase alfa in combination with miglustat for adults with LOPD.

B.2.12.4 Strengths and limitations of the clinical evidence base

Strengths of the clinical trials

PROPEL and ATB200-02 provide relevant and meaningful data for the efficacy and safety of cipaglucosidase alfa in combination with miglustat for the treatment of adults with LOPD, with results generalisable to UK clinical practice:

- A key strength of PROPEL is its active-controlled (head-to-head) superiority design, comparing the safety and efficacy of cipaglucosidase alfa in combination with miglustat with alglucosidase alfa.
- Evidence from PROPEL is supported by long-term safety and efficacy data from ATB200-02, through 48 months of treatment with cipaglucosidase alfa in combination with miglustat in adults with Pompe disease. Thus, these trials together provide evidence for the sustained benefits of treatment with cipaglucosidase alfa in combination with miglustat.
- PROPEL was conducted in 24 countries, including the UK. PROPEL is the first trial in LOPD to include participants who have previously been treated with alglucosidase alfa at the licensed dose, with a median of 7.4 years of prior ERT (alglucosidase alfa), as well as ERT-naïve participants. The inclusion of ERT-experienced participants provides data relevant to UK clinical practice in which almost all individuals have been treated with alglucosidase alfa.[21, 54]

Aside from prior ERT status, participants presented with heterogeneous demographic and baseline disease characteristics, including baseline 6MWD, FVC, MMT and GSGC score, and are therefore expected to capture the majority of the population of adults with LOPD in the UK. In addition, the PROPEL participant population was not filtered for those participants most likely to respond. Thus, the trial population represents a wide range of adults with LOPD and is therefore considered to be generalisable to UK clinical practice. This generalisability was further supported by expert opinion during a clinical advisory board.[22]

- Participants in both trials were required to be ≥18 years of age and have a documented diagnosis of LOPD based on GAA deficiency or *GAA* genotyping. Thus, the populations of the trials are highly representative of the intended population in UK clinical practice.
- The trial captured a number of disease-relevant endpoints including motor function, respiratory function, muscle function and PROs. Medical advisory boards and patient advisory boards were conducted to solicit feedback from people with LOPD on study design and endpoints continuously throughout the development programme.[55]
- Overall, both studies were considered to be high quality with a low risk of bias. In PROPEL, randomisation and blinding were adequate, and there were no unexpected imbalances between treatment groups and analysis of the ITT population. In ATB200-02, exposures and outcomes were accurately measured to minimise bias, authors identified and took confounding factors into account and precise reports were reported.
- Participants were permitted to continue using concomitant medication, in line with UK clinical practice. Treatment dosing was aligned with the draft SmPCs for cipaglucosidase alfa and miglustat.
- The study drug was permitted to be administered in the home, which reflects the intended real-world practice of home administration of cipaglucosidase alfa in combination with miglustat (Section B.3.5.2).

The relevance of the evidence base to the NICE final scope is further supported by the following:

- **Intervention**: Cipaglucosidase alfa in combination with miglustat was directly evaluated in line with its proposed indication as a treatment option for adults with LOPD.
- **Comparators**: PROPEL provided direct head-to-head evidence of cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa, which is considered to be the primary comparator in this submission due to its commercial availability in England at the time of submission. Although avalglucosidase alfa was included in the NICE final scope, given that this treatment is not yet commercially available and therefore has not been established in clinical use,[124] it has been considered as a secondary comparator in this submission and was included in scenario analyses of the economic analysis. Subsequently, an indirect comparison of the efficacy of cipaglucosidase alfa in combination with miglustat vs. avalglucosidase alfa was conducted (Section B.2.9).
- **Outcomes**: The two trials captured a number of disease-relevant endpoints, in line with feedback from people with Pompe disease. All outcomes in the NICE final scope were included in the trials, with the exception of mortality, because of the low expected number of events over the trial durations.

Limitations of the clinical evidence base

- The PROPEL trial is the largest known RCT in any lysosomal disorder,[53] with a total of 123 participants randomly assigned to receive cipaglucosidase alfa in combination with miglustat (n=85) or alglucosidase alfa in combination with placebo (n=38). However, as expected for a rare disease, the sample size was small overall, and clinicians have noted that these small subpopulations have led to uncertainty in the interpretation of results.[50]
- Additionally, at the time of this submission, there are no long-term, head-to-head trial data comparing the safety and efficacy of cipaglucosidase alfa in combination with miglustat and alglucosidase alfa, therefore the durability of treatment has been obtained from the single-arm ATB200-02 trial.
- Additionally, other clinical endpoints which may be more meaningful to people with LOPD than quantitative, measurable outcomes, such as the requirement for mobility aids or ventilator dependence, were not captured in PROPEL. Nevertheless, the trial was able to capture clinically and nominally significant benefit across a range of endpoints relevant to people with LOPD, as informed by patient and medical advisory boards.[4, 62]
- In the absence of head-to-head data comparing cipaglucosidase alfa in combination with miglustat vs. avalglucosidase alfa, an ITC has been performed. The evidence base for this ITC was limited, however, this analysis made use of the ML-NMR method to provide robust efficacy comparisons of cipaglucosidase alfa in combination with miglustat vs. avalglucosidase alfa using limited evidence, in line with the framework described by Phillippo, 2020[76] and NICE DSU TSD 3 (see Section B.2.9).[77]

Conclusions

PROPEL was a robust, multicentre, study with a head-to-head superiority trial design to allow for direct comparison of cipaglucosidase alfa in combination with placebo with the commercially available standard of care, alglucosidase alfa, in combination with placebo. Evidence from PROPEL is supported by long-term safety and efficacy data from ATB200-02, through 48 months of treatment with cipaglucosidase alfa in combination with miglustat in participants with LOPD. Both studies were of high quality, relevant to the NICE final scope, and included a population relevant to UK clinical practice. [redacted]. Together, evidence from these studies support the durable efficacy and safety of cipaglucosidase alfa in combination with miglustat and its ability to address the unmet need for durable and effective treatment options for adults with LOPD who have not received previous ERT treatment, as well as those who do not gain any benefit and those experiencing declining therapeutic efficacy while receiving alglucosidase alfa.

B.3 Cost-effectiveness

Model approach and structure

- A de novo patient-level simulation model was developed to estimate the cost-effectiveness of cipaglucosidase alfa in combination with miglustat vs. current standard of care (SoC), alglucosidase alfa, for adults with LOPD.
- The analysis is consistent with the NICE reference case with a National Health Service (NHS) and Personal Social Services (PSS) perspective; costs and benefits were discounted at a rate of 3.5% and a lifetime time horizon was adopted.
- Health states included in the model were in line with advice from the NICE Preliminary Independent Model Advice (PRIMA) service, clinical opinion,[125] and the committee's preferences during the NICE appraisal of avalglucosidase alfa (TA821).[2]
- The model contained seven 'alive' health states defined by the level of mobility and/or respiratory support required, and one deceased state, which could be transitioned to from all health states.

Model inputs

- Efficacy in the model was represented through deterioration in mobility and respiratory function (6MWD and FVC % predicted, respectively), as in TA821.[2] Each individual that entered the model was randomly assigned Baseline 6MWD and FVC % predicted values, based on pre-defined distributions from PROPEL. Health state transitions were determined by the decline in individuals' 6MWD and FVC % predicted below pre-specified threshold values, in line with clinical opinion.[4]
- Efficacy was represented in two stages, which is aligned with clinical opinion regarding treatment effects[126] and the methodology used in the NICE appraisal of avalglucosidase alfa (TA821).[2] The two stages were initial annual change from Baseline and subsequent annual change. It was expected that people who received any ERT treatment would experience an initial improvement in both 6MWD and FVC % predicted, followed by a subsequent, gradual decline, as observed with alglucosidase alfa.[20, 24] The model base case assumes [redacted] rate of subsequent annual disease progression beyond Year 3 of the model, as measured by 6MWD and FVC % predicted with cipaglucosidase alfa in combination with miglustat relative to alglucosidase alfa; this relative rate of progression was validated by clinical experts.[4]
- Mortality was assumed to be equivalent to UK general population norms (based on age and gender) until individuals required mobility and/or respiratory support, at which point hazard ratios for mortality sourced from the literature were applied.[18]
- As the majority of participants in the PROPEL trial had not yet progressed to more severe health states, protocol-driven EQ-5D-5L-derived utility data were deemed not suitable for informing the utility of individuals who required invasive respiratory support or a combination of mobility and respiratory support. There is a lack of data in the literature reporting utilities for the full range of health states in LOPD progression. Accordingly, a vignette study was conducted by Amicus in line with the DSU best practice recommendations to estimate utilities (EQ-5D-5L) across the spectrum of disease severities, in line with the model health states.[127]

- The variation in resource use across each health state was determined by clinical opinion and aligned with the recent NICE appraisal of avalglucosidase alfa where possible (TA821).[2, 125] Appropriate UK sources of unit costs were used for cost inputs in the model.

Cost-effectiveness results

- Over a lifetime time horizon in the base case of the model, treatment with cipaglucosidase alfa in combination with miglustat (when provided with the proposed confidential PAS) in adults with LOPD was associated with cost-savings of [redacted] per person and a QALY gain of [redacted] QALYs per person, meaning that cipaglucosidase alfa in combination with miglustat was dominant vs. alglucosidase alfa.
- The sensitivity analyses demonstrated the robustness of the base case model inputs and assumptions; in the base case PSA, cipaglucosidase alfa in combination with miglustat was associated with an estimated [redacted] probability of being cost-effective vs. alglucosidase alfa at a WTP threshold of £20,000/QALY. Across all scenario analyses, cipaglucosidase alfa in combination with miglustat remained dominant vs. alglucosidase alfa.

B.3.1 Published cost-effectiveness studies

An SLR was conducted in June 2022 to identify published cost-effectiveness studies in adults with Pompe disease from a global perspective. The population of this SLR was selected to be more inclusive than the population described in the decision problem (adults with LOPD) to ensure that no relevant publications were missed.

A total of [redacted] articles were identified from the searches, of which [redacted] papers relevant to cost-effectiveness were identified for full text review. Ultimately, one article potentially relevant to the UK setting met the eligibility criteria and was included in the review (Table 40). Full details of the search strategy and the complete results are presented in Appendix G.

Table 40: Summary of published economic evaluations included in the economic SLR

Study	Country and perspective	Summary of model	Participant population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in the UK
Kanters 2017[128] Study population overlapped with populations reported in Kanters 2011[129], Kanters 2015a[130], Kanters 2015b[131], Kuperus 2017[132], Kuperus 2018[133]	Dutch societal perspective	Cost-utility study • Patient-level simulation, following a double-loop model structure used to represent heterogeneity in clinical presentation and parameter uncertainty • The model compared two treatments: ST and ERT (+ ST) • A lifetime time horizon was used in the base case analyses • Survival probabilities were derived from an international dataset with observational data of individuals with Pompe disease • A previously developed conceptual model	• The baseline characteristics of 90 people with Pompe disease were included in the cost-effectiveness analyses • Age at first visit: 49.1 years (range: 23.0, 75.0 years) • Disease duration (since diagnosis): 7.7 years (range: 0.0, 27.6 years) • Female: 48% • Residual enzyme activity (in fibroblasts): 12.0% (range: 0.5, 19.9%) • Wheelchair use: 31% • Ventilation	• Scenario 1: no extrapolation of survival gains • ERT: 12.57 • ST: 10.53 • Difference [95% CI]: 2.04 [1.30, 2.57] • Scenario 2: extrapolated survival gains • ERT: 14.85 • ST: 10.60 • Difference [95% CI]: 4.26 [1.77, 6.62]	• Scenario 1: no extrapolation of survival gains • ERT: €6,795,495 • ST: €329,105 • Difference [95% CI]: €6,466,827 [€5,686,402, €7,340,316] • Scenario 2: extrapolated survival gains • ERT: €7,879,226 • ST: €324,967 • Difference [95% CI]: €7,554,844 [€6,885,851, €8,210,521]	• Scenario 1: no extrapolation of survival gains • ERT: €3,167,914 [95% CI: €2,348,946, €5,485,622] • Scenario 2: extrapolated survival gains • ERT: €1,774,390 [95% CI: €1,164,826, €4,159,592]	• The study was performed from a Dutch societal perspective, which makes it less relevant to UK decision making • The population included consisted of adults with Pompe disease, including adults with LOPD which aligns with the decision problem

Study	Country and perspective	Summary of model	Participant population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in the UK
		for adult Pompe disease, connecting clinical parameters with quality of life was used to obtain estimates for an individual's quality of life • Drug costs were based on Q2W infusions and were sourced via bottom-up research; other healthcare costs were retrieved from health economic questionnaires. For valuation, reference prices were used from the Dutch costing manual • Both healthcare utilisation costs (including informal care) and productivity costs were estimated using two GLM models • Effects were	use: 27% • Period at risk in ST survival analysis: 3.5 years (range: 0.0–8.9 years) • Period at risk in ERT survival analysis: 3.4 years (0.2–8.4 years)				

Study	Country and perspective	Summary of model	Participant population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in the UK
		discounted using a discount rate of 1.5%; costs were discounted at 4.0%, as recommended by the Dutch pharmacoeconomic guidelines • Costs were expressed in 2014 euros					

Abbreviations: CI: confidence interval; ERT: enzyme replacement therapy; GLM: generalised linear model; ICER: incremental cost-effectiveness ratio; Q2W: every other week; QALY: quality-adjusted life year; SLR: systematic literature review; ST: supportive treatment; UK: United Kingdom.

B.3.2 Economic analysis

A single economic evaluation identified in LOPD used a patient-level simulation model to compare the efficacy of ERT vs. conventional therapy from a Dutch societal perspective. Due to the paucity of relevant economic evaluations in LOPD, previous evaluations in IOPD were also considered. Two identified economic evaluations in IOPD have been conducted that used a Markov model structure over a lifetime time horizon to estimate the cost-effectiveness of ERT vs. conventional therapy.[134-136] The health states within these models were based upon the severity of symptoms (none, mild or severe) or whether individuals experienced treatment-related complications. One further patient-level simulation model in IOPD, comparing the efficacy of ERT to supportive treatment, was also identified.[128, 137] However, none of these models incorporated the primary, nor secondary, outcomes from the PROPEL clinical trial (i.e. 6MWD and FVC, respectively); outcomes which are used to determine Pompe disease progression within UK clinical practice (as confirmed by expert opinion and described further in Section B.3.3.2). In light of this, and in order to improve on previous modelling approaches and incorporate health states reflective of disease progression, a *de novo* economic model was developed to estimate the cost-effectiveness of cipaglucosidase alfa in combination with miglustat for the treatment of LOPD.

B.3.2.1 Population

The population addressed in this submission, and in particular in the economic analysis, is adults with LOPD. This population aligns with the NICE final scope, the full anticipated marketing authorisations for cipaglucosidase alfa in combination with miglustat and the population in the pivotal PROPEL trial. The baseline characteristics for individuals entering the model are summarised in Section B.3.3.

B.3.2.2 Model structure

Choice of model and rationale

A patient-level simulation model capturing respiratory and mobility support was produced to estimate the cost-effectiveness of cipaglucosidase alfa in combination with miglustat for the treatment of LOPD over a lifetime time horizon. The model was built in alignment with the patient-level simulation modelling Decision Support Unit Technical Support Document.[77]

A patient-level simulation was considered most appropriate because it allows respiratory and mobility progression to be captured separately. Additionally, a patient-level simulation model provides more granularity than a Markov model as it facilitates the estimation of 6MWD and FVC % predicted scores for each individual over annual increments. These continuous variables were then used to allocate individuals to each particular health state over the model time horizon, as described above. In contrast, the change in 6MWD and FVC % predicted in a Markov model would have remained fixed (i.e. the rate of change would have been the same for all individuals) and this would not have reflected the true variation observed in LOPD, as confirmed by clinical experts.[125]

The framework of the utilised patient-level simulation model incorporates health states to ensure accessibility of the model and enable a straightforward economic analysis. [redacted]. It was thus determined that this simple approach using clinically validated disease states was the most appropriate modelling approach.

The approach of using a patient-level simulation model using 6MWD and FVC % predicted to inform transition between health states (Section B.3.2.2) was previously accepted by the committee in the NICE appraisal of avalglucosidase alfa (TA821).[2, 125] The avalglucosidase alfa model utilised a Discretely Integrated Condition Event (DICE) simulation approach, which the Evidence Review Group (ERG) noted was overly complex due to the need for a substantial amount of patient-level data, and also difficult to interpret and validate.[2] The approach used in this submission is considered less complex and easier to interpret, maintaining the intuitiveness of a patient-level simulation model.

Model structure and health states

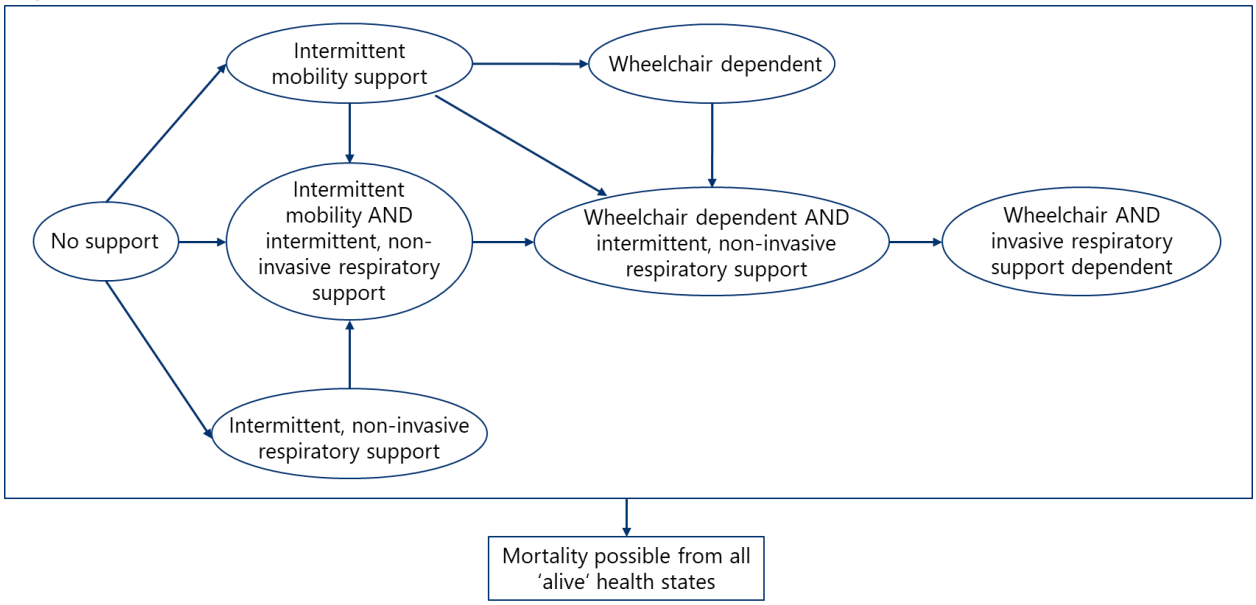
The model structure was based upon the pivotal PROPEL Phase III trial for cipaglucosidase alfa in combination with miglustat. The primary and key secondary outcomes, the 6MWD and FVC % predicted, were used to determine the deterioration of mobility and respiratory function, respectively; this approach is coincidentally also in line with the modelling approach for avalglucosidase alfa that was accepted by the committee (TA821).[2] As described in Section B.2.3.1, such outcomes are often presented as a percentage of predicted normal values to

account for age, height, weight and sex.[138, 139] In a series of patient advisory boards, individuals with Pompe disease and carers noted the relevance and importance of mobility and pulmonary function in their daily lives, supporting the use of 6MWD and FVC % predicted as endpoints and markers of disease progression in the model (Section B.2.6.1).

Defining health states based on the requirement for respiratory and/or mobility support was another aspect of the approach accepted by the committee appraising avalglucosidase alfa (TA821).[2]

As shown in Figure 21, seven 'alive' health states were ultimately defined based on the level of mobility and/or respiratory support required. One deceased state was also included, which could be transitioned to from all health states. Expert opinion from a group of UK consultants and nurses at specialist centres for Pompe disease validated that these health states capture the natural history of LOPD, as seen in UK clinical practice.[4]

Figure 21: Schematic of model structure



All individuals receiving non-invasive ventilation received intermittent respiratory support, and all individuals receiving invasive ventilation were ventilator-dependent.

Progression through the model

Progression through health states in the model, as shown in Figure 21, was defined by 6MWD and FVC % predicted, which is in line with the model for avalglucosidase alfa (TA821).[2] To model the decline in 6MWD and FVC % predicted, each individual that enters the patient-level simulation model is randomly assigned with probabilistically sampled values for Baseline 6MWD and FVC % predicted, based on pre-defined distributions from PROPEL. That individual is then assigned a probabilistically sampled rate of change in 6MWD and FVC % predicted, again based on relevant distributions, described further in Section B.3.3.

Transitions between health states were then determined by clinically validated pre-specified threshold values in 6MWD and FVC % predicted scores (Table 43), respectively. In alignment with clinical advice, it was assumed that there was no consistent association between the rate of mobility and respiratory decline: an individual experiencing a fast rate of mobility decline would not necessarily also have a fast rate of respiratory decline.[23-25, 125] For example, if their 6MWD

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. Depending on whether that individual also required respiratory support or not, the individual would then enter the relevant intermittent mobility support health state. Further information on the thresholds applied is provided in Section B.3.3.

As described above, it was assumed that the 6MWD and FVC % predicted scores of each individual would deteriorate beyond Year 3 due to the progressive nature of the disease, as confirmed by expert opinion.[125] The annual changes in 6MWD and FVC % predicted were simulated independently using a normal distribution for 30,000 individuals over a lifetime time horizon. It should be noted that a test of result stability was undertaken to determine the appropriate number of individuals to run through the model, using the methods outlined within the patient-level simulation modelling Decision Support Unit Technical Support Document.[77] This test indicated that 30,000 individuals was the lowest number that could be run through the model to achieve stability. These outcomes were then used to inform the transition of individuals between the health states within the model using a one-year cycle. A one-year cycle length was chosen to align with the primary outcome measure in the PROPEL trial (change from Baseline to Week 52) and the reporting of the change in 6MWD/FVC % predicted within the literature, which often reports an annual change. A one-year cycle length was also accepted by the committee in the NICE appraisal of avalglucosidase alfa (TA821).[2, 125] Furthermore, this cycle length was considered sufficient to capture meaningful changes in individual utility over the course of the disease.

It was also possible for individuals to transition to the deceased state from any of the 'alive' health states. The mortality rate was assumed to be equivalent to general population norms (based on age and gender) until individuals required any level of mobility and/or respiratory support, at which point hazard ratios for mortality were applied.[140] For more information, please see Section B.3.3.

Clinical expert opinion also advised that individuals with LOPD would not receive invasive ventilation until they were dependent on respiratory support.[125] Therefore, intermittent respiratory support would always comprise of non-invasive ventilation and dependence on respiratory support would always comprise of invasive ventilation. Expert opinion also validated the assumption that individuals with LOPD could not transition to the invasive, respiratory support dependent state without also requiring mobility support as a result of the amount of equipment that would need to be carried.[4]

The average number of years an individual spent in each health state was estimated over a lifetime horizon of the model. The HRQoL and economic costs were aggregated for each cohort of 30,000 simulated individuals to estimate the cost-effectiveness of cipaglucosidase alfa in combination with miglustat compared to alglucosidase alfa.

Summary of additional model features

Table 41 summarises features of the economic analysis as compared to the evaluation of avalglucosidase alfa (TA821),[2] including justifications for the approach taken. Half-cycle correction was applied at the point of determining health state occupancy to account for the fact that the transition of individuals between health states could occur at any point within the cycle.

Although alglucosidase alfa is included as a comparator, it was commissioned directly by NHS and does not have publicly available appraisal documentation.

Table 41: Features of the economic analysis

Factor	Avalglucosidase alfa evaluation	Current evaluation	
	TA821[2]	Chosen values	Justification
Time horizon	A lifetime time horizon (60 years) was applied in the analysis for LOPD	Lifetime	The cost-effectiveness of cipaglucosidase alfa in combination with miglustat was estimated over a lifetime time horizon to account for the lifelong, progressive nature of LOPD. Furthermore, this approach aligns with the NICE reference case which states that a lifetime time horizon should be used when an intervention will impact costs and outcomes over an individual's lifetime.[141] Details of the scenario analyses completed with 20-year time horizons are presented in Section B.3.10.3.
Cycle length	One-year	One-year	A one-year cycle length was chosen to align with the primary outcome measure in the PROPEL trial (change from Baseline to Week 52) and the reporting of the change in 6MWD/FVC % predicted within the literature, which often reports an annual change. This cycle length was also considered sufficient to capture meaningful changes in utility over the course of the disease. A one-year cycle length was also accepted by the committee in the NICE appraisal of avalglucosidase alfa (TA821).[2, 125]
Perspective	NHS and PSS	NHS and PSS	In line with the NICE reference case.[141] Details of the scenario analysis completed from a societal perspective are presented in Section B.3.10.3.
Discount rate (costs and benefits)	3.5%	3.5%	In line with the NICE reference case.[141] Details of the scenario analyses using a 0% and 1.5% discount rate is presented in Section B.3.10.3.
Long-term treatment effects	Efficacy inputs were split into two categories: short- and long-term	Efficacy inputs were split into two categories: initial annual change from Baseline and subsequent annual change	Efficacy inputs were split into two categories: initial annual change from Baseline to Year 3 and subsequent annual change from Year 3 onwards. A summary of sources used to inform initial and subsequent annual change is presented in Table 44. The model utilised an assumed [redacted] of long-term disease progression with cipaglucosidase alfa

			in combination with miglustat relative to alglucosidase alfa, which was validated by clinical experts.[4] Details of the scenario [redacted] of progression compared to alglucosidase alfa and [redacted] are also presented in Section B.3.10.3.
Source of utilities	EQ-5D data from the COMET trial informed HRQoL in the model	Vignette study conducted by Amicus	As the majority of participants in the PROPEL trial had not yet progressed to more severe health states, protocol-driven EQ-5D-5L-derived utility data were deemed not suitable for informing the utility of health states that required invasive respiratory support or a combination of mobility and respiratory support. In the absence of relevant data in the literature, health state vignettes were developed and valuated using EQ-5D in line with the NICE hierarchy of HRQoL evidence,[142] NICE reference case[141] and DSU best practice recommendations,[127] to estimate utilities across the spectrum of disease severities, in line with the model health states. Details of the scenario analyses completed using values from the literature and values calculated using a TTO assessment using the same vignettes are presented in Section B.3.10.3.
Source of costs	It was assumed that when an individual reached a ventilation-related milestone, a one-off cost was discretely accumulated, followed by the accumulation of annual costs. It was assumed that when an individual reached a wheelchair-related milestone, a one-off cost was incurred, which was followed by an annual maintenance cost. Individuals were assumed to require a new wheelchair every five years. The unit cost for alglucosidase alfa was assumed based on the BNF with no PAS applied. It was assumed for both treatments that individuals would initially receive three treatment infusions within a hospital and then all individuals would	Health state costs were informed by clinical opinion and aligned with the avalglucosidase alfa NICE appraisal (TA821) where possible. Treatment acquisition and administration costs were limited to the cost of the medicines. It was assumed that individuals would initially receive three treatment infusions within a hospital and then all individuals would	Only one study reporting both cost and resource use data associated with Pompe disease was identified. This was a cohort study including prospective and retrospective clinical, and patient-reported data on 54 individuals with a diagnosis of LOPD across treatment centres in England .[21] However, this study reported resource use for an average person with Pompe disease and was not stratified by particular health states. For this reason, the variation in resource use across each health state was determined by clinical opinion and aligned with the avalglucosidase alfa NICE appraisal (TA821)[2] where possible.

	receive treatment from home. Home administration could occur with or without a nurse to reconstitute the drug.	receive treatment from home. Home administration could occur with or without a nurse to reconstitute the drug.	It was assumed that individuals were not required to take any concomitant treatments alongside cipaglucosidase alfa in combination with miglustat or alglucosidase alfa. For the purposes of the model, expert opinion indicated that individuals would receive treatment from home after the first three administrations in hospital (Section B.3.5.1).

Abbreviations: BNF: British National Formulary; HRQoL: health-related quality of life; LOPD: late-onset Pompe disease; PAS: patient access scheme; PSS: personal social services; TA: technology appraisal; TTO: time trade off.

B.3.2.3 Intervention technology and comparators

In line with Section B.1.3, cipaglucosidase alfa in combination with miglustat is anticipated to be prescribed [redacted]

As noted in Section B.3.2.1, the population included in this cost-effectiveness analysis was all adults with a confirmed diagnosis of LOPD, in line with the population in the pivotal trial (PROPEL).

In line with Section 3 of the decision problem, the primary comparator included in this analysis is alglucosidase alfa. Additionally, avalglucosidase alfa (Nexviadyme®) received MHRA marketing authorisation in July 2022[1] and NICE guidance in August 2022 (TA821; with a 30-day implementation period)[2] for the treatment of Pompe disease of all ages. However, at the time of this submission, Amicus understands that avalglucosidase alfa is not commercially available in the UK for the treatment of adults with LOPD,[2, 3] and is hence not considered established practice. It would be unlikely to be widely used in clinical practice for some time even after it were to become commercially available. Hence, avalglucosidase alfa is not considered established practice nor a primary comparator for this appraisal. As agreed upon with the EAG during the NICE decision problem meeting, and in line with the NICE final scope, the approach has been taken to include avalglucosidase alfa in a scenario analysis for completeness (please see Section B.3.10.3 for further details).

In line with the intended indication, it has been assumed treatment with cipaglucosidase alfa in combination with miglustat will continue through an individual's lifetime.[8, 14]

B.3.3 Clinical parameters and variables

B.3.3.1 Population characteristics

All baseline characteristics (as presented in Table 42) were based upon the average values of the total population of the PROPEL study. Where available, data at Baseline were obtained from the clinical study report from the PROPEL study.[5] However, the average weight and height of individuals were calculated using individual patient-level data from the PROPEL trial.[5] All baseline characteristics were varied using a normal distribution within each simulation of the model.

Table 42: Baseline characteristics

Baseline demographics	Mean	Standard deviation	Impact on the model
Percentage male	[redacted]	[redacted]	Gender distribution used to convert 6MWD outcomes to 6MWD % predicted (as described in Section B.3.3).
Average age (years)	[redacted]	[redacted]	Age distribution used to convert 6MWD outcomes to 6MWD % predicted (as described in Section B.3.3). The health state utilities were age-adjusted (as described in Section B.3.4.4).

Average weight (kg)	[redacted]	[redacted]	Weight distribution used to convert 6MWD outcomes to 6MWD % predicted (as described in Section B.3.3).
Average height (cm)	[redacted]	[redacted]	Height distribution used to convert 6MWD outcomes to 6MWD % predicted (as described in Section B.3.3).
Baseline 6MWD	[redacted]	[redacted]	Baseline 6MWD was used to calculate the initial and annual subsequent changes from Baseline (as described in Section B.3.3.3).
Baseline FVC % predicted (sitting)	[redacted]	[redacted]	Baseline FVC % predicted (sitting) was used to calculate the initial and annual subsequent changes from Baseline (as described in Section B.3.3.3).

Abbreviations: 6MWD: six-minute walk distance; FVC: forced vital capacity; NA: not applicable.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[5]

B.3.3.2 Health state transitions

As described in Section B.3.2.2, the 6MWD and FVC % predicted were used to determine the deterioration of mobility and respiratory function, respectively, throughout the model time horizon. The committee evaluating avalglucosidase alfa (TA821) accepted this approach to capture the progressive nature of the disease.[2]

Specific threshold values were used to determine the point at which a person's 6MWD and FVC % predicted outcomes had declined to the point where they would require mobility and/or respiratory support. In alignment with clinical advice,[125] it was assumed that there was no consistent association between the rate of mobility and respiratory decline.[23-25, 125] For example, a person experiencing a fast rate of mobility decline would not necessarily have a fast rate of respiratory decline.

Due to a lack of precedence and published literature to determine values that would be representative of clinical practice, thresholds were informed and validated by UK Pompe disease clinical experts.[4, 125] As summarised in Table 43, Pompe disease clinical experts advised that a person with LOPD would need to use intermittent mobility support once they were unable to walk more than [redacted] metres within the 6MWT. Furthermore, in line with PROPEL inclusion criteria, experts indicated individuals would become wheelchair dependent once their 6MWD fell below 75 metres (indicating the individual was not stable enough to walk unassisted for six minutes).[4]

The model assumes that individuals require intermittent respiratory support once their FVC % predicted falls below [redacted]. This conservative assumption is based on the mid-point between the previous NICE evaluation (HST 3) in Duchenne Muscular Dystrophy,[143] which indicated that individuals require ventilation assistance once their FVC % predicted falls below [redacted], and evidence from idiopathic pulmonary fibrosis, which indicated individuals require ventilation support once their FVC % predicted falls below [redacted].[144] It was also assumed that individuals would become dependent on respiratory support once their FVC % predicted fell to [redacted] These assumptions were validated by clinical experts during a clinical advisory board, where it was noted that the [redacted] threshold may be conservative.[4]

Table 43: Thresholds required for support

Support	Threshold	Source
Intermittent mobility support (max m in 6MWT)	[redacted]	Clinical opinion[4]
Wheelchair dependent (max m in 6MWT)	[redacted]	
Intermittent respiratory support (FVC % predicted)	[redacted]	HST 3,[143] TA 504[144] and assumptions[4]
Respiratory support dependent (FVC % predicted)	[redacted]	Clinical opinion[4]

Abbreviations: 6MWT: six-minute walk test; HST: highly specialised technology; FVC: forced vital capacity; TA: technology assessment.

B.3.3.3 Treatment efficacy

There is a scarcity of data to inform the long-term efficacy of treatments for Pompe disease. Previous long-term evidence indicates that adults with Pompe disease will experience a gradual deterioration in FVC % predicted over time whilst receiving alglucosidase alfa.[25] However, Semplicini *et al*. showed that there was an initial improvement in 6MWD % predicted over the first 2.2 years of treatment with alglucosidase alfa, followed by a steady annual reduction.[25] To reflect this, efficacy inputs were split into two categories: initial annual change from Baseline to Year 3 and subsequent annual change from Year 3 onwards. A similar, split approach to modelling long-term treatment efficacy was taken in the model for avalglucosidase alfa (TA821).[2] This approach was also validated by clinical experts during an advisory board.[4] Details of external validation of the model are presented in Section B.3.13.

Table 44: Summary of sources informing initial and subsequent annual change

Treatment	Initial annual change		Subsequent annual change
	Baseline to Year 1	Year 1 to Year 3	
Cipaglucosidase alfa in combination with miglustat	PROPEL[5]	ATB200-02[55]	Assumed [redacted] rate of progression than with alglucosidase alfa[4]
Alglucosidase alfa	PROPEL[5]	Semplicini *et al*.[25]	Semplicini *et al*.[25]

The 6MWD is commonly reported as either an absolute value (m) or % predicted (calculated based upon gender, weight, age and height by comparing against population norm values). The efficacy data informing the long-term ambulatory progression of individuals receiving alglucosidase alfa were presented as 6MWD % predicted. To ensure consistency within the model, absolute 6MWD outcomes from PROPEL were converted to % predicted values using a validated algorithm.[139] The algorithm provides a reference equation to compare the 6MWD outcome obtained by an adult with LOPD to a healthy adult of the same gender, weight, height and age. The coefficients used to inform this reference equation are presented in Table 45. These coefficients were converted into a weighted average using the gender distribution presented in Table 42 ([redacted]% male).[5]

Table 45: Coefficients used to convert absolute 6MWD (m) to 6MWD % predicted

Coefficient	Male	Female	Weighted average
Height	7.57	2.11	[redacted]
Age	5.02	5.78	[redacted]

Weight	1.76	2.29	[redacted]
Metre conversion	-309	+667	[redacted]

Abbreviations: 6MWD: six-minute walk distance.
Source: Enright *et al*.[139]

Initial annual change from Baseline

It was anticipated that the probability (and/or magnitude) of initial improvement (from Baseline to Year 3), and rate of progression, would differ depending on the treatment received (i.e. rates of decline in 6MWD and FVC % predicted were treatment-specific). For example, the PROPEL trial provides evidence that individuals receiving treatment with cipaglucosidase alfa in combination with miglustat would experience a greater improvement in 6MWD and FVC % predicted than with alglucosidase alfa from Baseline to Year 1 (Section B.2.6.1). The ATB200-02 study was then used to inform the change from Year 1 to Year 2, and Year 2 to Year 3 (Table 44). The assumptions for initial annual change from Baseline used in the base case analysis for cipaglucosidase alfa in combination with miglustat and alglucosidase alfa are presented below (Table 46 and Table 47, respectively). Scenario analyses were conducted including avalglucosidase alfa as a comparator, using data from the ITC (Section B.2.9).[99] Results from the analyses are presented in Section B.3.10.3.

Cipaglucosidase in combination with miglustat

The base case analysis directly uses clinical trial data to inform initial annual change with cipaglucosidase alfa in combination with miglustat.[57] Data from PROPEL were used to inform treatment progression associated with cipaglucosidase alfa in combination with miglustat from Baseline to Year 1.[5] Data from the 36-month data cut-off of ATB200-02 were used to inform the change from Year 1 to Year 2, and Year 2 to Year 3.[57] Data reporting on the effectiveness (change in 6MWD and FVC % predicted) of cipaglucosidase alfa in combination with miglustat beyond Year 3 (through Month 48) have recently become available, however were not available early enough to be implemented in the model. As some results from ATB200-02 were stratified by ERT-naïve and ERT-experienced groups rather than in the total population, a weighted average of data from these groups was used to inform the change between Years 1 and 3.[57]

The initial annual changes in 6MWD and FVC % predicted with cipaglucosidase alfa in combination with miglustat for each year from Baseline to Year 3 are provided in Table 46.

Table 46: Initial annual change from Baseline to Year 3 in individuals receiving cipaglucosidase alfa in combination with miglustat

Outcome	Time period	N	Mean	SE	Source
6MWD (absolute m)	Baseline to Year 1	85	20.79	4.639	PROPEL[5]
	Year 1 to Year 2		[redacted]	[redacted]	Weighted average of data in the ERT-naïve and ERT-experienced treatment groups from ATB200-02[57]
	Year 2 to Year 3		[redacted]	[redacted]	
FVC % predicted	Baseline to Year 1	84	-0.9%	0.007	PROPEL[5]

	Year 1 to Year 2		[redacted]	[redacted]	Weighted average of data in the ERT-naïve and ERT-experienced treatment groups from ATB200-02[57]
	Year 2 to Year 3		[redacted]	[redacted]	

Abbreviations: 6MWD: six-minute walk distance; ERT: enzyme replacement therapy; FVC: forced vital capacity; SE: standard error.

Alglucosidase alfa

The change in FVC % predicted and 6MWD associated with alglucosidase alfa in the total population from Baseline to Year 1 was informed by data from PROPEL.[5] The change from Year 1 to Year 3, was informed by a prospective analysis from the French Pompe Registry published in 2020 (Semplicini *et al.*).[25] This study was considered the most appropriate source of FVC % predicted and 6MWD data for alglucosidase alfa as it was a large real-world evidence study, conducted over the longest maximum follow-up period identified which reported such data (reporting on 197 individuals with LOPD up to 2019, over a maximum follow-up of 13 years). Individuals receiving alglucosidase alfa within this study had a Baseline 6MWD % predicted of 56.95 (SD: 23.64) and a Baseline FVC % predicted of 64.38 (SD: 26.22).[25] Data for 6MWD and FVC % predicted with alglucosidase alfa for each year from Baseline to Year 3 are provided in Table 47.

Table 47: Initial annual change from Baseline to Year 3 in individuals receiving alglucosidase alfa

Outcome		Time period	N	Mean	SE	Source
6MWD	Absolute value	Baseline to Year 1	37	7.24	6.621	PROPEL[5]
	% predicted	Year 1 to Year 2	158	1.4%	0.003	Semplicini *et al*.[25]
		Year 2 to Year 3		1.4%	0.003	
FVC % predicted		Baseline to Year 1	37	-3.95%	0.008	PROPEL[5]
		Year 1 to Year 2	158	-0.9%	0.001	Semplicini *et al*.[25]
		Year 2 to Year 3		-0.9%	0.001	

Abbreviations: 6MWD: six-minute walk distance; FVC: forced vital capacity; SE: standard error.

Subsequent annual change

Data were only available to estimate the deterioration beyond Year 3 for individuals with LOPD receiving alglucosidase alfa. Following the application of the initial improvement, constant but varied rates of progression throughout the time horizon of the model were assumed for each treatment due to data limitations beyond Year 3, as described below.

Alglucosidase alfa

The change from Year 3 onwards in FVC % predicted and 6MWD associated with alglucosidase alfa in the total population was informed by the French Pompe Registry (Semplicini *et al.*), in line with the model used in the NICE appraisal for avalglucosidase alfa (TA821; for which alglucosidase alfa was a comparator).[2, 25] Semplicini *et al*. found that there was an initial improvement in 6MWD % predicted over the first 2.2 years of treatment with alglucosidase alfa, followed by a steady annual reduction for the remainder of the time horizon.[25] Data from the

same study indicated a gradual deterioration in FVC % predicted over time from Baseline.[25] To reflect this, an assumption was applied in the model where by individuals treated with alglucosidase will experience an annual decline in FVC % predicted and 6MWD after Year 3.[25]

Semplicini *et al.* reported that two types of linear mixed-effects models were fitted to assess the trends in FVC % predicted and 6MWD over time, respectively. Firstly, a mixed linear model with a constant slope was fitted, which included a single phase (i.e. the trend was fixed for the full time horizon). The authors judged that a single-phase model was more appropriate for outcomes related to FVC % predicted. The outcomes from this single-phase model indicated that there was no initial increase in FVC % predicted, and instead a steady decline was observed from treatment initiation (average annual reduction in FVC % predicted of -0.9% [95% CI: -0.8%, -1.0%]).[25]

Secondly, Semplicini *et al.* reported 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. The authors judged that a two-phase model better described the changes observed for the 6MWD % predicted within the study. Based on the fitting of this two-phase model, the data indicated that there was an initial improvement of 1.4% in 6MWD % predicted over the first 2.2 years of treatment with alglucosidase alfa, followed by a steady annual reduction of -2.3% (± 0.6%) for the remainder of the time horizon.[25]

More information on the linear mixed-effects models is provided in Semplicini *et al*.[25] Efficacy data used to inform the FVC % predicted and 6MWD values for alglucosidase alfa beyond Year 3 are reported in Table 48.

Table 48: Efficacy inputs for alglucosidase alfa beyond Year 3

Outcome	N	Mean annual predicted percentage change	SE	Source
6MWD % predicted	158	-2.3%	0.003	Semplicini *et al*.[25] (single-phase mixed linear model with a constant slope)
FVC % predicted	158	-0.9%	0.001	Semplicini *et al*.[25] (two-phase mixed linear discontinuous model)

Abbreviations: 6MWD: six-minute walk distance; FVC: forced vital capacity; SE: standard error.

Cipaglucosidase alfa in combination with miglustat

Data reporting on the effectiveness (change in 6MWD and FVC % predicted) of cipaglucosidase alfa in combination with miglustat beyond Year 3 (through Month 48) has recently become available however was not available early enough to use in the model. Subsequent annual change was informed by alglucosidase alfa long-term data.[25] The model assumes a [redacted] long-term disease progression with cipaglucosidase alfa co-administered with miglustat relative to alglucosidase alfa. Details of the scenario analyses assuming a [redacted] progression compared to alglucosidase alfa and [redacted] progression are presented in Section B.3.10.3.

Mortality

The mortality rate was assumed to be equivalent to UK general population norms (based on age and gender) until individuals required mobility and/or respiratory support.[140] An international observational study conducted to assess the impact of alglucosidase alfa on survival in individuals with LOPD between 2002 and 2011 was used to inform the increased risk of mortality associated with LOPD.[18] A hazard ratio, estimated from a primary multivariable Cox proportional hazard regression model based on the international observational study, was used to determine the increased risk of death incurred by individuals once mobility and/or respiratory support was required as presented in Table 49.

Table 49: Hazard ratios (mortality compared to general population mortality)

Health state	Hazard ratio	95% CI
No wheelchair use or respiratory support[a]	1.00	NA
Intermittent mobility support	2.87	(0.98, 8.36)
Wheelchair dependent	2.87	(0.98, 8.36)
Intermittent, non-invasive respiratory support	2.05	(0.62, 6.77)
Intermittent mobility and intermittent, non-invasive respiratory support	5.32	(2.25, 12.56)
Wheelchair dependent and intermittent, non-invasive respiratory support	5.32	(2.25, 12.56)
Wheelchair and invasive respiratory support dependent	5.32	(2.25, 12.56)

[a]When implemented into the model, this health state was divided into three "sub-states" based on the number of years alive from treatment initiation, to align with the utility values presented in Kanters *et al.*[129] The values for all three substates were the same and aligned with the single health state hazard presented in this table.
Abbreviations: CI: confidence interval; NA: not applicable.
Source: Gungor et al.[145]

It should be noted that the data from this study did not differentiate between mortality rates for non-invasive, intermittent and invasive, dependent respiratory support states.[18]

B.3.4 Measurement and valuation of health effects

B.3.4.1 HRQoL data from clinical trials

Clinicians confirmed that more severe health states are associated with a significant decrement to quality of life, predominantly due to an inability to perform usual activities and anxiety associated with reliance on invasive respiratory support (Section B.1.3.2). However, ATB200-02 did not collect EQ-5D data, as is characteristic of Phase I/II trials. In line with guidance received from NICE scientific advice, EQ-5D-5L were collected in PROPEL. However, the data from the PROPEL trial were not suitable for informing the utility of health states that required invasive respiratory support or a combination of mobility and respiratory support, because most included participants had not yet reached the later severe health states over the 52-week trial follow-up period. Therefore, EQ-5D data from clinical trials investigating cipaglucosidase alfa in combination with miglustat were not used in the economic model.

B.3.4.2 HRQoL studies

An SLR was conducted in June 2022 to identify published HRQoL and utility studies in adults with Pompe disease from a global perspective. The population of this SLR was selected to be more inclusive than the population described in the decision problem (adults with LOPD) to ensure that no relevant publications were missed.

A total of [redacted] articles were identified from the searches, of which [redacted] papers relevant to HRQoL and utilities were identified for full text review. Ultimately, 22 articles met the eligibility criteria and were included in the review.

The results of the HRQoL and utilities SLR are presented in Table 50; full details of the search strategy and the complete results are presented in Appendix H.

Whilst EQ-5D utility values were reported for 5 studies, no studies provided utilities for the full range of health states in the progression of LOPD in order to inform the model.[129, 146]

Table 50: Summary of published HRQoL/utility studies included in the economic SLR

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr>
<td>Aslan 2016[147]</td>
<td><u>Population</u>
People with LOPD

Median age = 59.0 (IQR: 35.5–60.7)

<u>Intervention</u>
IV infusions of alglucosidase alfa 20 mg/kg BW

Patients also undertook an IMT programme

<u>Recruitment</u>
Patients recruited from hospital neurology department</td>
<td><u>Country</u>
Turkey

<u>Setting</u>
Hospital – single centre

<u>Study Type</u>
Prospective interventional cohort</td>
<td>N=9

Evaluable HRQoL data was available for n=8 patients</td>
<td>HRQoL reported for patients at baseline, and after 8 weeks of IMT

Utilities for specific AEs NR</td>
<td>A validated Turkish version of the NHP (a generic quality of life tool scored from 0–100) was used to assess HRQoL</td>
<td>
<table>
<tr><th rowspan="2">NHP sub-scores</th><th colspan="2">Median (IQR)</th><th rowspan="2">p value</th></tr>
<tr><th>Baseline (n=8)</th><th>After IMT (8 weeks later) (n=8)</th></tr>
<tr><td>Energy level</td><td>80.4 (37.4 – 100.0)</td><td>88.0 (36.8–100.0)</td><td>1.0</td></tr>
<tr><td>Pain</td><td>33.8 (1.4–69.2)</td><td>20.5 (3.2–39.5)</td><td>0.7</td></tr>
<tr><td>Emotional reaction</td><td>15.7 (10.5–35.2)</td><td>5.2 (0.0–39.6)</td><td>0.3</td></tr>
<tr><td>Sleep</td><td>26.2 (3.1–55.9)</td><td>38.8 (0.0–73.8)</td><td>0.9</td></tr>
<tr><td>Social isolation</td><td>22.5 (22.1–69.8)</td><td>0.0 (0.0–16.9)</td><td>0.02</td></tr>
<tr><td>Physical abilities</td><td>82.8 (53.8–100.0)</td><td>77.8 (44.1–86.11)</td><td>0.2</td></tr>
</table>
p value measured using Wilcoxon signed-rank test.
</td>
<td><u>Consistency with NICE reference case</u>
EQ-5D was not used in this study, which is the NICE preferred measure of HRQoL in adults

NHP is not a preference based measure, and as a result, utility values were not reported. HRQoL data were reported directly by participants.

<u>Relevance to decision problem</u>
The study took place in Turkey, which may not be directly relevant to clinical practice in the UK

HRQoL information is not stratified by health states and therefore not suitable</td>
</tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>for use in a cost-effectiveness model
The included population consisted of people with Pompe disease which includes the patient population (adults with LOPD) and so is relevant to the decision problem</td></tr>
<tr><td>Boentert 2015[148]</td><td><u>Population</u>
Adults (≥18 years) with Pompe disease

Mean age = 47.6 (SD: ±15.0; Range: 18–75)

<u>Intervention</u>
Individuals were either receiving ERT, had not yet started ERT, or had discontinued the use of ERT

Individuals were either receiving HV or not</td><td><u>Country</u>
Germany

<u>Setting</u>
Hospital – multicentre

<u>Study type</u>
Cross-sectional – observational cohort</td><td>N=65

Evaluable HRQoL data were available for n=65 individuals

n=60 individuals were receiving ERT at Baseline

n=2 had not yet started ERT

n=3 individuals had discontinued ERT use

n=32 individuals</td><td>HRQoL reported for individuals at a single point in time

One individual was bed-bound, 16 individuals were wheelchair-bound, 11 individuals used one or two sticks, 22 individuals specified difficulties walking freely, and 15 reported walking</td><td>Self-reported HRQoL outcomes were collected using SF-36[b]</td><td><table><tr><th>SF-36 component</th><th>All individuals (N=65)</th><th>HV (n=32)</th><th>No HV (n=33)</th><th>p value</th></tr><tr><td>PCS subscale (SF-36)</td><td>32.1 (9.9)</td><td>28.9 (9.0)</td><td>36.1 (9.1)</td><td><0.001</td></tr><tr><td>MCS subscale (SF-36)</td><td>49.6 (9.2)</td><td>49.1 (9.9)</td><td>50.2 (8.5)</td><td>n.s.</td></tr></table>Spearman’s correlation coefficient used for associations between continuous variables.</td><td><u>Consistency with NICE reference case</u>

EQ-5D was not used in this study, which is the NICE preferred measure of HRQoL in adults

SF-36 is not a preference based measure, and as a result, utility values were not reported. HRQoL data were reported directly by individuals

<u>Relevance to decision problem</u>

The study took place in Germany, which may not be directly</td></tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td><u>Recruitment</u>
Individuals recruited from specialised outpatient clinics at three neuromuscular centres in Germany</td><td></td><td>were receiving HV</td><td>without major problems
Utilities for specific AEs NR</td><td></td><td></td><td>relevant to clinical practice in the UK

HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model
The included population consisted of adults with Pompe disease which includes the population (adults with LOPD) and so is relevant to the decision problem</td></tr>
<tr><td>Boentert 2016[149]</td><td><u>Population</u>
Adults (≥18 years old) with Pompe disease

Mean age = 51.9 (SD: 15.3)

<u>Intervention</u>
NIV was started in individuals with SDB

Individuals were either receiving ERT, treatment-naïve, or had</td><td><u>Country</u>
Germany

<u>Setting</u>
Hospital – single centre

<u>Study type</u>
Prospective observational</td><td>N=22

Evaluable HRQoL data were available for n=22 patients

n=14 patients were receiving ERT for 1–34 months prior to first evaluation

n=5 patients were treatment-naïve</td><td>HRQoL reported for patients prior to receiving NIV, and post-ERT treatment (if receiving ERT)

All patients were ambulatory

Utilities for specific AEs NR</td><td>HRQoL data were collected using SF-36[b]</td><td><table><tr><th>SF-36 component</th><th>All patients (n=22)</th><th>SDB Absent (n=7)</th><th>SDB Present (n=15)</th><th>p value</th></tr><tr><td>SF-36 PCS</td><td>33.3 (8.6)</td><td>38.8 (11.6)</td><td>30.8 (5.6)</td><td><0.05</td></tr><tr><td>SF-36 MCS</td><td>47.6 (7.5)</td><td>55.2 (3.1)</td><td>44.0 (6.1)</td><td><0.001</td></tr></table></td><td><u>Consistency with NICE reference case</u>
EQ-5D was not used in this study, which is the NICE preferred measure of HRQoL in adults

SF-36 is not a preference based measure, and as a result, utility values were not reported. HRQoL data were reported directly by patients</td></tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td>discontinued ERT

<u>Recruitment</u>
Participants recruited from a sleep laboratory</td><td></td><td>n=3 patients had discontinued ERT use 6–22 months prior to first evaluation</td><td></td><td></td><td></td><td><u>Relevance to decision problem</u>

The study took place in Germany, which may not be directly relevant to clinical practice in the UK

HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model

The included population consisted of adults with Pompe disease which includes the patient population (adults with LOPD) and so is relevant to the decision problem</td></tr>
<tr><td>Favejee 2015[150]</td><td><u>Population</u>
Adults with Pompe disease (≥18 years) mildly affected) receiving ERT for ≥1 year who were not dependent on a ventilator and/or walking device were</td><td><u>Country</u>
The Netherlands

<u>Setting</u>
Hospital – single centre

<u>Study type</u>
Prospective –</td><td>N=25

Evaluable HRQoL data was available for n=23 patients</td><td>HRQoL reported for patients at Baseline, and after 12 weeks of exercise training

Utilities for specific AEs NR</td><td>The R-PAct[c] and SF-36[b] scales were used to assess patient HRQoL</td><td><table><tr><th>HRQoL measure</th><th colspan="2">Median (range)</th><th>p value</th></tr><tr><th></th><th>Before training</th><th>After 12 weeks training</th><th></th></tr><tr><td>Motor function (R-PAct)</td><td>70 (54−100)</td><td>70 (48−89)</td><td>0.49</td></tr></table></td><td><u>Consistency with NICE reference case</u>
EQ-5D was not used in this study, which is the NICE preferred measure of HRQoL in adults

SF-36 and R-PAct are not preference based measures, and as a result, utility values were not</td></tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td>eligible to participate

Median age = 46.0 years (range: 20−71)

<u>Intervention</u>
Specific ERT NR, patients participated in a 12-week exercise programme

<u>Recruitment</u>
Patients recruited at Centre for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Centre, Rotterdam</td><td>interventional cohort</td><td></td><td></td><td></td><td><table><tr><td>SF-36 PCS</td><td>40 (24−53)</td><td>42 (21−51)</td><td>0.86</td></tr><tr><td>SF-36 MCS</td><td>56 (25−69)</td><td>59 (34−69)</td><td>0.06</td></tr></table>For the difference before and after training test Chi-square for proportions and Wilcoxon signed-rank test for continuous data used.</td><td>reported. HRQoL data were reported directly by patients

<u>Relevance to decision problem</u>
The study took place in the Netherlands, which may not be directly relevant to clinical practice in the UK
HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model
The included population consisted of adults with Pompe disease which includes the patient population (adults with LOPD) and so is relevant to the decision problem</td></tr>
<tr><td>Gungor 2013[151]</td><td><u>Population</u>
Adult patients with Pompe disease (≥18 years)</td><td><u>Country</u>
Germany and the Netherlands

<u>Setting</u></td><td>N=124

Evaluable HRQoL data were available for n=124 patients</td><td>HRQoL reported for patients at a single time point

Utilities for</td><td>HRQoL was assessed using the SF-36[b] and HADS scales in patient with and without pain</td><td><table><tr><th rowspan="2">HRQoL measure</th><th colspan="2">Median (range)</th><th rowspan="2">p value</th></tr><tr><th>Pain (n=56)</th><th>No pain (n=68)</th></tr></table></td><td><u>Consistency with NICE reference case</u>
EQ-5D was not used in this study, which is the NICE preferred measure of HRQoL in adults. SF-36 and</td></tr>
</table>

Source	Description of population, any interventions, recruitment method and follow-up time	Country, setting and study type	Sample size, response rate	Health states and adverse events	Methods of elicitation, valuation and mapping	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation[a]
	Median age = 53 years (range: 19−74) Intervention Specific ERT NR At time of survey, 81% of patients were receiving ERT, 12% had never received it and 6% had discontinued treatment Recruitment Patients recruited through German patient organisation or the Erasmus MC University Medical Centre, Rotterdam. Data were collected between June	Community Study type Cross-sectional – observational cohort	Response rate: 63% for Dutch patients, 56% for German patients	specific AEs NR	The HADS scale is used to assess the occurrence of anxiety and depression where lower scores represent better function.	SF-36 PCS: 30 (11−45) vs 35 (17−58), <0.001 SF-36 MCS: 54 (29−74) vs 58 (29−71), 0.049 HADS depression: 5 (0−13) vs 2 (0−14), 0.005 HADS anxiety: 5 (0−15) vs 3 (0−12), 0.003 *p* values represent difference between patients with and without pain at time of survey assessed with the Chi-square test and the Mann–Whitney U test for discrete and continuous data, respectively.	HADS are not preference based measures, and as a result, utility values were not reported. HRQoL data were reported directly by patients Relevance to decision problem The study took place in Germany and the Netherlands, which may not be directly relevant to clinical practice in the UK HRQoL information is not stratified by health states, and data is stratified by pain (with no overall values available). Therefore this is not suitable for use in a cost-effectiveness model The included population consisted of adults with Pompe disease which includes the patient population (adults with LOPD) and so is

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td>2011−November 2012</td><td></td><td></td><td></td><td></td><td></td><td>relevant to the decision problem</td></tr>
<tr><td>Gungor 2016[152]</td><td><u>Population</u>
Adults (≥18 years) with Pompe disease

Median age (at the start of ERT) = 50 (Range: 24–76)

<u>Intervention</u>
Patients were required to have been receiving ERT for ≥6 months

<u>Recruitment</u>
Patients from the Netherlands, the US, the UK, Germany and Australia were recruited through the national patient organisations, as were a smaller number of patients from other countries</td><td><u>Country</u>
International

<u>Setting</u>
Community

<u>Study type</u>
Prospective – observational cohort</td><td>N=174

Evaluable HRQoL data were available for n=174 patients</td><td>HRQoL reported for patients pre-ERT, 0–2 years during ERT and >2 years during ERT

At the start of ERT, 52% of patients used a wheelchair and 48% required ventilatory support

Utilities for specific AEs NR</td><td>HRQoL was assessed using SF-36[b]</td><td><table><tr><th>HRQoL measure</th><th colspan="3">Follow-up time intervals (years)</th></tr><tr><th></th><th>Pre-ERT Mean sp/y (95% CI)</th><th>0–2 years during ERT Mean sp/y (95% CI)</th><th>>2 years during ERT Mean sp/y (95% CI)</th></tr><tr><td colspan="4">SF-36 summary scores</td></tr><tr><td>PCS</td><td>-0.73 (-1.07; -0.39)**</td><td>1.49 (0.76; 2.21)**</td><td>-0.15 (-0.43; 0.13)</td></tr><tr><td>MCS</td><td>0.16 (-0.25; 0.57)</td><td>1.03 (-0.07; 2.13)</td><td>0.02 (-0.41; 0.46)</td></tr><tr><td colspan="4">SF-36 domain scores</td></tr><tr><td>Physical functioning</td><td>-1.80 (-2.41;-1.19)**</td><td>1.81 (0.38; 3.23)*</td><td>0.68 (0.12; 1.25)*</td></tr><tr><td>Role physical</td><td>-1.20 (-2.92; 0.52)</td><td>9.18 (5.83; 12.53)**</td><td>2.46 (1.15; 3.77)**</td></tr><tr><td>Bodily pain</td><td>-2.10 (-3.01; -1.19)**</td><td>0.76 (-1.39; 2.92)</td><td>-1.96 (-2.95; -0.98)**</td></tr><tr><td>General health</td><td>0.19 (-0.49; 0.87)</td><td>5.22 (3.58; 6.86)**</td><td>0.81 (0.13; 1.49)*</td></tr><tr><td>Vitality</td><td>-0.44 (-1.11; 0.24)</td><td>4.10 (2.44; 5.76)**</td><td>1.43 (0.77; 2.09)**</td></tr><tr><td>Social functioning</td><td>-0.74 (-1.66; 0.18)</td><td>2.11 (-0.16; 4.39)</td><td>0.41 (-0.54; 1.35)</td></tr><tr><td>Role emotional</td><td>-0.15 (-1.64; 1.34)</td><td>3.05 (-1.06; 7.16)</td><td>0.19 (-1.15; 1.53)</td></tr></table></td><td><u>Consistency with NICE reference case</u>
EQ-5D was not used in this study, which is the NICE preferred measure of HRQoL in adults. SF-36 is not a preference based measure, and as a result, utility values were not reported. HRQoL data were reported directly by patients

<u>Relevance to decision problem</u>
HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model

The included population consisted of adults with Pompe disease which includes the patient population (adults with LOPD) and so is relevant to the decision problem</td></tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td>Dutch patients were also recruited through the Centre for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Centre, Rotterdam, the national referral centre for Pompe disease</td><td></td><td></td><td></td><td></td><td><table><tr><td>Mental health</td><td>0.13 (-0.60; 0.87)</td><td>2.09 (0.57; 3.61)**</td><td>0.29 (-0.37; 0.95)</td></tr></table>*Change is significant at the 0.05 level, **Change is significant at the 0.01 level. Data shown are mean changes in score points per year (sp/y) as calculated by univariate analysis using mixed model ANOVA.</td><td></td></tr>
<tr><td>Hagemans 2004[153]</td><td><u>Population</u>
Adults with LOPD (≥18 years)

Mean age (SD) = 48.1 (13.5)

<u>Intervention</u>
NR

<u>Recruitment</u>
Patients recruited through patient organisations</td><td><u>Country</u>
Australia, Germany, the Netherlands, UK and US

<u>Setting</u>
Community

<u>Study type</u>
Prospective observational cohort</td><td>N=237

n=214 patients (all ≥18 years) responded to survey

Evaluable HRQoL data were available for n=210 patients

Response rate: 100% in Australia, 77% in Germany,</td><td>HRQoL reported for all patients at Baseline

Utilities for specific AEs NR</td><td>HRQoL was assessed using the SF-36 scales[b]</td><td><table><tr><th>SF-36 sub-scores (overall – all countries)</th><th>Mean Baseline (n=210)</th><th>p value</th></tr><tr><td>Physical functioning</td><td>24.3</td><td>0.75</td></tr><tr><td>Role functioning-physical</td><td>46.2</td><td>0.44</td></tr><tr><td>Bodily pain</td><td>65.0</td><td>0.21</td></tr><tr><td>General health</td><td>48.2</td><td>0.73</td></tr><tr><td>Vitality</td><td>44.8</td><td>0.01</td></tr><tr><td>Social functioning</td><td>65.6</td><td>0.52</td></tr><tr><td>Role functioning-emotional</td><td>73.9</td><td>0.03</td></tr><tr><td>Mental health</td><td>70.2</td><td>0.04</td></tr></table></td><td><u>Consistency with NICE reference case</u>
EQ-5D was not used in this study, which is the NICE preferred measure of HRQoL in adults. SF-36 is not a preference based measure, and as a result, utility values were not reported. HRQoL data were reported directly by patients

Relevance to decision problem</td></tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td>affiliated with the IPA</td><td></td><td>70% in the Netherlands, 58% in the UK, and 44% in the US</td><td></td><td></td><td>p value for between-country differences (analysis of variance).

<table>
<tr><th>SF-36 sub-scores (Australia)</th><th>Mean
Baseline (n=14)</th></tr>
<tr><td>Physical functioning</td><td>25.0</td></tr>
<tr><td>Role functioning-physical</td><td>46.2</td></tr>
<tr><td>Bodily pain</td><td>61.1</td></tr>
<tr><td>General health</td><td>46.5</td></tr>
<tr><td>Vitality</td><td>43.6</td></tr>
<tr><td>Social functioning</td><td>58.9</td></tr>
<tr><td>Role functioning-emotional</td><td>56.4</td></tr>
<tr><td>Mental health</td><td>67.1</td></tr>
</table>

<table>
<tr><th>SF-36 sub-scores (Germany)</th><th>Mean
Baseline (n=48)</th></tr>
<tr><td>Physical functioning</td><td>23.8</td></tr>
<tr><td>Role functioning-physical</td><td>52.3</td></tr>
<tr><td>Bodily pain</td><td>67.4</td></tr>
<tr><td>General health</td><td>48.6</td></tr>
<tr><td>Vitality</td><td>48.1</td></tr>
<tr><td>Social functioning</td><td>69.9</td></tr>
<tr><td>Role functioning-emotional</td><td>86.8</td></tr>
<tr><td>Mental health</td><td>64.7</td></tr>
</table>

<table>
<tr><th>SF-36 sub-scores (The Netherlands)</th><th>Mean
Baseline (n=51)</th></tr>
<tr><td>Physical functioning</td><td>26.0</td></tr>
<tr><td>Role functioning-physical</td><td>49.5</td></tr>
<tr><td>Bodily pain</td><td>70.9</td></tr>
<tr><td>General health</td><td>50.8</td></tr>
</table></td><td>HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model
The included population consisted of adults with LOPD which is relevant to the decision problem</td></tr>
</table>

Source	Description of population, any interventions, recruitment method and follow-up time	Country, setting and study type	Sample size, response rate	Health states and adverse events	Methods of elicitation, valuation and mapping	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation[a]
						Vitality 51.5 Social functioning 67.8 Role functioning-emotional 79.3 Mental health 75.5 **SF-36 sub-scores (UK)** / **Mean Baseline (n=20)** Physical functioning 17.5 Role functioning-physical 32.0 Bodily pain 62.9 General health 51.3 Vitality 37.2 Social functioning 63.2 Role functioning-emotional 68.4 Mental health 66.8 **SF-36 sub-scores (US)** / **Mean Baseline (n=77)** Physical functioning 25.3 Role functioning-physical 44.0 Bodily pain 60.9 General health 45.8 Vitality 40.6 Social functioning 63.3 Role functioning-emotional 67.3 Mental health 71.5	

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr>
<td>Harfouche 2020[154]</td>
<td><u>Population</u>
Adults (≥18 years), with a confirmed diagnosis of LOPD by molecular or enzymatic testing

Mean age = 51 years (Range: 18–79)

<u>Intervention</u>
ERT for a duration of 1–12 years at time of study

<u>Recruitment</u>
Patients recruited during routine clinical visit to the Duke University Pompe Clinical and Research Programme</td>
<td><u>Country</u>
US

<u>Setting</u>
Hospital – single centre

<u>Study type</u>
Cross-sectional observational</td>
<td>N=30</td>
<td>HRQoL reported for patients at a single point in time. All patients were ambulatory

Utilities for specific AEs NR</td>
<td>Five PROMIS questionnaires were administered which covered pain interference on ADL and HRQoL, upper extremity mobility, fatigue, physical function and breathlessness

Higher scores for pain interference, fatigue and breathlessness represent lower impacts on health, whilst higher scores for upper extremity and physical function represent lower impact impacts of health.</td>
<td>
<table>
<tr><th>PROMIS questionnaire</th><th>n</th><th>Mean (SD)</th><th>Median (range)</th></tr>
<tr><td>Pain interference</td><td>29</td><td>16.72 (9.180)</td><td>16.00 (8–35.0)</td></tr>
<tr><td>Fatigue</td><td>29</td><td>23.48 (8.671)</td><td>22.00 (8–40.0)</td></tr>
<tr><td>Upper extremity</td><td>30</td><td>25.10 (7.174)</td><td>25.00 (13–35.0)</td></tr>
<tr><td>Physical function</td><td>30</td><td>71.47 (±13.761)</td><td>70.50 (44–100)</td></tr>
<tr><td>Dyspnoea</td><td>30</td><td>24.96 (±19.099)</td><td>22.80 (0–67.6)</td></tr>
</table>
</td>
<td><u>Consistency with NICE reference case</u>
EQ-5D was not used in this study, which is the NICE preferred measure of HRQoL in adults. PROMIS is not a preference based measure, and as a result, utility values were not reported. HRQoL data were reported directly by patients

<u>Relevance to decision problem</u>
The study took place in the US, which may not be directly relevant to clinical practice in the UK
HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model
The included population consisted of adults with LOPD which is relevant to the decision problem</td>
</tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr>
<td>Hu 2021[155]</td>
<td><u>Population</u>
Patients with Pompe disease who could complete a questionnaire or have their primary caregiver complete the questionnaire on their behalf

Age: NR

<u>Intervention</u>
Patients did not receive ERT

<u>Recruitment</u>
Patients recruited through their doctors, online and offline platforms and networks, and rare diseases organisations inviting patients to participate</td>
<td><u>Country</u>
China

<u>Setting</u>
Community

<u>Study type</u>
Cross-sectional observational study</td>
<td>N=4</td>
<td>HRQoL reported for patients at a single time point

Utilities for specific AEs NR</td>
<td>EQ-VAS and EQ-5D-3L were used to assess HRQoL</td>
<td>Mean EQ-VAS: 52.0 ± SD:12.9

<table>
<tr><th>EQ-5D-3L outcomes</th><th>n (%)</th></tr>
<tr><td rowspan="2">Mobility</td><td>0 (0.0)</td></tr>
<tr><td>4 (100.0)</td></tr>
<tr><td rowspan="2">Self-care</td><td>2 (50.0)</td></tr>
<tr><td>2 (50.0)</td></tr>
<tr><td rowspan="2">Usual activities</td><td>1 (25.0)</td></tr>
<tr><td>3 (75.0)</td></tr>
<tr><td rowspan="2">Pain/discomfort</td><td>1 (25.0)</td></tr>
<tr><td>3 (75.0)</td></tr>
<tr><td rowspan="2">Anxiety/depression</td><td>1 (25.0)</td></tr>
<tr><td>3 (75.0)</td></tr>
</table>
</td>
<td><u>Consistency with NICE reference case</u>
EQ-5D was used in this study, which is the NICE preferred measure of HRQoL in adults, however no preference data was applied and therefore no utility data were generated. Some HRQoL data could were reported by patients' caregivers which also deviates from NICE reference case

<u>Relevance to decision problem</u>
The study took place in China, which may not be directly relevant to clinical practice in the UK

HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model</td>
</tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>The age of patients with Pompe disease was not reported so it is not clear if patients were adults (as in the decision problem)</td></tr>
<tr><td>Jones 2020[156]</td><td><u>Population</u>
Adults with LOPD (≥18 years) receiving ERT for ≥26 weeks who were able to complete a home-based RMT regimen were eligible to participate

Mean (SD) age: RMT group = 53.2 (12.7) years

Sham-RMT group = 46.6 years (13.9)
<u>Intervention</u>
Specific ERT NR,
patients participated in a 12-week</td><td><u>Country</u>
US

<u>Setting</u>
Hospital - single centre

<u>Study type</u>
Prospective - interventional cohort</td><td>N=28

Evaluable HRQoL data were available for n=22 patients</td><td>HRQoL reported for patients at Pre-test and Post-test after 12 weeks of exercise training and after 3 and 6 months detraining

Utilities for specific AEs NR</td><td>The R-PAct scale[c] was used to assess HRQoL</td><td>
<table>
<tr><th rowspan="2">Change in R-PAct</th><th colspan="2">Mean (SD)</th><th rowspan="2">p value</th></tr>
<tr><th>RMT (n=12)</th><th>Sham-RMT (n=10)</th></tr>
<tr><td>Pre-test to post-test</td><td>−0.1 (2.1)</td><td>−0.1 (2.3)</td><td>0.9733</td></tr>
</table>
Difference between treatment arms measured with Wilcoxon test.
<table>
<tr><th rowspan="2">Change in R-PAct</th><th colspan="2">Mean (SD)</th><th rowspan="2">p value</th></tr>
<tr><th>RMT (n=11*)</th><th>Sham-RMT (n=10)</th></tr>
<tr><td>Post-test to 3-month follow up</td><td>−0.2 (1.3)</td><td>−0.9 (1.9)</td><td>0.5251</td></tr>
</table>
<table>
<tr><th rowspan="2">Change in R-PAct</th><th colspan="2">Mean (SD)</th><th rowspan="2">p value</th></tr>
<tr><th>RMT (n=11*)</th><th>Sham-RMT (n=10)</th></tr>
</table>
</td><td><u>Consistency with NICE reference case</u>
EQ-5D was not used in this study, which is the NICE preferred measure of HRQoL in adults. R-PAct is not a preference based measure, and as a result, utility values were not reported. HRQoL data were reported directly by patients

<u>Relevance to decision problem</u>
The study took place in the US, which may not be directly relevant to clinical practice in the UK
HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model</td></tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td>RMT programme

<u>Recruitment</u>
NR</td><td></td><td></td><td></td><td></td><td><table><tr><td>Post-test to 6-month follow up</td><td>−0.5 (2.0)</td><td>0.2 (1.3)</td><td>0.5439</td></tr></table>p values represent difference between patient in RMT and sham-RMT groups. Difference between treatment arms measured with Wilcoxon test. *One patient in the RMT group withdrew from the study after the Post-test visit.</td><td>Patients had LOPD and were all adults (≥18 years old) which is aligned to the decision problem</td></tr>
<tr><td>Kanters 2011[129]

Study population overlapped with populations reported in Kanters 2015a[130], Kanters 2015b[131], Kanters 2017[128], Kuperus 2017[132], Kuperus 2018[133]</td><td><u>Population</u>
Adult patients (≥18 years old) with Pompe disease who completed ≥1 questionnaire and were receiving only supportive care at the time of study

Mean age at Baseline (SD) = 51.0 (12.2)

<u>Intervention</u>
No intervention, patients received only supportive care

<u>Recruitment</u></td><td><u>Country</u>
The Netherlands

<u>Setting</u>
Hospital – single centre

<u>Study type</u>
Prospective – observational cohort</td><td>N=80

Evaluable HRQoL data were available for n=72 patients</td><td>HRQoL reported for patients at a single time point

51% of patients required ambulatory support at the time of the study, and 28% required respiratory support

Specific utilities were reported for patients requiring ambulatory or respiratory support and stratified by</td><td>The EQ-5D instrument was used to assess HRQoL and calculate utilities

As EQ-5D utility scores were estimated using a Dutch tariff, the utilities derived can be regarded as a valuation of the specific health state by the Dutch general population</td><td><table><tr><th>Patient category</th><th>Number (%)</th><th>Mean EQ-5D utility score (SD)</th></tr><tr><td>Overall (SD; min-max)</td><td>72</td><td>0.72 (0.18; 0.17–1.00)</td></tr><tr><td colspan="3">Disease duration</td></tr><tr><td>≤5 years</td><td>31 (43)</td><td>0.74 (0.15)</td></tr><tr><td>6–15 years</td><td>18 (25)</td><td>0.70 (0.16)</td></tr><tr><td>>15 years</td><td>22 (31)</td><td>0.69 (0.23)</td></tr><tr><td>Ambulatory support</td><td>37 (51)</td><td>0.67 (0.21)</td></tr><tr><td>Respiratory support</td><td>20 (28)</td><td>0.61 (0.26)</td></tr></table></td><td><u>Consistency with NICE reference case</u>

EQ-5D utility values are reported, which is aligned with NICE preference

HRQoL data were reported directly by patients

<u>Relevance to decision problem</u>

The study took place in the Netherlands, which may not be directly relevant to clinical practice in the UK

Utility values were stratified by ‘earlier’ health states but did not include information for ‘later’</td></tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td>Patients recruited from the Centre for Lysosomal and Metabolic Diseases at Erasmus MC University Medical Centre, Rotterdam

Data were collected between January 2005–October 2009</td><td></td><td></td><td>disease duration</td><td></td><td></td><td>health states in the model for cipaglucosidase alfa in combination with miglustat

The included population consisted of adults with Pompe disease which includes the patient population (adults with LOPD) and so is relevant to the decision problem</td></tr>
<tr><td>Kanters 2015a[130]

Study population overlapped with populations reported in Kanters 2011[129], Kanters 2015b[131], Kanters 2017[128], Kuperus 2017[132], Kuperus 2018[133]</td><td><u>Population</u>
Adult Dutch patients (≥18 years old) with Pompe disease who were able to complete the EQ-5D every 3-6 months and the SF-36 annually

Mean age = 49.4 years

<u>Intervention</u></td><td><u>Country</u>
The Netherlands

<u>Setting</u>
Hospital – single centre

<u>Study type</u>
Prospective – observational cohort</td><td>N=80

Evaluable HRQoL data was available for n=80 patients</td><td>HRQoL reported for patients at Baseline and at multiple follow up time point (patients completed an average of 3.9 (range 1–9) questionnaires each and the average time between the first and</td><td>The EQ-5D and SF-36[b] scales were used to assess patient HRQoL</td><td><table><tr><th rowspan="2">SF-6D score</th><th colspan="6">Frequency distribution of SF-6D score by dimension</th></tr><tr><th>Physical functioning</th><th>Role limitations</th><th>Social functioning</th><th>Pain</th><th>Mental health</th><th>Vitality</th></tr><tr><td>1</td><td>1 (1%)</td><td>30 (38%)</td><td>31 (39%)</td><td>18 (23%)</td><td>22 (28%)</td><td>3 (4%)</td></tr><tr><td>2</td><td>7 (9%)</td><td>28 (35%)</td><td>23 (29%)</td><td>15 (19%)</td><td>22 (28%)</td><td>21 (26%)</td></tr><tr><td>3</td><td>25 (31%)</td><td>2 (3%)</td><td>20 (25%)</td><td>34 (43%)</td><td>29 (36%)</td><td>34 (43%)</td></tr><tr><td>4</td><td>28 (35%)</td><td>20 (25%)</td><td>5 (6%)</td><td>10 (13%)</td><td>7 (9%)</td><td>19 (24%)</td></tr></table></td><td><u>Consistency with NICE reference case</u>

EQ-5D utility values are reported, which is aligned with NICE preference

HRQoL data were reported directly by patients

<u>Relevance to decision problem</u>

The study took place in the Netherlands, which may not be</td></tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr>
<td></td>
<td>NR

<u>Recruitment</u>
Patients recruited from the Erasmus MC University Medical Centre, Rotterdam between January 2005–August 2011</td>
<td></td>
<td></td>
<td>last observation was 2.8 years (range 0.5–6.3)

Utilities for specific AEs NR</td>
<td></td>
<td>
<table>
<tr><td>5</td><td>15 (19%)</td><td>NR</td><td>1 (1%)</td><td>3 (4%)</td><td>0 (0%)</td><td>3 (4%)</td></tr>
<tr><td>6</td><td>4 (5%)</td><td>NR</td><td>NR</td><td>0 (0%)</td><td>NR</td><td>NR</td></tr>
</table>
<table>
<tr><th rowspan="2">EQ-5D Score</th><th colspan="5">Frequency distribution of EQ-5D scores by dimension</th></tr>
<tr><th>Mobility</th><th>Self-care</th><th>Usual activities</th><th>Pain/ discomfort</th><th>Anxiety/ depression</th></tr>
<tr><td>1</td><td>17 (21%)</td><td>57 (71%)</td><td>23 (29%)</td><td>27 (34%)</td><td>62 (78%)</td></tr>
<tr><td>2</td><td>61 (76%)</td><td>17 (21%)</td><td>54 (68%)</td><td>52 (65%)</td><td>18 (23%)</td></tr>
<tr><td>3</td><td>2 (3%)</td><td>6 (8%)</td><td>3 (4%)</td><td>1 (1%)</td><td>0 (0%)</td></tr>
</table>
<table>
<tr><th>Descriptive statistics</th><th>EQ-5D utility</th><th>SF-6D utility</th></tr>
<tr><td>Mean (SD)</td><td>0.670 (0.201)</td><td>0.699 (0.092)</td></tr>
<tr><td>Median (range)</td><td>0.691 (−0.043–1.000)</td><td>0.687 (0.497–0.894)</td></tr>
<tr><td>Correlation (Spearman)</td><td>0.591</td><td>NR</td></tr>
</table>
<table>
<tr><th colspan="6">Discriminative properties of EQ-5D and SF-6D utilities</th></tr>
<tr><th></th><th>n</th><th>Mean EQ-5D</th><th>p value</th><th>Mean SF-6D</th><th>p value</th></tr>
</table>
</td>
<td>directly relevant to clinical practice in the UK

Utility values were not stratified by health states and therefore not suitable for use in a cost-effectiveness model

The included population consisted of adults with Pompe disease which includes the patient population (adults with LOPD) and so is relevant to the decision problem</td>
</tr>
</table>

Source	Description of population, any interventions, recruitment method and follow-up time	Country, setting and study type	Sample size, response rate	Health states and adverse events	Methods of elicitation, valuation and mapping	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation[a]

Overall	80	0.670	NA	0.699	NA	
Wheelchair (yes)	24	0.533	0.0014	0.666	0.046	
Wheelchair (no)	56	0.729		0.713		
Ventilation (yes)	18	0.593	0.332	0.688	0.458	
Ventilation (no)	61	0.693		0.704		

p values represent differences between categories (wheelchair or ventilation) (Mann-Whitney test)

Utility	n	Mean change	Effect size

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><th></th><th></th><th>EQ-5D</th><th>SF-6D</th><th>EQ-5D</th><th>SF-6D</th></tr>
<tr><td>Decreased pulmonary function (-7.206 FVC % predicted)</td><td>35</td><td>0.026</td><td>−0.003</td><td>0.152</td><td>−0.039</td></tr>
<tr><td>Increased pulmonary function (-5.967 FVC % predicted)</td><td>35</td><td>0.054</td><td>0.020</td><td>0.255</td><td>0.198</td></tr>
<tr><td>Decreased muscle strength (-4.545 MRC*)</td><td>25</td><td>0.020</td><td>−0.019</td><td>0.179</td><td>−0.240</td></tr>
<tr><td>Increased muscle strength (-4.392 MRC*)</td><td>41</td><td>0.055</td><td>0.026</td><td>0.239</td><td>0.286</td></tr>
</table>
*MRC scores did not change for four patients, and these patients were not included in the analyses with respect to MRC.
</td><td></td></tr>
<tr><td>Kanters 2015b[131]

Study population overlapped with</td><td><u>Population</u>
Adult Dutch patients (≥18 years old) with</td><td><u>Country</u>
The Netherlands</td><td>N=79

Evaluable HRQoL data</td><td>HRQoL reported for patients at a</td><td>The SF-36[b] and EQ-5D scales were used to assess</td><td>
<table>
<tr><th>Utility</th><th colspan="4">Patient characteristics at Baseline</th></tr>
<tr><th></th><th>n</th><th>Mean</th><th>Min</th><th>Max</th></tr>
<tr><td>EQ-5D VAS</td><td>49</td><td>65.0</td><td>30.0</td><td>95.0</td></tr>
</table>
</td><td><u>Consistency with NICE reference case</u>

EQ-5D utility values are reported, which is</td></tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr>
<td>populations reported in Kanters 2011[129], Kanters 2015a[130], Kanters 2017[128], Kuperus 2017[132], Kuperus 2018[133]</td>
<td>Pompe disease who were untreated at the time of observation were included

Mean age (min–max) = 49.3 years (23.0–72.6)

<u>Intervention</u>
No intervention

<u>Recruitment</u>
Patients recruited from the Erasmus MC University Medical Centre, Rotterdam between January 2005–August 2011</td>
<td><u>Setting</u>
Hospital – single centre

<u>Study type</u>
Prospective – observational cohort</td>
<td>was available for n=79 patients</td>
<td>single time point

Utilities for specific AEs NR</td>
<td>HRQoL and utilities, respectively

Health perceptions are measured using the EQ-5D

VAS measures health perception: higher scores represent better perceived health status
The EQ-5D was used to derive utilities, using a Dutch tariff</td>
<td><table><tr><td>SF-36 MCS</td><td>60</td><td>53.8</td><td>24.2</td><td>74.0</td></tr><tr><td>SF-36 PCS</td><td>60</td><td>35.4</td><td>17.6</td><td>53.3</td></tr><tr><td>EQ-5D Utility</td><td>50</td><td>0.736</td><td>0.201</td><td>1.000</td></tr></table></td>
<td>aligned with NICE preference

HRQoL data were reported directly by patients

<u>Relevance to decision problem</u>

The study took place in the Netherlands, which may not be directly relevant to clinical practice in the UK

Utility values were not stratified by health states and therefore not suitable for use in a cost-effectiveness model

The included population consisted of adults with Pompe disease which includes the patient population (adults with LOPD) and so is relevant to the decision problem</td>
</tr>
<tr>
<td>Kanters 2017[128]

Study population overlapped with</td>
<td><u>Population</u>
Adult patients (≥ 18 years old) with</td>
<td><u>Country</u>
The Netherlands</td>
<td>N=82</td>
<td>NA; utility estimates were estimated by</td>
<td>Utilities were derived from the EQ-</td>
<td><table><tr><th>Utilities for ERT</th><th>ST</th><th>ERT</th><th>Difference</th><th>Difference 95% CI</th></tr></table></td>
<td><u>Consistency with NICE reference case</u></td>
</tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr>
<td>populations reported in Kanters 2011[129], Kanters 2015a[130], Kanters 2015b[131], Kuperus 2017[132], Kuperus 2018[133]</td>
<td>Pompe disease (including both ERT-treated and ERT-naïve patients)

Mean age = 49.1 (range: 23.0–75.0)

Intervention
ERT (as an add-on to ST)

Recruitment
Patients recruited from the national reference centre for Pompe disease</td>
<td>Setting
Hospital – single centre

Study type
Retrospective observational cohort</td>
<td></td>
<td>regression analysis overall rather than for health states</td>
<td>5D questionnaire

Dutch tariffs were used to calculate utilities</td>
<td>
<table>
<tr><th>and ST by Scenario</th><th></th><th></th><th></th><th></th></tr>
<tr><td>Scenario 1: no extrapolation of survival</td><td>0.42</td><td>0.45</td><td>0.03</td><td>0.02; 0.05</td></tr>
<tr><td>Scenario 2: extrapolation of survival</td><td>0.42</td><td>0.45</td><td>0.03</td><td>0.02; 0.05</td></tr>
</table>
</td>
<td>EQ-5D utility values are reported, which is aligned with NICE preference

HRQoL data were reported directly by patients

Relevance to decision problem

The study took place in the Netherlands, which may not be directly relevant to clinical practice in the UK

Utility values were stratified by survival scenarios with no overall values provided and therefore were not suitable for use in a cost-effectiveness model

The included population consisted of adults with Pompe disease which includes the patient population (adults with LOPD) and so is</td>
</tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>relevant to the decision problem</td></tr>
<tr><td>Kuperus 2017[132]

Study population overlapped with populations reported in Kanters 2015a[130], Kanters 2011[129], Kanters 2015b[131], Kanters 2017[128], Kuperus 2018[133]</td><td><u>Population</u>
Adult patients (≥18 years) with symptomatic Pompe disease (muscle weakness and/or reduced pulmonary function), who had not yet received ERT before enrolment in the study

Median age (at the start of ERT) = 52 (IQR: 20; range: 24–76)

<u>Intervention</u>
88 patients received 20 mg/kg of IV alglucosidase alfa BW

<u>Recruitment</u></td><td><u>Country</u>
The Netherlands

<u>Setting</u>
Hospital – single centre

<u>Study type</u>
Prospective – interventional cohort</td><td>N=102

Evaluable HRQoL data were available for n=102 patients (n=88 of these patients received ERT, n=14 contributed natural-course data only)</td><td>HRQoL reported for patients at 3–6 month intervals before and after start of ERT

On initiation of ERT, 32 patients were fully or partially wheelchair dependent, and 27 required mechanical ventilation

Utilities for specific AEs NR</td><td>HRQoL was assessed using the R-PAct scale[c] to determine the effect of Pompe disease on patient's ability to carry out daily life activities</td><td><table><tr><th>Years receiving ERT</th><th>Difference in R-PAct of patients on ERT relative to natural disease course</th><th>p value</th><th>Better than expected if untreated (%)[a]</th></tr><tr><td>0.5</td><td>+2.7</td><td><0.0001</td><td>80</td></tr><tr><td>1</td><td>+4.7</td><td><0.0001</td><td></td></tr><tr><td>5</td><td>+10.8</td><td>0.002</td><td></td></tr></table>Effect of ERT expressed in percentage points. Bonferroni corrections were applied to adjust for multiple testing: a value of p<0.006 was considered statistically significant using the F test.
[a]For patients who had been treated for <5 years, their last follow-up measurement was taken for comparison.

<table><tr><th>Scale</th><th>Difference in score of patients receiving ERT for 5 years, relative to Baseline</th><th>p value</th><th>Improved/ stable compared to Baseline (%)[a]</th></tr></table></td><td><u>Consistency with NICE reference case</u>

EQ-5D was not used in this study, which is the NICE preferred measure of HRQoL in adults. R-PAct is not a preference based measure, and as a result, utility values were not reported. HRQoL data were reported directly by patients

<u>Relevance to decision problem</u>

The study took place in the Netherlands, which may not be directly relevant to clinical practice in the UK

HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model</td></tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr>
<td></td>
<td>Patients recruited from the Centre for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Centre, Rotterdam between January 1st 2005–December 31st 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td>R-PAct</td><td>+3.6</td><td>0.004</td><td>59</td></tr>
</table>
<table>
<tr><td rowspan="2">Utility</td><td colspan="10">Change in R-PAct: patients receiving ERT for 5 years vs. natural disease course</td></tr>
<tr><td colspan="3">Sex</td><td colspan="3">Age at start of ERT (years)</td><td colspan="3">Disease duration (years)</td></tr>
<tr><td></td><td>Male</td><td>Female</td><td>p value</td><td><45</td><td>≥45</td><td>p value</td><td><15</td><td>≥15</td><td>p value</td></tr>
<tr><td>PAct</td><td>+22.4</td><td>+3.3</td><td>0.005</td><td>+13.7</td><td>+5.8</td><td>0.26</td><td>+16.0</td><td>-2.1</td><td>0.02</td></tr>
</table>
Values represent the difference between the observed values under treatment and those of the extrapolated natural disease course at the 5-year time-point, expressed in percentage points. p values represent the difference between subgroups. Bonferroni corrections were applied to adjust for multiple testing: a p value of p<0.006 was considered statistically significant using the F test.
</td>
<td>The included population consisted of adults with Pompe disease which includes the patient population (adults with LOPD) and so is relevant to the decision problem</td>
</tr>
<tr>
<td>Kuperus 2018[133]

Study population overlapped with populations reported in Kanters 2011[129], Kanters 2015a[130], Kanters 2015b[131], Kanters 2017[128], Kuperus 2017[132]</td>
<td><u>Population</u>
Adults (≥18 years) with Pompe disease with known genotypes and available DNA</td>
<td><u>Country</u>
The Netherlands

<u>Setting</u>
Hospital – single centre

<u>Study type</u></td>
<td>N=131

Evaluable HRQoL data (in the form of R-PAct) were only recorded for adults (n=NR)</td>
<td>HRQoL reported for patients at first visit and at start of ERT

Utilities for</td>
<td>HRQoL was assessed using R-PAct[c] to determine the effects of Pompe disease on patient's abilities to carry out</td>
<td>
<table>
<tr><td rowspan="2">Scale</td><td colspan="5">Genotype group</td></tr>
<tr><td>Total</td><td>II</td><td>DD</td><td>ID</td><td>p value</td></tr>
<tr><td>R-PAct (at first</td><td>54 (7–100)</td><td>58 (7–100)</td><td>50 (7–94)</td><td>55 (17–83)</td><td>ns</td></tr>
</table>
</td>
<td><u>Consistency with NICE reference case</u>

EQ-5D was not used in this study, which is the NICE preferred measure of HRQoL in adults. R-PAct is not a preference based measure, and as a result, utility values</td>
</tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td>Median age = NR

Intervention
112 patients had started ERT at the first visit

Recruitment
Patients were recruited from the Centre for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Centre, Rotterdam

Data were collected from January 1st1999–January 1st 2016</td><td>Prospective – observational</td><td></td><td>specific AEs NR</td><td>daily life activities</td><td>clinic visit)

II, DD and ID are the three different ACE genotypes, which represent three different patient groups.

<table><tr><th>Scale</th><th colspan="5">Genotype group</th></tr><tr><th></th><th>Total</th><th>II</th><th>DD</th><th>ID</th><th>p value</th></tr><tr><td>R-PAct (at start of ERT)</td><td>52 (7–86)</td><td>59 (7–86)</td><td>44 (7–75)</td><td>56 (17–83)</td><td>ns</td></tr></table>II, DD and ID are the three different ACE genotypes, which represent three different patient groups.
n number for sub-groups for R-PAct is NR.</td><td>were not reported. HRQoL data were reported directly by patients

Relevance to decision problem

The study took place in the Netherlands, which may not be directly relevant to clinical practice in the UK

HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model

The included population consisted of adults with Pompe disease which includes the patient population (adults with LOPD) and so is relevant to the decision problem</td></tr>
<tr><td>Malottki 2022[146]</td><td>Population
Patients with LOPD</td><td>Country
UK</td><td>N=708</td><td>HRQoL and utility values reported for patients at a</td><td>Patient records with at least one SF-36[b]</td><td><table><tr><th>Health state of patients treated with ERT</th><th>Mean utility score (SD)</th></tr></table></td><td>Consistency with NICE reference case</td></tr>
</table>

Source	Description of population, any interventions, recruitment method and follow-up time	Country, setting and study type	Sample size, response rate	Health states and adverse events	Methods of elicitation, valuation and mapping	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation[a]
	Mean age (at diagnosis) = 40.2 (SD: ±16.6) Intervention 94.2% of patients have at some point received ERT Recruitment Patient data from the Pompe Registry	Setting Community Study type Retrospective observational	Evaluable HRQoL data were available for N=NR	single point in time Utilities for specific AEs NR	assessment were identified and SF-36 scores were mapped to EQ-5D index scores using a published algorithm derived from UK patient values For each mapped utility value, the use of a wheelchair or ventilator was ascertained. Utility values were then summarised for each health state SF-36 was used to assess HRQoL	Not requiring wheelchair/ventilator: 0.69 (0.19) Requiring wheelchair: 0.50 (0.17) Requiring non-invasive ventilation: 0.62 (0.18) Requiring invasive ventilation: 0.54 (0.25)	EQ-5D utility values are reported, which is aligned with NICE preference HRQoL data were reported directly by patients Relevance to decision problem The study took place in the UK, which aligns with the decision problem Utility values were stratified by 'earlier' health states but did not include information for 'later' health states in the model for cipaglucosidase alfa in combination with miglustat The included population consisted of adults with LOPD which is relevant to the decision problem
Pollissard 2021[157]	Population	Country	N=100 (N=51 avalglucosida	HRQoL reported for	HRQoL was assessed	**EQ-5D-5L utility** / **Mean (SD)** / ***p* value**	Consistency with NICE reference case

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr>
<td></td>
<td>Patients with LOPD
Age NR

<u>Intervention</u>
Patients randomised 1:1 to avalglucosidase alfa or alglucosidase alfa

<u>Recruitment</u>
Patients recruited as part of the Phase 3 COMET trial</td>
<td>NR

<u>Setting</u>
Hospital – NR

<u>Study type</u>
Randomised controlled trial – Interventional</td>
<td>se alfa, N=49 alglucosidase alfa)

Evaluable HRQoL data were available for n=95 patients (n=51 avalglucosidase alfa, n=44 alglucosidase alfa)</td>
<td>patients at Baseline, and Week 49 of treatment

Utilities for specific AEs NR</td>
<td>using the EQ-5D-5L scale

Higher scores represent better outcome (general population score = ≥0.8, scores of ≤0.5 indicates hospitalisation required)</td>
<td>
<table>
<tr><th>index scores</th><th>Avalglucosidase alfa (n=51)</th><th>Alglucosidase alfa (n=44)</th><th></th></tr>
<tr><td>Baseline</td><td>0.58 (0.21)</td><td>0.59 (0.22)</td><td>NR</td></tr>
<tr><td>Mobility (CfB)</td><td>−0.50 (0.89)</td><td>−0.14 (0.68)</td><td><0.05</td></tr>
<tr><td>Usual activities (CfB)</td><td>−0.34 (0.89)</td><td>0.00 (0.73)</td><td><0.05</td></tr>
<tr><td>EQ-5D VAS (CfB)</td><td>8.80 (15.01)</td><td>−0.33 (16.13)</td><td><0.01</td></tr>
<tr><td>EQ-5D-5L index (CfB)</td><td>0.08 (0.18)</td><td>0.04 (0.16)</td><td>n.s.</td></tr>
</table>
p value represents difference between treatment arms (Wilcoxon-Mann-Whitney test).
</td>
<td>EQ-5D was used in this study, which is the NICE preferred measure of HRQoL in adults, however no preference data was applied and therefore no utility data were generated. HRQoL data was reported directly by patients

<u>Relevance to decision problem</u>

The location of the study was not reported and therefore may not be relevant to the decision problem

HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model

The age of patients with Pompe disease was not reported so it is not clear if patients were adults (as in the decision problem)</td>
</tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr>
<td>Sechi 2020[158]</td>
<td><u>Population</u>
Adults (≥18 years) with LOPD; regular ERT for ≥2 years.

Median age at the beginning of the study: 49.0 ±11.0 years

<u>Intervention</u>
All patients on ERT during study period (20 mg/kg every 2 weeks)

Non-pharmacological exercise training alone or in combination with high-protein diet

<u>Recruitment</u>
Patients were enrolled by two different</td>
<td><u>Country</u>
Italy

<u>Setting</u>
Hospital – multicentre

<u>Study type</u>
Prospective randomised interventional crossover study</td>
<td>N=13

Evaluable HRQoL data were available for n=13</td>
<td>SF-36 scores reported before and after exercise and exercise + diet periods

Utilities for specific AEs NR

Disease severity in patients was variable</td>
<td>A validated, standardised Italian version of the SF-36[b] was used</td>
<td>
<table>
<tr><th>SF-36 Component</th><th>Before exercise (median)</th><th>Before exercise and diet (median)</th></tr>
<tr><td>Physical functioning</td><td>25</td><td>45</td></tr>
<tr><td>Role-physical</td><td>50</td><td>25</td></tr>
<tr><td>Bodily pain</td><td>52</td><td>52</td></tr>
<tr><td>General health</td><td>45</td><td>30</td></tr>
<tr><td>Vitality</td><td>40</td><td>40</td></tr>
<tr><td>Social functioning</td><td>75</td><td>50</td></tr>
<tr><td>Role-emotional</td><td>100</td><td>66.67</td></tr>
<tr><td>Mental health</td><td>72</td><td>56</td></tr>
<tr><td>PCS</td><td>34.25</td><td>33.61</td></tr>
<tr><td>MCS</td><td>53.92</td><td>41.15</td></tr>
</table>
</td>
<td><u>Consistency with NICE reference case</u>
EQ-5D was not used in this study, which is the NICE preferred measure of HRQoL in adults. SF-36 is not a preference based measure, and as a result, utility values were not reported. HRQoL data were reported directly by patients

<u>Relevance to decision problem</u>
The study took place in Italy (and summary measures were calculated using US population coefficients), which may not be directly relevant to clinical practice in the UK

HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model</td>
</tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td>centres: the Regional Coordinator Centre for Rare Disease of the Academic Hospital of Udine, and the Carlo Besta Neurological Institute of Milan</td><td></td><td></td><td></td><td></td><td></td><td>Patients had LOPD and were all adults (≤18 years old) which is aligned to the decision problem</td></tr>
<tr><td>Simon 2019[159]</td><td><u>Population</u>
Nationally representative sample of adults (≥18 years old) (median age of 55)

<u>Intervention</u>
ERT (not further specified)

<u>Recruitment</u>
Respondents were drawn from a commercially available panel of US adults, the GfK panel.</td><td><u>Country</u>
US

<u>Setting</u>
Community

<u>Study type</u>
Survey</td><td>N=862 (40% response rate)

Evaluable health utility data were available for n=169–171 respondents, depending on health state</td><td>Health states were based on a combination of attributes including stage of disease (mild, moderate, or severe), age of symptom onset (infancy, childhood, or adulthood), adherence to therapy (low or high) and treatment

Utilities for specific AEs NR</td><td>An online, stated-preference survey was used to elicit health utilities using direct valuation (TTO)

Each respondent evaluated 6–9 parallel health states

Mean health utility weights were calculated based on responses to the TTO questions</td><td><table><tr><th>Disease state</th><th>n</th><th>Mean health utility score</th><th>95% CI[a]</th></tr><tr><td>Mild symptoms</td><td>170</td><td>0.853</td><td>0.811; 0.892</td></tr><tr><td>Moderate symptoms</td><td>170</td><td>0.683</td><td>0.634; 0.729</td></tr><tr><td>Severe symptoms</td><td>171</td><td>0.536</td><td>0.480; 0.594</td></tr><tr><td>ERT treatment</td><td>169</td><td>0.673</td><td>0.621; 0.723</td></tr></table>[a]Bootstrapped. Disease health states listed are derived from Frame 1 TTO: Adult health state questionnaires.</td><td><u>Consistency with NICE reference case</u>

EQ-5D utilities were not used in this study, which is the NICE preference

HRQoL data was not reported directly by patients which deviates from the NICE reference case

<u>Relevance to decision problem</u>

The study took place in the US and therefore may not be directly relevant to</td></tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td>GfK recruits panel members via random digit dialling and address-based sampling</td><td></td><td></td><td></td><td></td><td></td><td>clinical practice in the UK

Utility values were stratified by health state however these health states were not granular enough to represent the disease course of LOPD</td></tr>
<tr><td>Vaeggemose 2021[160]</td><td><u>Population</u>
Adult patients (≥18 years old) with LOPD

Mean age = 36 (range: 19–62)

<u>Intervention</u>
All patients were receiving ERT. Patients received either alglucosidase alfa or avalglucosidase alfa

<u>Recruitment</u>
Patients recruited from hospitals via</td><td><u>Country</u>
Germany and Denmark

<u>Setting</u>
Hospital – multicentre centre

<u>Study type</u>
Prospective interventional cohort</td><td>N=10

Evaluable HRQoL data was available for n=10 patients</td><td>HRQoL reported for patients at Baseline, and after a 12 month follow up period

Utilities for specific AEs NR</td><td>SF-36 was used to assess HRQoL</td><td><table><tr><th></th><th>Baseline</th><th>Follow-up</th></tr><tr><td>SF-36, mean (SD)</td><td>532.98±168.28</td><td>464.07±175.37</td></tr></table></td><td><u>Consistency with NICE reference case</u>

EQ-5D was not used in this study, which is the NICE preferred measure of HRQoL in adults

SF-36 is not a preference based measure, and as a result, utility values were not reported. HRQoL data were reported directly by patients

<u>Relevance to decision problem</u>

The study took place in Germany and</td></tr>
</table>

<table>
<tr><th>Source</th><th>Description of population, any interventions, recruitment method and follow-up time</th><th>Country, setting and study type</th><th>Sample size, response rate</th><th>Health states and adverse events</th><th>Methods of elicitation, valuation and mapping</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation[a]</th></tr>
<tr><td></td><td>invitation between September 2015–May 2017</td><td></td><td></td><td></td><td></td><td></td><td>Denmark, which may not be directly relevant to clinical practice in the UK

HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model

The included population consisted of adults with LOPD which is relevant to the decision problem</td></tr>
<tr><td>Wyatt 2012[21]</td><td><u>Population</u>
Adult patients (≥18 years old) with adult-onset Pompe disease

Mean age = 46.5 (range: 16.3 – 76.6)

<u>Intervention</u>
ERT or alglucosidase alfa

<u>Recruitment</u>
Patients recruited from designated</td><td><u>Country</u>
United Kingdom

<u>Setting</u>
Hospital – multicentre

<u>Study type</u>
Longitudinal observational cohort study</td><td>N=62

Evaluable HRQoL data was available for n=8 patients</td><td>HRQoL reported for patients with adult-onset Pompe disease
Utilities for specific AEs NR</td><td>The EQ-5D and SF-36 were used to assess patient HRQoL

EQ-5D scores were reported solely as part of a linear mixed-effects model and therefore are not included here</td><td><table><tr><th></th><th colspan="2">SF-36 PCS</th><th colspan="2">SF-36 MCS</th></tr><tr><th></th><th>Mean</th><th>SD</th><th>Mean</th><th>SD</th></tr><tr><td>Overall (n=134)</td><td>29.8</td><td>8.73</td><td>50.07</td><td>12.5</td></tr><tr><td>≤3 years on ERT (n=93)</td><td>29.8</td><td>8.9</td><td>49.7</td><td>12.8</td></tr><tr><td>>3 years on ERT (n=35)</td><td>28.4</td><td>7.7</td><td>52.1</td><td>12.5</td></tr></table></td><td><u>Consistency with NICE reference case</u>

EQ-5D was used in this study, which is the NICE preferred measure of HRQoL in adults, however no preference data was applied and therefore no utility data were generated.

HRQoL data were reported directly by patients</td></tr>
</table>

Source	Description of population, any interventions, recruitment method and follow-up time	Country, setting and study type	Sample size, response rate	Health states and adverse events	Methods of elicitation, valuation and mapping	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation[a]
	treatment centres across the UK						Relevance to decision problem The study took place in the UK in a multicentre study and therefore is relevant for UK clinical practice HRQoL information is not stratified by health states and therefore not suitable for use in a cost-effectiveness model The included population consisted of adults with Pompe disease which includes the patient population (adults with LOPD) and so is relevant to the decision problem

Abbreviations: 6MWD: six-minute walk distance; ADL: activities of daily living; AE: adverse event; BW: biweekly; CfB: change from Baseline; ECG: electrocardiogram; EQ-5D: EuroQol-5-Dimensions; EQ-5D-5L: EuroQol-5-Dimensions 5-Level; EQ-VAS: European quality of life visual analogue scale; ERT: enzyme replacement therapy; FVC: forced vital capacity; GfK: Growth from Knowledge; HADS: hospital anxiety and depression scale; HRQoL: health related quality of life; HV: home ventilation; IMT: inspiratory muscle training; IPA: international Pompe association; IQR: interquartile range; IV: intravenous; kg: kilogram; LOPD: late-onset Pompe disease; max: maximum; MC: medical centre; MCS: mental component summary; mg: milligram; MRC: Medical Research Council; min: minimum; NA: not applicable; NHP: Nottingham Health Profile; NICE: National Institute for Health and Care Excellence; NIV, non-invasive ventilation; NR: not reported; ns: not significant; PCS: physical component summary; pred: predicted; PPF: Patient-Reported Outcomes Measurement Information System (PROMIS) Physical function; PRO: patient-reported outcomes; PROMIS: Patient-Reported Outcomes Measurement Information System; QoL: quality of life; RMT: respiratory muscle training; R-PAct: Rasch-built Pompe-specific Activity; SF-36: 36-Item Short-Form Health Survey; SF-6D, short form-6D; SD: standard deviation; SDB: sleep-disordered breathing; SLR: systematic literature review; sp/y: score points per year; ST: supportive treatment; TTO: time trade-off; UK: United Kingdom; US: United States; VAS: visual analogue scale.

B.3.4.3 Adverse reactions

As described in Section (Section B.3.4.3), the incidence of treatment-related adverse events in PROPEL was similar between treatment arms. The incidence of adverse events leading to study drug discontinuation was low and also similar between treatment arms, and most treatment-related adverse events were mild or moderate in severity.[5] The low incidence of adverse events was also observed in ATB200-02 (Section B.3.4.3).[57] The SLR conducted to identify published HRQoL and utility studies in adults with Pompe disease (Section B.3.4.2) confirmed there is a lack of literature to support the impact of adverse events on HRQoL. UK clinicians also validated the assumption that differences in adverse events experienced when treated with either alglucosidase alfa, or cipaglucosidase alfa in combination with miglustat would be negligible enough not to impact overall quality of life.[4] Additionally, whilst infusion reactions associated with treatment were relatively common in both studies, the costs associated with the treatment of these reactions are relatively low (generic low-cost medications such as paracetamol and steroids are used).[5, 57] Therefore, overall, adverse reactions were not accounted for within the analysis due to the anticipated minor impact they would have on results.

The approach to exclude adverse events from the cost-effectiveness analysis was accepted by the committee during the recent NICE appraisal for avalglucosidase alfa (TA821),[2] as adverse events were consistent across both arms in the trial informing the analysis.[2]

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Vignette development and utility valuation study

As described in Section B.3.4.1, the majority of participants in the PROPEL trial had not yet progressed to more severe health states. Therefore, protocol-driven EQ-5D-5L-derived utility data were not suitable for informing the utility of individuals who required invasive respiratory support or a combination of mobility and respiratory support.

The SLR described previously (Section B.3.4.2) did identify published HRQoL and utility studies in adults with Pompe disease, but no identified utility values were stratified by health state that were granular enough to represent the disease course of LOPD.

Therefore, in the absence of relevant EQ-5D utility data from PROPEL, ATB200-02 and the published literature, health state vignettes were developed and valuated using EQ-5D in line with the NICE hierarchy of HRQoL evidence,[142] NICE reference case[141] and DSU best practice recommendations,[127] to estimate utilities across the spectrum of disease severities, in line with the model health states. The vignette study, conducted by Amicus, is summarised below.

Development of health state vignettes

Health state vignettes describing the quality of life of adults with LOPD were developed to reflect different stages of LOPD defined in terms of the need for mobility and/or respiratory support. The vignettes were robustly developed using clinical trial data and a targeted literature search, and revised and validated using interviews with adults with LOPD and HCPs:

- PROPEL participants were classified in line with the model health state definitions based on e.g., use of mobility support at Baseline. The most reported items in Baseline responses to the

PROs R-PAct and EQ-5D-5L in PROPEL (for participants in each health state) were used to draft the vignettes. Where there were no trial participants representing a health state description, vignettes were extrapolated from other vignettes.

- A targeted literature review of the clinical, economic, resource and utility evidence in Pompe disease was reviewed to identify studies reporting the symptoms and impact of Pompe disease. Fourteen relevant, peer-reviewed studies and a further 41 written testimonies from people with Pompe disease were identified from the International Pompe Association website and reviewed. These studies also informed the development of the vignettes, particularly those for which trial data were not available.
- Interviews were conducted with 12 adults with LOPD, recruited via patient advocacy organisations, Pompe Support UK and the Association for Glycogen Storage Disease UK (AGSD-UK). Participants were asked to describe their experience with LOPD and its impact on different areas of their lives. Participants then reviewed the vignettes for their own current and previously experienced health states, for relevance and accuracy. The vignettes were revised following participant feedback.
- Interviews were also conducted with two UK HCPs specialised in treating people with LOPD. The HCPs were shown the draft vignettes and asked to comment on their clinical accuracy, and to identify any missing content important to the description of the impact of LOPD on an adult's life. The draft vignettes were further revised following the HCP feedback.

The final seven vignettes reflected validated health states aligned with those in the economic model.

Health state valuation

Health state valuation was completed through one-hour interviews with 100 members of the UK general public. Participants were recruited through convenience and snowball sampling. The sample was recruited to be a representative sample based on most recent UK census data.[161] Participants completed a socio-demographic form including their age, gender and employment status before participation. All participants were required to give written informed consent prior to the interview.[162]

The UK sample had demographics representative of the UK population, including a mean age of 42.9 (SD: 17.7) years and 51% male participants (based on the UK census 2011). The demographics in this sample were considered generalisable to the PROPEL clinical trial also (e.g. mean age in the sample was 42.9 years, compared with [redacted] years in PROPEL).[5, 162]

During the interview, participants valued each health state using the EQ-5D-5L questionnaire. The EQ-5D-5L rating for each state was scored using a mapping function for the EQ-5D-5L,[163] with scores reflecting UK preference weights. Table 51 shows the EQ-5D-5L index scores for the health states ranging from 0.61 (no wheelchair use or respiratory support) to -0.08 (intermittent mobility support).[5] Clinical experts generally agreed with the utilities for each health state, and the use of EQ-5D in their estimation.[4] The TTO technique was also used to value the health state vignettes; a scenario analysis using utility values from the TTO assessment is presented in Section B.3.10.3.

Age- and sex-specific general population EQ-5D-3L utilities were derived using methods from Ara and Brazier.[164] [redacted]

Table 51: Health state utility values from the vignette study

Health state	Absolute utility values (SD) N = 100
No wheelchair use or respiratory support[a]	0.61 (0.12)
Intermittent mobility support	0.43 (0.19)
Intermittent, non-invasive respiratory support	0.36 (0.19)
Intermittent mobility support and intermittent, non-invasive respiratory support	0.29 (0.24)
Wheelchair dependent	0.11 (0.23)
Wheelchair dependent and intermittent, non-invasive respiratory support	0.08 (0.22)
Wheelchair and invasive respiratory support dependent	-0.08 (0.22)

[a]When implemented into the model, this health state was divided into three "sub-states" based on the number of years alive from treatment initiation, to align with the utility values presented in Kanters *et al.*[129] The values for all three substates were the same and aligned with the single health state utility values presented in this table.
Abbreviations: SD: standard deviation.
Source: Amicus Therapeutics Data on File (Vignette Study Poster).[162]

Summary of HRQoL data used in the model

In the absence of appropriate utilities from clinical trials and the published literature aligned with health states in the economic model, a vignette study was conducted by Amicus to estimate utilities across the spectrum of disease severities, in line with the model health states.[5] These utility data informed the base case of the economic model for each health state. Two scenario analyses were conducted using TTO weights from the same vignette study and using utilities from Kanters *et al*. from the literature (Section B.3.10.3).[129] As described in Section B.3.4.3, adverse reactions were not accounted for within the analysis due to the anticipated minor impact they would have on results. Therefore, the only utilities used in the base case of the model are those provided in Table 51.

Scenario analyses using utility values from the literature and from the TTO assessment of the health state vignettes described above are presented in Section B.3.10.3.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

The base case economic analysis is consistent with the NICE reference case with an NHS and PSS perspective and therefore included costs that would be incurred by the NHS and PSS. Appropriate UK sources of unit costs, such as NHS reference costs 2020/2021, the British National Formulary (BNF) and Personal Social Services Research Unit (PSSRU) 2021 costs were used to inform the cost inputs in the model.[165-167]

Treatment acquisition costs

Cipaglucosidase alfa in combination with miglustat

Drug acquisition costs for the comparator, alglucosidase alfa, were sourced from the BNF, in line with the NICE reference case.[141] For each simulation (i.e. person with LOPD) of the model,

doses of cipaglucosidase alfa, miglustat and alglucosidase alfa were calculated based on the baseline participant weight from PROPEL (as described in Section B.3.3.1) and recommended dose per kg. For both cipaglucosidase alfa and alglucosidase alfa, drug acquisition costs were calculated based on the number of vials required per infusion as per the SmPC and the cost per vial. In each case no vial sharing was assumed. For miglustat, drug acquisition costs were calculated based on the dosage required and cost per dose. It was assumed that individuals were not required to take any alternative treatments alongside cipaglucosidase alfa in combination with miglustat or alglucosidase alfa.

The proposed list price per one 105 mg vial is cipaglucosidase alfa is [redacted]. An example overall annual cost based on average participant weight in PROPEL is presented in Table 52 (£[redacted] per adult with LOPD); for each simulation in the patient-level simulation model, the overall annual cost would differ.

Table 52: Example annual treatment costs per individual with LOPD for cipaglucosidase alfa in combination with miglustat

Element	Value	Source
Cipaglucosidase alfa		
Example patient weight (kg)[a]	[redacted] (SD: [redacted])	PROPEL[5]
Recommended mg/kg per dose	20	Draft SmPC[8]
Required mg per infusion	[redacted]	Calculation: [redacted] kg * 20 mg
Units per vial (mg)	105	Draft SmPC[8]
Mean vials required per infusion	[redacted]	Calculation: [redacted] / 105, rounded up
Number of infusions per year	26.07	Q2W dosing (Draft SmPC)[8]
Mean vials required per year	[redacted]	Calculation: 26.07 * [redacted], rounded up
Total cost per vial [redacted]	£[redacted]	Amicus data on file
Total annual cost	£[redacted]	Calculation: [redacted] * £[redacted]
Miglustat		
Example patient weight (kg)[a]	[redacted] (SD: [redacted])	PROPEL[5]
Recommend mg per dose (<50 kg)	195	PROPEL trial protocol[5]
Recommend mg per dose (≥50 kg)	260	PROPEL trial protocol[5]
Number of annual doses	26.07	Q2W dosing (Draft SmPC)[14]
Total mg per year	[redacted]	Calculation: [redacted] mg * 26.07
Tablets per pack	4	Draft SmPC[14]
mg per tablet	65	Draft SmPC[14]

Cost per pack	£[redacted]	Amicus data on file
Cost per mg	£[redacted]	Calculation: £([redacted]/4)/65
Total annual cost	**£[redacted]**	(£[redacted] * [redacted])
Cipaglucosidase alfa in combination with miglustat		
Overall annual cost	£[redacted]	Calculation: (£[redacted] + £[redacted])

[a]Example weight, and therefore cost, provided based on an individual with the average weight in the PROPEL trial. Actual costs will vary with each simulated individual (baseline weight as varied for each simulation).
Abbreviations: PAS: patient access schemes; Q2W: every other week; SD: standard deviation; SmPC: summary of product characteristics.

Alglucosidase alfa

The unit cost per one 50 mg vial of alglucosidase alfa, sourced from the BNF, is £356.06.[124] An example overall annual cost based on average participant weight in PROPEL is presented in Table 53 ([redacted]).

Table 53: Example annual treatment costs per individual with LOPD for alglucosidase alfa

Element	Value	Source
Example patient weight (kg)[a]	[redacted] (SD: [redacted])	PROPEL[5]
Recommended mg/kg per dose	20	BNF (alglucosidase alfa)[124] aligned with PROPEL trial protocol[5]
Required mg per infusion	[redacted]	Calculation: 20 mg * [redacted] kg
Units per vial (mg)	50	BNF (alglucosidase alfa)[124]
Mean vials required per infusion	[redacted]	Calculation: [redacted] / 50, rounded up
Number of annual infusions	26.07	Q2W dosing (BNF [alglucosidase alfa])[124]
Mean vials required per year	[redacted]	Calculation: 26.07 * [redacted], rounded up
Total cost per vial	£356.06	BNF (alglucosidase alfa)[124]
Total annual cost	**£[redacted]**	Calculation: [redacted] * £356.06

[a]Example weight, and therefore cost, provided based on an individual with the average weight in the PROPEL trial. Actual costs will vary with each simulated individual (baseline weight as varied for each simulation).
Abbreviations: BNF: British National Formulary; Q2W: every other week; SD: standard deviation.

Treatment administration costs

In alignment with expert opinion, and with the recent avalglucosidase alfa NICE submission (TA821),[2] it was assumed that all individuals would receive treatment with either cipaglucosidase alfa in combination with miglustat or alglucosidase alfa from home after the first three administrations in a hospital setting.[125] The unit cost of £281.11 (NHS Reference Costs, Deliver Simple Parenteral Chemotherapy at First Attendance, Outpatient) was applied to the first three infusions of alglucosidase alfa and cipaglucosidase alfa.[167]

For subsequent treatment administration at home, the time from a nurse required for each administration was informed by the NICE appraisal of avalglucosidase alfa (TA821).[2] Expert

opinion indicated that the majority of individuals would require a nurse to monitor the individual during treatment administration in case of any potential complexities associated with treatment administration, including obtaining venous access for cannulation and setting the infusion rate. As such, associated costs were applied for 90% of individuals in the model.[125] The remaining 10% were assumed to be able to self-infuse (although time from a nurse was still required for the reconstitution). The unit cost per hour of time from a nurse (£55.00) was informed by the PSSRU and was based on a Band 6 nurse.[166] The time required from nurses for reconstitution and administration were sourced from the NICE submission for avalglucosidase alfa (TA821).[2] The total administration cost for cipaglucosidase alfa infusion is lower than alglucosidase alfa for Year 1 and Year 2 onwards as it requires less nursing time for those requiring treatment administration than alglucosidase alfa (Table 54).

As miglustat is administered orally, no administration costs are incurred separately for miglustat.

Table 54: Summary of administration costs

Element		Cipaglucosidase alfa	Alglucosidase alfa	Source
Hospital administration				
Number of administrations in hospital		3 in Year 1 None beyond Year 1		Clinical opinion[125]
Cost of nurse time per administration		£281.11		NHS Reference Costs 2020/21, Outpatient Deliver Simple Parenteral Chemotherapy at First Attendance, Outpatient)[167]
Cost for 3x hospital administrations		**£843.33**		Calculation: £281.11 * 3
Home administration, after the first three infusions in hospital				
Number of administrations at home	Year 1	23.07		Q2W dosing (Draft SmPC)[8] (first 3 infusions in hospital in Year 1)
	Year 2 onwards	26.07		Q2W dosing (Draft SmPC)[8]
Cost of nurse time per hour (band 6 nurse)		£55.00		PSSRU 2021 [166]
Self-infusion	Proportion of individuals requiring nurse support for treatment reconstitution	10%		Clinical opinion[125]
	Time from nurse required for treatment reconstitution (hours)	1.375	0.875	Avalglucosidase alfa NICE submission (TA821)[2]
	Cost of nurse time per infusion	£75.625	£48.125	Calculation: £55.00 * (time required)
Nurse administration	Proportion of individuals requiring nurse support for treatment administration	90%		Clinical opinion[125]
	Time from nurse required for treatment administration (hours)	4.7	5.2	Avalglucosidase alfa NICE submission (TA821)[2]
	Cost of nurse time per infusion	£258.50	£286.00	Calculation: £55.00 * (time required)
Cost for home administration per year	**Year 1**	**£5,541.70**	**£6,049.24**	Calculation: e.g. 23.07 * (£75.625 * 10% + £258.50 * 90%)
	Year 2 onwards	**£6,262.34**	**£6,835.88**	Calculation: e.g. 26.07 * (£48.125 * 10% + £286.00 * 90%)

Total administration cost			
Total administration cost (first year)	**£6,385.03**	**£6,892.57**	Calculation: e.g. £5,541.70 + £843.33
Total administration cost per year (second year onwards)	**£6,262.34**	**£6,836.88**	N/A

Abbreviations: Q2W: every other week; NHS: National Health Service.

B.3.5.2 Health-state unit costs and resource use

The SLR for cost and HCRU studies was conducted to identify evidence that could be used to inform differences in resource use associated with each health state, irrespective of treatment. Two studies were identified reporting cost and/or resource use data associated with the management of individuals with Pompe disease. The first study, Hagemans *et al.* conducted in 2004, reported resource use of adults in an international cohort (including the UK; see Appendix I).[129] However, reported data were not applicable to the current model approach. A cohort study including prospective and retrospective clinical and patient-reported data on 54 individuals with a diagnosis of LOPD across treatment centres in England was also identified.[21] However, this study reported resource use for an average person with Pompe disease and was not stratified by particular health states.

The variation in resource use across each health state was therefore determined by clinical opinion and aligned with the NICE appraisal of avalglucosidase alfa where possible (TA821).[2] The same health state costs were applied regardless of treatment. Details on the unit costs and resource use associated with respiratory and mobility support are provided in Table 55.

Table 55: Summary of unit costs associated with equipment

	Upfront unit cost	Annual costs	Source
Non-invasive ventilation	-	£1,908.19	Dretzke 2015,[168] in line with TA821[2]
Invasive ventilation	£133,277.00	£142,790.00	Noyes 2006,[169] in line with TA821[2]
Intermittent mobility (manual wheelchair)	£703.64	£49.08	NHS reference costs (Repair And Maintenance, All Needs, Manual WC07 and WC09)[167]
Wheelchair dependent state			
Powered wheelchair	£1,374.00	£207.20	NHS reference costs (Repair And Maintenance, All Needs, Manual WC10),[167] in line with TA821[2]
Home adjustment	£30,000.00	-	TA821[2]
Hoist	£826.48	-	TA821[2]

Abbreviations: NHS: National Health Service.

In addition to the equipment costs presented above, it was assumed individuals would require follow-up visits and assessments, the costs of which are outlined in Table 56. The six month follow-ups with a consultant neurologist were validated to be reflective of clinical practice by UK clinical experts.[125] It is conservatively assumed that only one appointment with a respiratory physiology consultant takes place per year, in line with the recently accepted model submitted to NICE for avalglucosidase alfa (TA821).[2]

Table 56: Summary of follow-up visits and assessments

	Cost per visit	Annual cost	Source
All individuals			

Regular six-monthly follow-up outpatient appointment with a consultant neurologist	£215.72	£431.44	NHS reference costs[167]
Individuals receiving non-invasive ventilation			
Annual assessment	£194.68		NHS reference costs[167]
Individuals receiving invasive ventilation			
Annual appointment with a respiratory physiology consultant	£168.77		NHS reference costs[167]

Abbreviations: NHS: National Health Services

B.3.5.3 Adverse reaction unit costs and resource use

As described in B.3.4.3, the incidence of treatment-related adverse events in PROPEL was similar between treatment arms.[5] As such, adverse events are not accounted for within the model due to the anticipated minor impact they would have on the cost-effectiveness results.[125] This approach was validated by clinicians[4] and is also in line with the approach used in the NICE appraisal avalglucosidase alfa (TA821).[2]

B.3.5.4 Miscellaneous unit costs and resource use

No further costs were included in the base case of the economic model.

As LOPD is associated with a high economic burden for both patients and families (Section B.1.3.2), productivity and carer costs associated with LOPD are also considered within a scenario analysis (Section B.3.5.4).

B.3.6 Severity

In this submission, baseline characteristics from the PROPEL trial, which were used in the model, also informed the QALY shortfall (Table 57). The total life expectancy for the modelled general population was calculated using population mortality data from the ONS for 2018–2020 in England.[140] The total life expectancy for the general population was quality-adjusted using the latest UK population values for EQ-5D-3L by age and sex reported from the Health Survey from England (HSE) 2014, as recommended by the NICE DSU.[170] QALYs for people with LOPD are derived from the cost-effectiveness model results (Section B.3.9).

Despite the severity of disease and large unmet need in adults with LOPD, cipaglucosidase alfa in combination with miglustat does not meet the criteria for a severity weight in this indication. This QALY calculation captures the overall characteristics of the LOPD population however it does not account for the heterogeneity in response to treatment with alglucosidase alfa; for the proportion of adults with LOPD who are unable to receive alglucosidase alfa treatment, or those who do not respond to alglucosidase alfa (Section B.1.3.4), the QALY shortfall is expected to be larger. No previous evaluations in Pompe disease (i.e., avalglucosidase alfa [TA821])[2] have included a QALY shortfall.

Table 57: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
% Female	[redacted]	B.2.3.3
Baseline age (years)	[redacted]	B.2.3.3

Abbreviations: QALY: quality-adjusted life year

Table 58: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with alglucosidase alfa	Absolute QALY shortfall	Proportional QALY shortfall
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY: quality-adjusted life year

B.3.7 Uncertainty

As described in Section B.1.1, although cipaglucosidase alfa in combination with miglustat is undergoing appraisal through an STA, its assessment is anticipated to have several features that are commonly seen in the HST programme such as the rarity of the condition.

As highlighted in Section B.2, the PROPEL trial was unable to demonstrate statistically significant benefit in change from Baseline in 6MWD with cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa in the total population.[5] Previous clinical opinion has suggested that this is most likely due to the small sample size of the trial.[4, 171]

In addition, the slow rate of disease progression in LOPD limited the clinical decline that could be observed within the one-year trial duration of PROPEL. Participants in the trial therefore generally did not progress to very severe disease states characterised by dependence on respiratory or mobility support, impacting the availability of clinical data and health utilities in these health states. These challenges are further compounded by the generally limited understanding of the natural history of LOPD. Therefore, assumptions were required to be made in the economic modelling process (Section B.3.8.2), particularly surrounding extrapolation of clinical benefit and disease progression beyond the trial timeframes over the model horizon, and the need for EQ-5D utilities to be estimated outside of the trials using vignettes.

Therefore, we ask the Committee to consider the strength of the data presented despite the rarity of the condition and the paucity of understanding around natural history of the disease impacting the ability to generate evidence. Flexibility in NICE's STA process is therefore expected to be relevant in this submission, when compared to products being assessed through STA for conditions with a much higher prevalence.

B.3.8 Summary of base case analysis inputs and assumptions

B.3.8.1 Summary of base case analysis inputs

A summary of the numerical inputs described above that are used for the base case is presented in Table 59.

Table 59: Summary of variables applied in the economic model

Variable	Value	Reference to section in submission
Baseline demographics: percentage male	[redacted]	B.3.3.1 (Table 42)
Baseline demographics: average participant age	[redacted]	B.3.3.1 (Table 42)

Baseline demographics: average participant weight (kg)	[redacted]	B.3.3.1 (Table 42)
Baseline demographics: average participant height (cm)	[redacted]	B.3.3.1 (Table 42)
Baseline demographics: Baseline 6MWD	[redacted]	B.3.3.1 (Table 42)
Baseline demographics: Baseline FVC % predicted (sitting)	[redacted]	B.3.3.1 (Table 42)
Discount rate: Costs and QALYs	3.5%	B.3.3.1 (Table 42)
Initial annual change in 6MWD (absolute value) from Baseline to Year 3 in individuals receiving cipaglucosidase alfa in combination with miglustat	Various	B.3.3.3 (Table 46)
Initial annual change in FVC % predicted from Baseline to Year 3 in individuals receiving cipaglucosidase alfa in combination with miglustat	Various	B.3.3.3 (Table 46)
Initial annual change in 6MWD % predicted from Baseline to Year 3 in individuals receiving alglucosidase alfa	Various	B.3.3.3 (Table 47)
Initial annual change in FVC % predicted from Baseline to Year 3 in individuals receiving alglucosidase alfa	Various	B.3.3.3 (Table 47)
Long term annual predicted percentage change: 6MWD % predicted with alglucosidase alfa	-2.3%	B.3.3.3 (Table 48)
Long term annual predicted percentage change: FVC % predicted with alglucosidase alfa	-0.9%	B.3.3.3 (Table 48)
Relative rate of long-term annual decline in 6MWD and FVC % predicted beyond Year 3 with cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa	[redacted]	B.3.3.3
Mortality: hazard ratios compared to the general population	Various	B.3.3.3 (Table 49)
Cipaglucosidase alfa in combination with miglustat: annual costs per individual[a]	[redacted]	B.3.5.1 (Table 52)
Alglucosidase alfa: annual treatment costs per individual [a]	[redacted]	B.3.5.1 (Table 53)
First year administration cost: cipaglucosidase alfa	£6,385.03	B.3.5.1 (Table 54)

First year administration cost: alglucosidase alfa	£6,892.57	B.3.5.1 (Table 54)
Second year onward administration cost: cipaglucosidase alfa	£6,262.34	B.3.5.1 (Table 54)
Second year onward administration cost: alglucosidase alfa	£6,836.88	B.3.5.1 (Table 54)
Health-state unit costs: equipment	Various	B.3.5.2 (Table 55)
Health-state unit costs: follow-up visits and assessments	Various	B.3.5.2 (Table 56)

[a]Treatment acquisition costs are based on an individual with the average weight of individuals in PROPEL
Abbreviations: 6MWD: six-minute walk distance; FVC: force vital capacity; QALY: quality-adjusted life year.

B.3.8.2 Assumptions

As discussed in Section B.3.7, due to the challenges associated with clinical data generation and economic modelling in a rare condition such as LOPD, it was necessary to make assumptions during the economic modelling, as described in Table 60.

Table 60. Summary of key assumptions used in the base case

Assumption	Reference to section in submission	Validation (Section B.3.13)
Thresholds of values for 6MWD and FVC % predicted for requiring support	B.3.3.2	Clinical Advisory Board (September 2022)[4] and expert engagement.[125]
[redacted] disease progression with cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa	B.3.3.3	Clinical Advisory Board (September 2022)[4]
Mortality rate was assumed to be equivalent to UK general population norms (based on age and gender) until individuals required mobility and/or respiratory support, at which point hazard ratios for mortality were applied	B.3.3.3	Clinical Advisory Board (September 2022)[4]
The relative risk of mortality was assumed equivalent between the invasive and non-invasive ventilation health states	B.3.3.3	Clinical Advisory Board (September 2022)[4]
The assumption that adverse events experienced when treated with cipaglucosidase alfa in combination with miglustat would	B.3.4.3	Clinical Advisory Board (September 2022)[4] and expert engagement.[125]

be negligible enough not to impact overall quality of life		

Abbreviations: 6MWD: six-minute walk distance; FVC: forced vital capacity; UK: United Kingdom.

B.3.9 Base case results

B.3.9.1 Base case incremental cost-effectiveness analysis results

The base case analysis results expressed in terms of ICERs, net health benefit (NHB) and net monetary benefit (NMB) are presented in Table 23. For all results, cipaglucosidase alfa in combination with miglustat has been included at proposed PAS price and alglucosidase alfa at list price. Over a lifetime time horizon, treatment with cipaglucosidase alfa in combination with miglustat in adults with LOPD was associated with cost-savings of [redacted] per person and a QALY gain of [redacted] QALYs per person, meaning that cipaglucosidase alfa in combination with miglustat was dominant vs. alglucosidase alfa.

The lower costs and greater QALYs associated with cipaglucosidase alfa in combination with miglustat (when provided with the confidential proposed PAS) compared with alglucosidase alfa resulted in a NHB of [redacted] and [redacted] at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY, respectively.

Disaggregated results from the base case cost-utility analysis are presented in Appendix J.

Table 61: Base case results

	Cipaglucosidase alfa in combination with miglustat	Alglucosidase alfa	Incremental	
Total cost	[redacted]	[redacted]	[redacted]	
Total QALYs	[redacted]	[redacted]	[redacted]	
Total life years (discounted)	[redacted]	[redacted]	[redacted]	
Total life years (undiscounted)	[redacted]	[redacted]	[redacted]	
Cost per QALY	[redacted]	[redacted]	[redacted]	
Incremental cost-effectiveness ratio (ICER)			Dominant	
Willingness to pay threshold			**£20,000/QALY**	**£30,000/QALY**
Net monetary benefit			[redacted]	[redacted]
Net health benefit			[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

B.3.10 Exploring uncertainty

B.3.10.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted in order to assess the impact uncertainty around parameter values on the results of the base case model. Three hundred iterations were performed each with 10,000 patient simulations, giving a total of 3,000,000 simulations, as a pragmatic approach.

As described in Section B.3.7, the assessment of cipaglucosidase alfa in combination with miglustat has many features that are commonly seen in the HST programme given that the condition is very rare. Evidence generation in LOPD presents challenges characteristic of rare diseases, such as heterogeneity and small sample sizes, which result in a relatively higher degree of reported uncertainty surrounding input parameters and the potential for highly spread probabilistic outputs. In the probabilistic sensitivity analysis, efficacy data (i.e. change from Baseline in 6MWD and FVC % predicted) continued to be probabilistically sampled as part of the first-order patient simulations (as undertaken for the base case analysis). However, since first-order uncertainty in efficacy inputs was already assessed, second-order uncertainty in these inputs was not additionally assessed within the presented PSA. If conducted, the cumulative uncertainty from testing both first- and second-order uncertainty simultaneously, would excessively distort the results of the PSA. This is because individuals would survive disproportionately longer and incur incrementally more costs when treated with cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa; this was tested and confirmed by restricting survival to 73 years in Scenario analysis #8 (see Section B.3.10.3).

For hazard ratios of mortality sourced from Güngor *et al.*,[151] a lognormal distribution was fitted with the lower and upper bounds equal to ±20% of the mean value for each health state. The confidence intervals for the hazard ratios reported by Güngor *et al.*,[151] were considered to be too wide to represent the realistically expected uncertainty (especially with regard to the upper threshold hazard ratios). When the ranges of hazard ratios reported by Gungor *et al.,*[151] were tested, individuals were predicted to survive far longer and incur incrementally more costs when treated with cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa. Instead, a ±20% variation in hazard ratios for mortality was used in the PSA which still represents a considerable level of parameter uncertainty; this approach enabled uncertainty in mortality to be assessed without disproportionately undermining the value of cipaglucosidase alfa in combination with miglustat.

For remaining inputs (Table 59), in each PSA iteration a value was drawn at random for each variable from its predefined distribution simultaneously. For disutilities associated with each health state (as compared with the general population utility), a gamma distribution was used to prevent values less than zero. For aggregate costs associated with each health state (stratified by ‘new’ for individuals entering a health state and ‘ongoing’ for individuals remaining in a health state) a gamma distribution was also fitted to prevent values less than zero. The resulting costs, outcomes, and incremental results were recorded for each of the individual PSA iterations to generate the overall probabilistic average results. Model settings used in the analysis are presented in Appendix N.

The results of the base case PSA are presented in Table 62 below, with the scatterplot and cost-effectiveness acceptability curves presented in Figure 22 and Figure 23, respectively, with a WTP threshold of £20,000 per QALY.

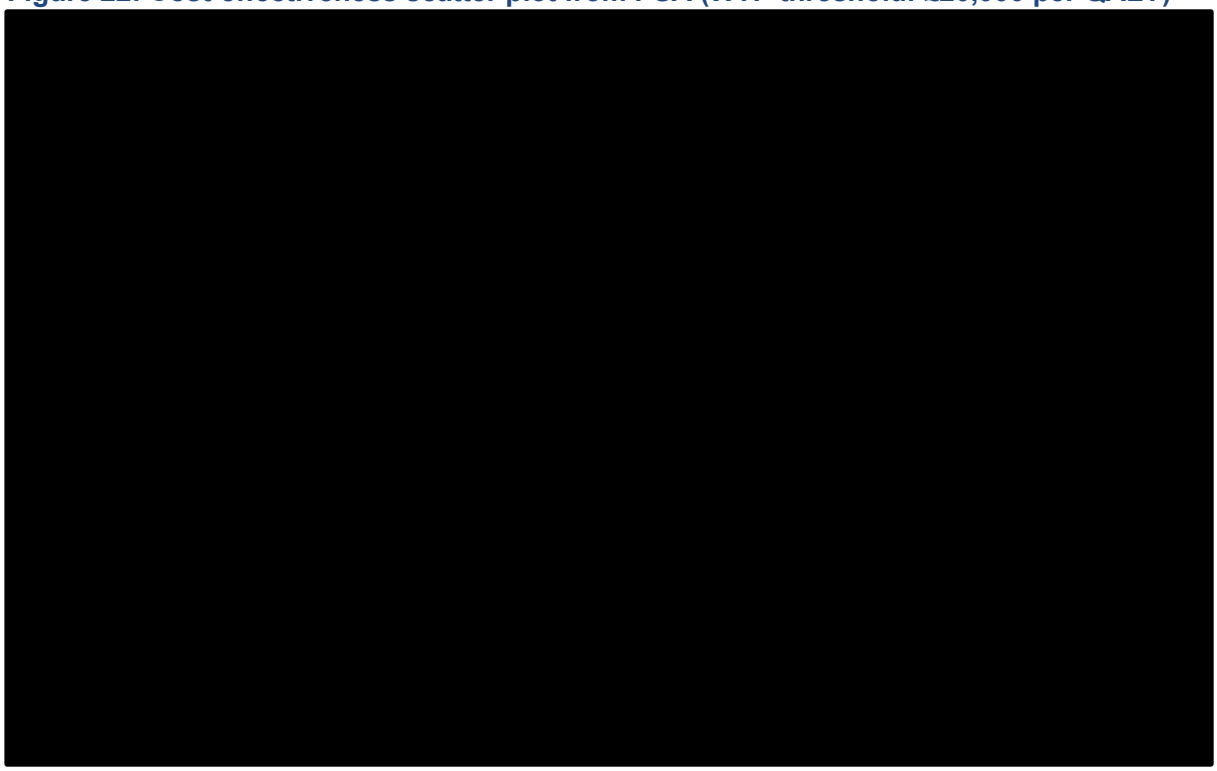
The mean PSA results were similar to the base case results. Cipaglucosidase alfa in combination with miglustat (with proposed PAS) remained dominant due to its cost-savings of £[redacted] per person and a QALY gain of [redacted] QALYs per person vs. alglucosidase alfa (list price). The probability that cipaglucosidase alfa in combination with miglustat is cost-effective is [redacted]% and [redacted]% at WTP thresholds of £20,000 and £30,000 per QALY, respectively.

Table 62: Base case PSA results

	Incremental costs	Incremental QALYs	ICER	NMB	
				£20,000/ QALY	£30,000/ QALY
Cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year

Figure 22: Cost-effectiveness scatter plot from PSA (WTP threshold: £20,000 per QALY)



Abbreviations: ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay.

Figure 23: Cost-effectiveness acceptability curve from PSA (WTP threshold: £20,000 per QALY)

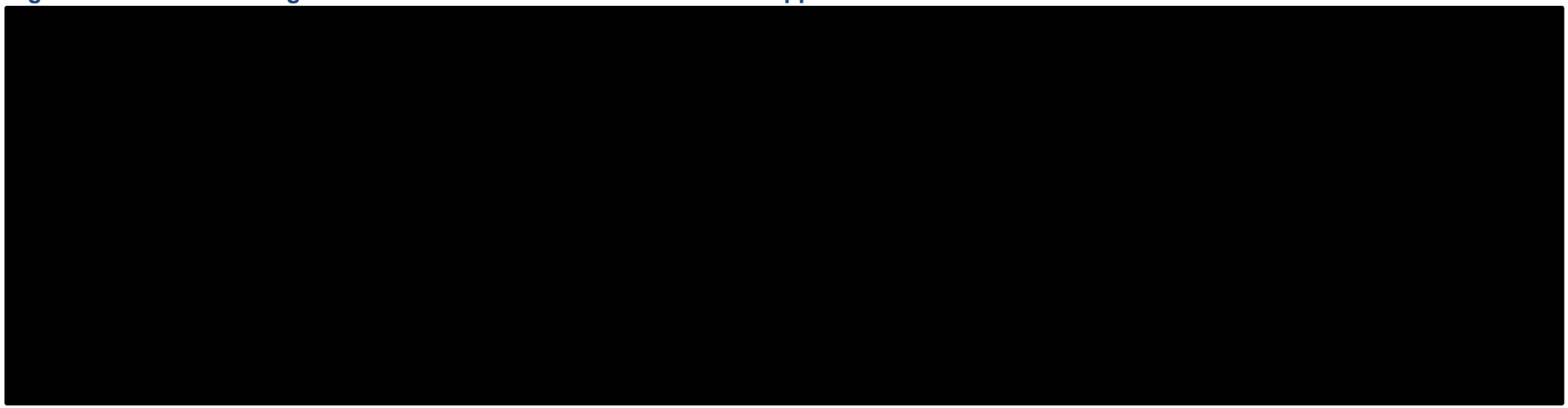
Abbreviations: PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay.

B.3.10.2 Deterministic sensitivity analysis

In order to account for first-order uncertainty around the data used for all input parameter values, all cost, utility and mortality parameters were tested in a deterministic sensitivity analysis (DSA). Parameter values were by allocating a 'low' value and a 'high' value to each parameter using the 95% CI where available. In the absence of CI data, the variation was assumed to be a set percentage of the mean (±20% for mortality hazard ratios, ±15% for drug unit costs, ±10% for health state costs); upper and lower values were either calculated directly by adding or subtracting the respective percentage (for the cost inputs), or by using this to further calculate appropriate variations (in the case for the lognormal variation of the mortality hazard ratios). Upper and lower bound values used in the DSA are detailed in the Appendix N.

The model was run for 100 iterations (due to the time taken to run each iteration). Due to the small number of iterations, the results were not stable enough to centre around a particular NMB and hence it was not possible to produce a traditional tornado diagram. However, the outputs generated by the DSA were sufficient to identify the key input parameters of the model (Figure 24). The most influential parameter on the cost-effectiveness results were the unit cost per vial of alglucosidase alfa. The next most influential parameters were change from Baseline to Year 1 in 6MWD with alglucosidase alfa and cipaglucosidase alfa in combination with miglustat.

Figure 24: Absolute change in incremental NMB in the DSA between upper and lower values in the DSA



All analyses have included the proposed PAS for cipaglucosidase alfa in combination with miglustat. Alglucosidase alfa is included at list price.
Abbreviations: 6MWT: six-minute walk test; DSA: deterministic sensitivity analysis; FVC: forced vital capacity; NMB: net monetary benefit; RR: risk ratio.

B.3.10.3 Scenario analysis

A range of scenario analyses were conducted to test the robustness of the model results to alternative model inputs and assumptions. Each scenario was run deterministically with 30,000 simulations, as with the base case; scenario analyses were not run probabilistically due to the run-time required.

All of the scenarios supported the robustness of the base case ICER, with cipaglucosidase alfa in combination alfa remaining dominant in all scenarios. A description of each scenario analysis, as well as the results of each scenario, are presented in Table 72.

Scenario analyses #1 and #2: Inclusion of avalglucosidase alfa as a comparator

As mentioned in Section B.3.2.3, avalglucosidase alfa (Nexviadyme®) received MHRA marketing authorisation in July 2022[1] and NICE guidance in August 2022 (TA821; with a 30-day implementation period)[2] for the treatment of Pompe disease of all ages. However, at the time of this submission, Amicus understands that avalglucosidase alfa is not commercially available in the UK for the treatment of adults with LOPD,[2, 3] and would be unlikely to be widely used in clinical practice for some time even after it were to become commercially available. Hence, avalglucosidase alfa is not considered established practice nor a primary comparator for this appraisal. As agreed upon with the EAG during the NICE decision problem meeting, and in line with the NICE final scope, the approach has been taken to include avalglucosidase alfa in scenario analyses for completeness. Two scenario analyses have been conducted including avalglucosidase alfa as a comparator in line with the NICE final scope for completeness, using different rates of long-term disease progression.

Treatment efficacy

As described in Section B.2.9, an ITC was conducted to generate comparative efficacy evidence for cipaglucosidase alfa in combination with miglustat, vs. alglucosidase alfa and avalglucosidase alfa.

Initial change from Baseline in 6MWD and FVC % predicted were applied from Baseline to Year 1 of the model only, as treatment efficacy data were available from the ITC at 52 weeks (Table 63). However, the ITC did not explore treatment effectiveness beyond 52 weeks due to the duration of some of the trials informing the ITC. Beyond Year 1 of the model in Scenario analyses #1 and #2, the subsequent annual change in 6MWD and FVC % predicted was informed by alglucosidase alfa long-term data from Semplicini *et al*.[25] as in the base case of the model from Year 3 onwards. Two scenario analyses were therefore conducted:

- Scenario analysis #1: [redacted] rate between avalglucosidase alfa and alglucosidase alfa
- Scenario analysis #2: [redacted] rate with avalglucosidase alfa vs. alglucosidase alfa

Table 63: Initial annual change from Baseline to Year 1 (Scenario analyses #1 and #2)

Treatment	N	Initial annual change from Baseline in 6MWD, m	Initial annual change from Baseline relative in FVC, % predicted

Cipaglucosidase alfa in combination with miglustat (from PROPEL)[5]	85	20.8 (SE: 4.639)	-0.9% (SE: 0.007)
Relative effects of comparator vs. cipaglucosidase alfa in combination with miglustat			
Alglucosidase alfa, relative to cipaglucosidase alfa in combination with miglustat	[redacted]	[redacted]	[redacted]
Avalglucosidase alfa, relative to cipaglucosidase alfa in combination with miglustat		[redacted]	[redacted]

Abbreviations: 6MWD: six-minute walk distance; CI: confidence interval; FVC: forced vital capacity; SE: standard error.

Table 64 presents the rates of long-term disease progression used in Scenario analyses #1 and #2.

Table 64: Effectiveness inputs beyond Year 1 (Scenario analyses #1 and #2)

Outcome	Mean annual predicted percentage change (SE) with alglucosidase alfa	Mean annual predicted percentage change (SE) with avalglucosidase alfa	
		Scenario #1	Scenario #2
6MWD % predicted	-2.3% (0.003)[25]	[redacted]	[redacted]
FVC % predicted	-0.9% (0.001)[25]	[redacted]	[redacted]

Abbreviations: 6MWD: six-minute walk distance; FVC: forced vital capacity; SE: standard error.

Costs and healthcare resource use

As avalglucosidase alfa is not yet commercially available in the UK and a list price not yet published on the BNF, an assumption was made that the cost per mg is equivalent to the UK list price of alglucosidase alfa. Therefore, in these scenarios, the cost per vial of avalglucosidase alfa was set equal to twice the cost per vial of alglucosidase alfa (£356.06 * 2 = £712.12, as a vial of avalglucosidase alfa has 100 mg, twice the dose in a vial of alglucosidase alfa, which has 50 mg). An example overall annual cost based on average participant weight in PROPEL is presented in Table 65 (£[redacted] per adult with LOPD); for each simulation in the patient-level simulation model, the overall annual cost would differ.

Table 65: Example annual treatment costs per person with LOPD for avalglucosidase alfa (Scenario analyses #1 and #2)

Element	Value	Source
Example patient weight (kg)[a]	[redacted] (SD: [redacted])	ClinicalTrials.gov (PROPEL)[63]
Recommended mg/kg per dose	20	PROPEL trial protocol[5]
Required mg per infusion	[redacted]	Calculation: 20 mg * [redacted] kg
Units per vial (mg)	100	EMA (Nexviadyme)[172]
Mean vials required per infusion	[redacted]	Calculation: [redacted] / 100, rounded up

Number of annual infusions	26.07	PROPEL trial protocol[5]
Mean vials required per year	392	Calculation: 26.07 * [redacted], rounded up
Total cost per vial	£712.12	Calculation: £356.06 * 2 (£356.06 from BNF for alglucosidase alfa)[124]
Total annual cost	£[redacted]	Calculation: £712.12 * [redacted]

[a]Example weight, and therefore cost, provided based on an individual with the average weight in the PROPEL trial. Actual costs will vary with each simulated individual (baseline weight as varied for each simulation).
Abbreviations: EMA: European Medicines Agency.

As with the base case, in Scenario analyses #1 and #2 it was assumed that all individuals would receive treatment from home after the first three administrations in a hospital setting.[125] The cost per administration of avalglucosidase alfa was assumed to be the same as that for cipaglucosidase alfa in combination with miglustat (Section B.3.5.1), based on unit sourced from NHS reference costs 2020/21,[167] PSSRU 2021[166] and TA821 (Table 66).[2]

Table 66: Summary of administration costs (Scenario analyses #1 and #2)

Cost	Value	Source
Total administration cost (first year)	£6,385	See Section B.3.5.1
Total administration cost (second year onwards)	£6,262	See Section B.3.5.1

Abbreviations: NHS: National Health Service.

All other costs (e.g. health state unit costs) remained the same as those used in the base case.

Scenario analyses #3 and #4: Relative long-term progression rates

As data reporting on the effectiveness (change in 6MWD and FVC % predicted) of cipaglucosidase alfa in combination with miglustat beyond Year 3 were not available in time for incorporation into the model, subsequent annual change beyond Year 3 in the base case was informed by alglucosidase alfa long-term data.[25] The base case of the model assumed a [redacted] with cipaglucosidase alfa in combination with miglustat relative to alglucosidase alfa (Section B.3.3.3). To test the robustness of model results using this assumption, two conservative scenario analyses were run:

- Scenario analysis #3: [redacted] rate between cipaglucosidase alfa in combination with miglustat and alglucosidase alfa
- Scenario analysis #4: [redacted] rate with cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa

As in the base case, the long-term rate of disease progression with alglucosidase alfa was based on results of the study by Semplicini *et al*.[25] Table 67 presents the rates of long-term disease progression used in Scenario analyses #3 and #4.

Table 67: Efficacy inputs beyond Year 3 (Scenario analyses #3 and #4)

Outcome	Mean annual predicted percentage change (SE) with alglucosidase alfa	Mean annual predicted percentage change (SE) with cipaglucosidase alfa in combination with miglustat

		Scenario #3	Scenario #4
6MWD % predicted	-2.3% (0.003)[25]	[redacted]	[redacted]
FVC % predicted	-0.9% (0.001)[25]	[redacted]	[redacted]

Abbreviations: 6MWD: six-minute walk distance; FVC: forced vital capacity; SE: standard error.

Scenario analysis #5: TTO weights for utilities

In addition to EQ-5D-5L, the vignette study described in Section B.3.4.4 also used a time trade-off (TTO) assessment to estimate utilities for the health state vignettes. Given that EQ-5D utilities are considered more appropriate in line with the NICE evidence hierarchy,[142] TTO utilities were used in a scenario analysis only. The same 100 members of the UK general population who answered EQ-5D-5L also participated in the TTO assessment. TTO weights were rescaled to ensure the utilities for the deceased state was fixed at zero. As such, the age- and sex-specific general population EQ-5D-3L utility based on the mean age and percentage male of the participants in the vignette study, derived using methods from Ara and Brazier,[164] was also estimated to be 0.889.

TTO weights used in Scenario analysis #5, from the vignette study, are shown in Table 68. TTO and EQ-5D results showed a similar pattern, with results from some participants yielding utilities worse than death for the most advanced clinical presentations with both methods, highlighting the severity of more progressed LOPD. TTO weights were slightly higher than EQ-5D utilities as observed in previous research.[173, 174]

Table 68. TTO weights from the vignette study (Scenario analysis #5)

Health state	Absolute utility value (SD) N=100
No wheelchair use or respiratory support	[redacted]
Intermittent mobility support	[redacted]
Wheelchair dependent	[redacted]
Intermittent, non-invasive respiratory support	[redacted]
Intermittent mobility support and intermittent, non-invasive respiratory support	[redacted]
Wheelchair dependent and intermittent, non-invasive respiratory support	[redacted]
Wheelchair and invasive respiratory support dependent	[redacted]

Abbreviations: SD: standard deviation; TTO: time-trade-off.

Scenario analysis #6: Utilities from the literature

As described in Section B.3.4.2, there are a lack of data in the literature reporting utilities for the full range of health states in LOPD progression. Accordingly, a vignette study was conducted by Amicus in line with the DSU best practice recommendations to estimate utilities (EQ-5D-5L) across the spectrum of disease severities, in line with the model health states.[127]

However, two of the identified studies (Malottki 2022, Kanters 2011) provided EQ-5D utility data stratified by 'earlier' health states but did not include information for 'later' health states. Of these, Malottki *et al.* investigated utilities in the Pompe Registry (NCT00231400), which included both

individuals receiving ERT treatment and those who were not;[146] the use of ERT in some individuals may have impacted the estimated utility. It was therefore determined that Kanters *et al.*, which investigated a population who were not being treated with ERT, would be the most appropriate study from which to source utility information for 'earlier' health states in a scenario analysis.

The utilities provided by Kanters *et al.* were based upon a study population of 72 adults (mean age: 51.0 years; 51% male, which is similar to the population in PROPEL)[129] and were reported separately for individuals with LOPD that did, and did not, require ambulatory and respiratory support. Therefore, the utility values were considered to align well with the 'earlier' health states in the model and informed these health states in Scenario analysis #7.

No studies were identified that reported utilities for the 'later' LOPD health states (invasive ventilation dependent or a combination of mobility and respiratory support). Therefore, in line with clinical opinion, disutilities associated with the 'later' health states in Duchenne muscular dystrophy were considered a suitable proxy to inform the economic analysis. Additional targeted searching was conducted to obtain utility data in Duchenne muscular dystrophy, which identified a cost-effectiveness model by Landfeldt *et al.* reporting EQ-5D-3L UK-based utilities for people who were wheelchair dependent.[175]

No utilities for individuals that required both mobility and respiratory support were identified. Therefore, utilities for these health states in Scenario analysis #7 are based on assumptions and were ordered to ensure logical values were produced for each iteration (i.e., the utility value of a particular health state could not be higher than an 'earlier' state). Table 69 presents the utilities used in Scenario analysis #7 sourced from the literature and based on assumption. These values were generally viewed as appropriate for the scenario analysis by clinicians.[4]

The general population utility was again estimated using methods by Ara and Brazier based on the average age and proportion male reported above.[164]

Table 69. Utilities from the literature (Scenario analysis #6)

Health state	Absolute utility value (SD)	General population utility	Source
No wheelchair use or respiratory support (0–5 years alive from treatment initiation)	0.74 (0.15)	0.862	Kanters *et al.*[129]
No wheelchair use or respiratory support (6–15 years alive from treatment initiation)	0.70 (0.16)		
No wheelchair use or respiratory support (>15 years alive from treatment initiation)	0.69 (0.23)		
Intermittent mobility support	0.67 (0.21)		
Wheelchair dependent	0.146 (0.010)		Landfeldt *et al.*[175]
Intermittent, non-invasive respiratory support	0.61 (0.26)		Kanters *et al.*[129]
Intermittent mobility support and intermittent, non-invasive respiratory support	[redacted]		Assumption
Wheelchair dependent and intermittent, non-invasive respiratory support	[redacted]		

Wheelchair and invasive respiratory support dependent	[redacted]		

Abbreviations: SD: standard deviation.
Source: Amicus Therapeutics Data on File (Vignette Study Poster).[162]

Scenario analyses #7 and #8: Survival

As described in Section B.3.3.3, in the base case of the model, the mortality rate was assumed to be equivalent to UK general population norms (based on age and gender) until individuals required mobility and/or respiratory support[140] over a lifetime horizon. Hazard ratios for death were then informed by a study of people with LOPD when respiratory and/or mobility support were required.[18]

In addition, cipaglucosidase alfa in combination with miglustat [redacted]. In order to explore the impact of long-term survival on cost-effectiveness results, two scenario analyses were conducted:

- Scenario analysis #7: Maximum survival = [redacted] years (average UK life expectancy based on average age in PROPEL and ONS National life tables)[140]
- Scenario analysis #8: Maximum survival = [redacted] years ([redacted] years less than average UK life expectancy)

Scenario analysis #9: 20-year time horizon

The base case analysis estimates costs and QALYs over a lifetime horizon. A scenario analysis has been conducted using a 20-year time horizon to explore the impact of using a shorter lifetime horizon on cost-effectiveness results.

Scenario analysis #10: NHS, PSS and societal perspective

As described in Section B.1.3.2, Pompe disease is associated with a substantial economic burden on people with LOPD and their caregivers. In addition to resource savings for the NHS, treatment with cipaglucosidase alfa in combination with miglustat is anticipated to result in productivity gains for individuals with LOPD and caregivers as compared with alglucosidase alfa, due to the assumed slower rate of disease progression. Therefore, a scenario analysis was conducted to explore the cost-effectiveness benefit to wider society, in addition to the NHS and PSS, provided by the use of cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa.

It was assumed a healthy person (without Pompe disease) would work full time once they had reached the age of 18 years, and until they reach the national UK retirement age of 67.5. The economic model captured the economic burden associated with people unable to work at all, or reducing hours worked, due to LOPD. It was anticipated that the economic burden will be lower for a treatment with a slower rate of disease progression.

Productivity loss was derived using the average wage per hour, calculated using the median UK annual wage in 2021 (£25,971) and the average hours worked a week (36.2) sourced from the ONS Annual Survey of Hours and Earnings (ASHE) estimates and the average actual weekly hours of work for full-time workers (pre-COVID-19 pandemic).[176, 177] This equated to an average wage per hour of £13.80.

A study of 80 adults aged 25–76 with LOPD in the Netherlands reported that 40% of people with LOPD are required to stop work due to their condition. Furthermore, 52% of people with LOPD were required to work fewer hours per week due to their condition, with an average reduction of 14 hours per week per individual who needed to reduce their working hours.[129]

Furthermore, a Dutch study estimating the impact of informal care for 67 people with Pompe disease suggested that each individual receives on average 17.7 hours of informal care weekly, with 34.0% of work hours substituted for informal care time.[178] Therefore, the productivity cost of informal care was also captured within this scenario.

The inputs used in this scenario are presented in Table 70 (adults with LOPD) and Table 71 (caregivers).

Table 70: Productivity loss inputs for adult with LOPD (Scenario analysis #10)

Health state	% stopping work completely	Source	% required to reduce hours	Source
No wheelchair use or respiratory support	[redacted]	Assumption	[redacted]	Assumption
Intermittent mobility support	[redacted]		[redacted]	
Wheelchair dependent	[redacted]		[redacted]	
Intermittent respiratory support, non-invasive respiratory support	[redacted]		[redacted]	
Intermittent mobility and intermittent, non-invasive respiratory support	[redacted]		52.0%	Kanters *et al.*[129]
Wheelchair dependent and intermittent, non-invasive respiratory support	40.0%	Kanters *et al.*[129]	52.0%	
Wheelchair and invasive respiratory support dependent	40.0%		52.0%	

Table 71: Caregiver productivity loss inputs (Scenario analysis #10)

Health state	% individuals requiring informal care	Number of hours of care required per week	% work hours substituted for informal care time	Source
No wheelchair use or respiratory support	[redacted]	17.7	34.0%	Kanters *et al.* 2013[178]
Intermittent mobility support	[redacted]			
Wheelchair dependent	[redacted]			
Intermittent respiratory support (non-invasive ventilation)	[redacted]			
Intermittent mobility support and intermittent respiratory support (non-invasive ventilation)	[redacted]			
Intermittent respiratory support and wheelchair dependent (non-invasive ventilation)	[redacted]			

Wheelchair and respiratory support dependent (non-invasive ventilation)	[redacted]			
Wheelchair and respiratory support dependent (invasive ventilation)	[redacted]			

[a]Based on assumption

Scenario analyses #11 and #12: Discount rate

Based on the anticipated long-term survival of people with LOPD receiving ERT treatment (e.g., undiscounted life years in the base case with cipaglucosidase alfa in combination with miglustat: [redacted] years), two scenario analyses were conducted:

- Scenario analysis #11: A 0% annual discount rate for costs and health benefits
- Scenario analysis #12: A 1.5% annual discount rate for costs and health benefits

Summary of scenario analysis results

A summary of the results of the scenario analyses is provided below in Table 72.

Table 72: Results of scenario analyses

#	Scenario analysis description	Results				
		Incr. costs	Incr. QALYs	ICER	NMB at £20,000/QALY	NHB at £20,000/QALY
-	Base case	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Inclusion of avalglucosidase alfa as a comparator						
1	Comparison vs. avalglucosidase alfa [redacted] between avalglucosidase alfa and alglucosidase alfa)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
2	Comparison vs avalglucosidase alfa ([redacted] with avalglucosidase alfa vs. alglucosidase alfa)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Relative long-term progression rates						
3	[redacted] between cipaglucosidase alfa in combination with miglustat and alglucosidase alfa	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
4	[redacted] with cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Utility data						
5	TTO weights for utilities	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
6	Utilities from the literature	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Survival						
7	Maximum survival = [redacted] (average UK life expectancy)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
8	Maximum survival = [redacted] (10 years less than average UK life expectancy)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Time horizon						
9	20-year time horizon	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Perspective						
10	NHS, PSS and societal perspective	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Discount rate (costs and benefits)						
11	Discount rate = 0%	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

12	Discount rate = 1.5%	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; NHS: National Health Service; NMB: net monetary benefit; PSS: Personal Social Services; QALY: quality-adjust life year; TTO: time trade-off; UK: United Kingdom.

B.3.11 Subgroup analysis

As described in Section B.2.7, the submission focuses on the total population of adults with LOPD without considering treatment groups defined by prior treatment status, in line with [redacted], the total population considered in the NICE final scope, and the NICE appraisal for avalglucosidase alfa (TA821). Therefore, subgroups were not analysed for cost-effectiveness.

B.3.12 Benefits not captured in the QALY calculation

Cipaglucosidase alfa in combination with miglustat is associated with a number of benefits which are not captured in the QALY calculation. Amicus understands that avalglucosidase alfa is not commercially available in the UK at the time of this submission for the treatment of adults with LOPD.[2, 3] Therefore, there are no alternative treatment options for adults with LOPD who are unable to receive alglucosidase alfa treatment. Similarly, there are no options for those who do not respond to, or whose response declines with, alglucosidase alfa. Cipaglucosidase alfa in combination with miglustat represents an important alternative for those who are otherwise left without satisfactory treatment options.

[redacted]

In the PROPEL trial, greater numerical improvement in muscle function (as measured by MMT) was demonstrated in participants treated with cipaglucosidase alfa in combination with miglustat in comparison to participants treated with alglucosidase alfa (Section B.2.6.2). Muscle function was not assessed in the economic model (in addition to 6MWD and FVC % predicted) to avoid unnecessary complexity in the model, and because clinical opinion confirmed that 6MWD and FVC % predicted accurately captured LOPD disease progression.[4] As a result, the improvements in MMT observed in PROPEL are not captured in the QALY calculation.

B.3.13 Validation

The economic model was [redacted]

[redacted], a series of engagement activities were used to gather feedback from UK expert clinical advisors, and information related to clinical inputs, which have been cited throughout. The key activities validating the modelling approach are described below, with further engagement activities informing the clinical development programme listed in Appendix M.

Expert engagement[125]

Two Pompe disease clinical experts, practicing in major UK centres, were interviewed in January 2021 and April 2022. These meetings aimed to validate key aspects of the model. During these calls, experts validated:

- The use of 6MWD and FVC % predicted as markers of disease progression

- The robustness and appropriateness of model health states for capturing the cost and quality of life implications of Pompe disease
- Thresholds of values for 6MWD and FVC % predicted that indicate respiratory or mobility support are required
- The at-home administration of cipaglucosidase alfa in combination with miglustat after the first three administrations in the hospital
- The linear decline in annual 6MWD and FVC % predicted scores.

Clinical advisory board and model validation (September 2022)[4]

The aim of this advisory board was to further validate the modelling approach and assumption, especially where data from the trials or literature were unavailable or their applicability to the model required validation. During this advisory board, a group of consultants and nurses from Pompe disease specialist centres in the UK validated:

- The clinical decline observed in Semplicini *et al*. is reflective of clinical practice and the unmet need for people LOPD
- The same treatment approach and pathway for the total LOPD population, regardless of previous treatment
- The generalisability of the PROPEL trial population to the UK adult Pompe disease population
- The [redacted] with cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa
- The use of data from PROPEL in Year 1 of the model, and data from the ATB200-02 for Years 2 and 3
- The thresholds and use of 6MWD and sitting FVC % predicted to model disease progression
- The use of EQ-5D values derived from the vignette study conducted by Amicus to inform utility
- The assumption that the mortality rate for people with Pompe disease is equivalent to UK general population norms (based on age and gender) until they transitioned into worse disease health states requiring mobility and/or respiratory support
- The assumption that adverse events experienced when treated with either alglucosidase alfa, or cipaglucosidase alfa in combination with miglustat would be negligible enough not to impact overall quality of life.

B.3.14 Interpretation and conclusions of economic evidence

Summary of the cost-effectiveness results

In the deterministic base case economic analysis, cipaglucosidase alfa in combination with miglustat (with the confidential proposed PAS discount) was associated with cost-savings of [redacted] per person and a QALY gain of [redacted] QALYs per person vs. currently commercially available ERT, alglucosidase alfa (at list price) in adults with LOPD over a lifetime time horizon, meaning that cipaglucosidase alfa in combination with miglustat was dominant vs. alglucosidase alfa.

In the PSA based on 300 iterations each with 10,000 simulations, the mean PSA results were similar to the base case results. Cipaglucosidase alfa in combination with miglustat (with proposed PAS) remained dominant due to its cost-savings of [redacted] per person and a QALY gain of [redacted] QALYs per person vs. alglucosidase alfa (list price). The probability that cipaglucosidase alfa in combination with miglustat (with proposed PAS) is cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained is [redacted]%. In the DSA, the most influential parameter on the cost-effectiveness results were the unit cost per vial of alglucosidase alfa. The next most influential parameters were change from Baseline to Year 1 in 6MWD with alglucosidase alfa and cipaglucosidase alfa in combination with miglustat.

Twelve scenario analyses explored the impact of key model inputs and assumptions on cost-effectiveness results. In all scenario analyses, cipaglucosidase alfa in combination with miglustat remained dominant vs. alglucosidase alfa,[redacted]. These results demonstrate the robustness of, and conservative approach taken for the base case.

Strengths and limitations of the cost-effectiveness analysis

The model was developed in line with the NICE reference case and decision problem with an NHS and PSS perspective, with direct health effects on people with LOPD considered over a lifetime horizon and costs and benefits discounted at a rate of 3.5% annually.

Whilst it was necessary to make various assumptions regarding the model structure, inputs and assumptions, many of these key aspects of the model were largely aligned with the model recently accepted by NICE for avalglucosidase alfa (TA821),[2] validated by clinical experts in England (Section B.3.13) and robustly explored with scenario analyses in which cipaglucosidase alfa in combination with miglustat remained dominant. Appropriate UK inputs were used where possible and appropriate (e.g. unit costs were sourced from NHS reference costs, PSSRU costs and the BNF).

- Health states included in the model were developed considering [redacted], and the committee's preferences during the NICE appraisal of avalglucosidase alfa (TA821),[2] and were also determined by clinical experts to best capture the natural history of Pompe disease according to motor and respiratory function, as seen in UK clinical practice.[4, 125]
- In line with clinical opinion[4, 126] and TA821,[2] individuals in the model were assumed to experience an initial improvement in both 6MWD and FVC % predicted based on trial data, followed by a subsequent, gradual decline, as observed with alglucosidase alfa.[20, 24]
- Results of PROPEL, which informed the initial change from Baseline in 6MWD and FVC % predicted, were considered generalisable to clinical practice in England.[4] Data from 36-months of follow-up of ATB200-02 informed annual change from Year 1 to Year 3 for cipaglucosidase alfa in combination with miglustat,. Data from 48-month follow-up were recently published, but not available at the time of the development of the submitted economic model.
- The model base case subsequently assumed a [redacted] with cipaglucosidase alfa in combination with miglustat relative to alglucosidase alfa. Cipaglucosidase alfa in combination with miglustat remained dominant in scenario analyses which used yet more conservative rates of disease progression for cipaglucosidase alfa in combination with miglustat.

Differences compared with the model for avalglucosidase alfa (TA821)[2] include:

- The model for cipaglucosidase alfa in combination with miglustat was considered to be appropriate and clear [redacted], in contrast to the model for avalglucosidase alfa which was considered to be overly complex and difficult to interpret due to its use of a DICE approach
- The model for cipaglucosidase alfa in combination with miglustat adopted a lifetime horizon to ensure full costs and health benefits were captured
- A vignette study informed utilities in the base case of the model for cipaglucosidase alfa in combination with miglustat. As the majority of participants in the PROPEL trial had not yet progressed to more severe health states, protocol-driven EQ-5D-5L-derived utility data were not suitable for informing the utility of individuals who were dependent on invasive respiratory support or required a combination of mobility and respiratory support. Due to a lack of utility data available in the literature for health states which were sufficiently granular to represent the disease course of LOPD, a vignette study was conducted by Amicus in line with the DSU best practice recommendations to estimate utilities (EQ-5D) across the spectrum of disease severities, in line with the model health states.[127] The use of HRQoL data in the model was therefore in line with the NICE hierarchy of preferred methods and clinical opinion.[4] Although utilities identified in the literature were less appropriate for use in the model than the health state vignette utilities, scenario analysis explored the use of these alternative utility inputs from the literature, and the results found cipaglucosidase alfa in combination with miglustat to remain dominant
- Discontinuation was not modelled in this analysis, because the incidence of AEs leading to treatment discontinuation in PROPEL was low and similar between treatment arms[5]
- Rather than using a parametric survival curve, mortality was assumed to be equivalent to UK general population norms (based on age and gender) until individuals required mobility and/or respiratory support, at which point published hazard ratios for mortality were applied.[4] Again, cipaglucosidase alfa in combination with miglustat remained dominant in scenario analyses exploring the use of life expectancy cut-offs to assess the impact of long-term survival on cost-effectiveness

Other limitations of the analysis include the following:

- As is common in rare diseases, limited participant numbers in the trials and studies informing the analysis may have led to uncertainty in effect sizes; however, despite this uncertainty, results robustly demonstrated the dominance of cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa in the PSA
- Limited HRQoL, cost and resource use that were conducted in the UK and relevant to this model were identified from the SLRs, but as mentioned above, assumptions and inputs were validated by UK clinicians where possible and explored in scenario analyses
- The price of avalglucosidase alfa is unknown and hence was assumed to be equal to the price of alglucosidase alfa in Scenario analyses #1 and #2.

Conclusion

There is therefore a substantial unmet need for an effective treatment for individuals who do not gain any benefit from alglucosidase alfa and those experiencing the well-established declining effectiveness of alglucosidase alfa. For these individuals, it is crucial that further decline is avoided, in order to improve clinical and quality of life outcomes. There is also an unmet need for individuals who are unable to receive alglucosidase alfa. [redacted]

[redacted] This demonstrates a clear demand to seek an alternative to established care. Cipaglucosidase alfa in combination with miglustat is expected to provide an alternative treatment option for these individuals, as well as for adults with LOPD who have not received prior ERT.

The results of the base case cost-effectiveness analysis demonstrate that cipaglucosidase alfa in combination with miglustat (with proposed PAS) is associated with cost savings and health benefits vs. alglucosidase alfa (list price) over a lifetime horizon, thus providing a cost-effective use of NHS resources. In all scenario analyses, cipaglucosidase alfa in combination with miglustat remained dominant vs. alglucosidase alfa and avalglucosidase alfa. Additionally, in the PSA, cipaglucosidase alfa had a [redacted]% chance of remaining cost-effective at a willingness to pay threshold of £20,000 per QALY. Given that the use of clinical trial data is generalisable to the UK, as well as the validation of the modelling approach by clinical experts in England and the use of UK cost and resource use inputs, the model and its results are considered to be generalisable to clinical practice in England.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease (ID3771)

Summary of Information for Patients (SIP)

October 2022

File name	Version	Contains confidential information	Date
ID3771_Cipaglucosidase alfa with miglustat_SIP_26Oct22	2.0	No	17Nov22

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Cipaglucosidase alfa in combination with miglustat.

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults (aged 18 years or older) with late-onset Pompe disease (LOPD). (Please see Section 2a for an explanation of what LOPD is.)

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The marketing authorisation for cipaglucosidase alfa in combination with miglustat is currently pending. The anticipated date of approval can be found in Section B.1.1. of the main submission (Document B).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The table below shows Amicus' involvement with patient groups in England in terms of how they are engaged and supported.

Patient group	Amicus engagement/activity with each group	Financial support provided
2020		
Genetic Alliance UK	Unrestricted funding Rare Disease Day 2020	Y
Specialised Healthcare Alliance	Membership 2020	Y
Pompe Support Network	Unrestricted core funding	Y
AGSD-UK	Unrestricted core funding	Y
Metabolic Support UK	Unrestricted core funding	Y
Genetic Alliance UK	Unrestricted funding to support Covid Appeal	Y
Find a Cure (now Beacon)	Unrestricted core funding	Y
Genetic Alliance UK	Unrestricted funding for Rare Disease Day 2021	Y
The Patients' Association	Unrestricted funding to support general activities	Y
2021		
AGSD-UK	Unrestricted core funding	Y
AGSD-UK	Resources for digital content and outreach	Y
Find a Cure	Unrestricted core funding	Y
Gene People	Unrestricted core funding	Y
Genetic Alliance UK	Unrestricted core funding	Y
Metabolic Support UK	Unrestricted core funding	Y
Pompe Support Network	Unrestricted core funding	Y
Pompe Support Network	Resources for digital content and outreach	Y
Specialised Healthcare Alliance	Membership 2021	Y
Genetic Alliance UK	Membership for Rare Diseases UK	Y
Allan Muir, Pompe Support Network	Patient advisory board participation	Y
2022 YTD (1st Jan 2022 - 30th Sept 2022)		
AGSD-UK	Unrestricted funding for core activities	Y
Pompe Support Network	Unrestricted funding for core activities	Y
Metabolic Support UK	Unrestricted core funding	Y
Genetic Alliance UK	Unrestricted funding for Rare Disease Day UK Campaign 2022	Y
Genetic Alliance UK	Rare Disease UK Awareness Campaign and Membership	Y
Specialised Healthcare Alliance	Membership 2022	Y
Gene People UK	Unrestricted core funding	Y
AGSD-UK	Collaboration to conduct Pompe patient survey including virtual poster presentations	Y (conference registration fee only)
Pompe Support Network	Collaboration to conduct Pompe Patient survey including virtual poster presentations	Y (conference registration fee only)

Allan Muir, Pompe Support Network	Patient advisory board participation	Y
Allan Muir, Pompe Support Network	Readability review	Y

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Condition being assessed by NICE

Pompe disease is a rare condition where muscle cells do not have enough of a protein called acid alfa-glucosidase (GAA). When GAA is present in muscle cells, it is responsible for breaking down a substance called glycogen. When there is not enough GAA, or no GAA, glycogen can build up in muscle cells. This causes permanent damage to muscles throughout the body, especially in the arms, legs and lungs.(1) Symptoms of Pompe disease get worse over time.(1) Muscle damage often means that people cannot move or breathe as well as normal. Breathing problems are the most common reason for death of people with Pompe disease.(1)

There are two main types of Pompe disease. When symptoms start before 12 months (1 year) of age, this is called infantile-onset Pompe disease (IOPD). When symptoms start after 12 months of age, this is called late-onset Pompe disease (LOPD). There are also other differences between the two types. This submission focuses on adults with LOPD.

Symptoms of LOPD

LOPD has effects all over the body. The symptoms of LOPD include:(2)

- Weakness
- Nerve pain
- Tiredness
- Difficulty walking
- Brain blood vessel bulging or bleeding
- Difficulty breathing
- Poor appetite
- Difficulty speaking
- Sleep apnoea (when breathing stops and starts during sleep)

How many people have the condition?

The exact number of people with LOPD is difficult to estimate. The Association for Glycogen Storage Disease UK (AGSD-UK) estimate that there are currently around 200 people with LOPD living in the United Kingdom (UK).(3)

Impact on individuals with LOPD

The symptoms of LOPD impact the way people experience life – this is often referred to as quality of life (see Section 2d for more details from people with Pompe disease). People with LOPD may find it difficult to complete everyday tasks than people without LOPD. Additionally, when people need support with breathing and moving around, and feel tired, this severely reduces their quality of life.(4, 5) Individuals who have difficulties with speaking can also find social situations very challenging.(1) As symptoms worsen, individuals may also experience more challenges in their relationships with their families and carers, and in their working life.(4) People with Pompe disease are also more likely to experience depression and anxiety than people without Pompe disease.(6-9) People with Pompe disease also experience a feeling of uncertainty throughout their diagnosis and treatment because their doctors may not have enough knowledge and experience of such a rare disease.(10)

Impact on carers

Carers of people with Pompe disease spend a lot of time on long hospital stays, frequent medical visits and maintaining health equipment. This means carers often have less time to work and socialise than other people. They also experience a negative impact on their finances.(11) In addition, carers are often concerned about what would happen if they had to stop supporting the person they care for.(11) A lot of carers experience a negative impact on their mental health and physical health.(11)

Life expectancy

People with Pompe disease, who have not been treated, live on average for 55 years (this is an overall estimate for IOPD and LOPD).(12) Death is more likely in people whose disease is more severe, such as those who use a wheelchair or ventilator, compared with those whose disease is less severe.(12, 13)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How LOPD is diagnosed

LOPD has similar symptoms to other conditions, which makes LOPD difficult to diagnose.(1, 14, 15)

When a person, or their doctor, feels like they are experiencing symptoms of LOPD, such as difficulty walking, their doctor may take a small amount of blood from their veins (a blood test).(16) This blood sample will be sent to a laboratory to see how much GAA there is within the body and how well the GAA is working. Deoxyribonucleic acid (DNA) instructs the body to produce proteins such as GAA. The blood sample would be checked to see if DNA is instructing the body to produce GAA incorrectly.(1) In addition to these blood tests, the doctor may also arrange other tests, such as an x-ray or heart examination, in order to assess symptoms and determine the best treatment.(1)

LOPD can be diagnosed at any time over the age of one.(1) However, a quick diagnosis of Pompe disease is important to avoid more permanent muscle damage and worsening of symptoms.

2c) Current treatment options

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What treatment options are currently available?

Until recently, alglucosidase alfa (known as Myozyme®) was the only medication for people with LOPD available in the UK. Alglucosidase alfa is a type of treatment known as an 'enzyme replacement therapy' (ERT). This means it replaces the missing GAA proteins with working GAA proteins. The new GAA breaks down the glycogen that has built-up in muscle cells, preventing more damage to the muscles.(17)

Avalglucosidase alfa is another enzyme replacement therapy that has recently been approved for people with Pompe disease. However, it was not yet commercially available for use at the time of this submission.(18)

People with Pompe disease may go to heart, lung and brain specialists to receive care. People may also visit a physiotherapist to help them move around better and strengthen their muscles.(1)

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Amicus has conducted surveys, patient advisory boards and roundtables to gain as much input as possible from people with Pompe disease. Advisory boards and roundtables are types of meetings in which people discuss certain predefined topics. Gaining this input from people with Pompe disease has been a core pillar of Amicus' extraordinary patient focus within its business for 14 years. Amicus has been using these insights to develop programmes for

Pompe disease since it was first set up. Two examples of the more recent activities are outlined below. The activities detailed below all included people who had been receiving alglucosidase alfa.

2021 patient survey

Amicus worked with two UK patient advocacy organisations to conduct a survey to help understand the experiences of 27 adults with LOPD living in the UK. Most of the people surveyed felt that Pompe disease severely affected their lives. On average, the participants ranked the effect of Pompe disease on their lives to be 8.5 out of 10 (0 meant no impact at all, and 10 meant a severe impact).(4)

Participants expressed their anxiety due to uncertainties around activities they will be able to do on any given day. Participants described how Pompe disease affects basic activities of life:(19)

- "Pompe disease, it does affect your day-to-day life. And for me, life is revolving around toilets, accessible toilets, and it's very difficult and it is frustrating."
- "I use tongs to be able to grab a snack of cheese and crackers. It is very difficult to lift a full mug."

The condition also has a considerable impact on carers and family members:(19)

- "I'm still not an old woman or anything. My mum carries my shopping and I don't like that. It should be the other way around. It affects me and then I'm sad".

2022 online patient survey

In an online survey completed by 37 people with LOPD in the UK, one person described the impact of their symptoms as "extremely life limiting". Another described their experience as a "slow death" due to the knowledge that when they grow up, they "won't be able to do normal things". People also acknowledged their negative experiences of social isolation.(20)

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Cipaglucosidase alfa is a separate medicine to miglustat, but people are expected to use both medicines.

Cipaglucosidase alfa

Cipaglucosidase alfa is a type of enzyme replacement therapy that is expected to be used in the treatment of adults with LOPD (see Section 2c for an explanation of enzyme replacement therapy). Cipaglucosidase alfa must always be used with miglustat, otherwise it may not work properly (see below).

Cipaglucosidase alfa controls glycogen levels. It does this by entering the muscle cells that are affected by Pompe disease. When in the cells, the medicine works like GAA: it helps to break down glycogen so that too much glycogen does not build up. Cipaglucosidase alfa is a version of GAA that has been modified so that it can enter muscle cells more easily than alglucosidase alfa.(21)

Miglustat

Miglustat is a medicine that must be used with cipaglucosidase alfa to treat LOPD in adults. Miglustat attaches to cipaglucosidase alfa during treatment. This makes the shape of cipaglucosidase alfa more stable, so it can be more easily absorbed from the blood by the muscle cells that are affected by Pompe disease.(22)

The innovative combination of cipaglucosidase alfa and miglustat means that muscle cells absorb more of the medication which breaks down glycogen. This leads to better mobility, strength and breathing compared with alglucosidase alfa.(23)

Safety and side effect information is presented in Section 3g. If you have any questions about your medicines, please ask your doctor or pharmacist.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No. Cipaglucosidase alfa is expected to be used with miglustat (see Section 3a above). People are not expected to need to take other medicines alongside cipaglucosidase alfa in combination with miglustat.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How to take the medicine

A person with LOPD must always use this medicine exactly as their doctor has told them.

Cipaglucosidase alfa is given by a doctor or nurse. It is given through a drip into a vein. This is called an intravenous infusion.(24) Miglustat is a capsule that is swallowed.(22)

It is expected that in some situations, a person with LOPD may be able to have treatment at home. They should check with their doctor or pharmacist if they are not sure how the medicine should be used.

How much medicine to take

- The amount of cipaglucosidase alfa a person with LOPD is expected to receive depends on their body weight. The recommended dose of cipaglucosidase alfa is expected to be 20 milligrams (mg) for each kilogram (kg) of body weight.(24)
- If a person with LOPD weighs 50 kg or more, the recommended dose of miglustat is expected to be 4 capsules which each contain 65 mg of miglustat. If they weigh between 40 kg and 50 kg, the recommended dose is expected to be 3 capsules.(22)

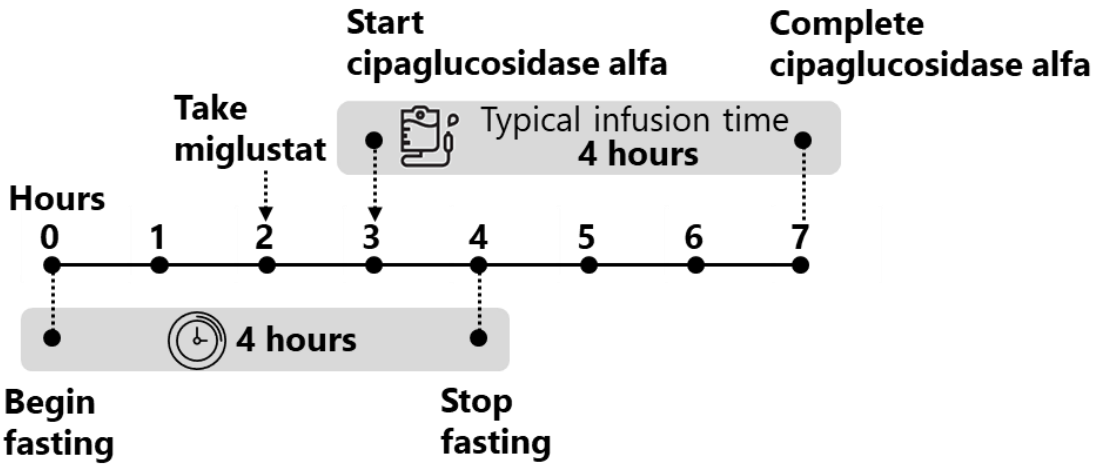
How often to take the medicine

- It is expected that a person with LOPD will receive the medicine once every two weeks. Both medicines are used on the same day.(22, 24)

Taking the medicines with food

- It is expected that a person with LOPD will need to receive the medicines on an empty stomach. This includes fasting for 2 hours before and 2 hours after taking miglustat.(22, 24)
- During this 4-hour fasting period, water and tea or coffee can be consumed. Do not use cream, whole/semi-skimmed cow's milk, non-dairy milks, sugar or sweeteners. Fat-free (skimmed) cow's milk can be consumed with coffee.(22, 24)
- Two hours after taking miglustat, normal eating and drinking can be resumed.(22, 24)

The diagram below shows when to take the medicines.



3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The following table outlines the five clinical trials studying cipaglucosidase alfa in combination with miglustat in Pompe disease. Further information can be found on the ClinicalTrials.gov website (www.clinicaltrials.gov). Each row in the table is a different clinical trial, and the details of each trial can be read along each row.

Trial name/ Phase	Location	Number of participants	Participant population (who could enter the trial)	Comparators (the medicine compared against)	Key eligibility criteria (criteria for participating in the trial)	Estimated completion date of trial
PROPEL (NCT03729362) Phase III	International	123 participants	Male and female adults (aged 18 years or older) with LOPD	Alglucosidase alfa (in combination with placebo (see Section 3e)	Participants were included in the trial if they had: • A forced vital capacity (FVC; see Section 3e for definition) 30% or more of the predicted value for healthy adults. • Two six-minute walk distances (6MWDs; see Section 3e for definition), of 75 m or more, but less than 90% of the predicted distance for healthy adults. Participants were excluded from participating if: • They received previous treatment with a gene therapy. • They required support with breathing for more than six hours a day.	Complete

ATB200-02 (NCT02675465) (25) Phase I/II	International	23 participants	Male and female adults (aged between 18 and 75 years) with Pompe disease	None	Participants were excluded from participating if they had an allergy to miglustat or similar substances.	December 2023 (this study is ongoing at the time of this submission)
ATB200-04 (NCT03911505) (26) Phase III	International	Estimated: 22 participants	Male and female children (aged 0 to 18 years old) with LOPD	None	All included participants had an FVC 30% or more than what is predicted for a healthy person similar to them. Included participants aged between 12 and 18 years old had a 6MWD of 75 m or more. Included participants aged 5 years and older and less than 12 years old had a 6MWD of 40 m or over. Participants were excluded from participating if: • They received previous treatment with a gene therapy. • They required support with breathing for more than six hours a day.	June 2026
ATB200-07 (NCT04138277) (27) Phase III (Open Label Extension)	International	Estimated: 110 participants	Male and female adults (aged 18 years or older) with LOPD	None	This trial is a continuation of the PROPEL trial, so all participants in this trial were in the PROPEL trial.	December 2023
ATB200-08 (NCT04808505) (28) Phase III	International	Estimated: 22 participants	Male and female children (aged between 0 to 18 years old) with IOPD	None	If participants were already taking an enzyme replacement therapy, they must have experienced a decline in how well it was working to be included.	February 2025

Abbreviations: 6MWD: six-minute walk distance; FVC: forced vital capacity; IOPD: infantile-onset Pompe disease; LOPD: late-onset Pompe disease.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

How well does cipaglucosidase alfa in combination with miglustat work?

Amicus conducted the PROPEL trial, a Phase III clinical trial of 123 adults with LOPD. This study measured the efficacy (how well the drug works) and safety (side effects) of cipaglucosidase alfa in combination with miglustat. This was compared with alglucosidase alfa.(29)

Amicus also conducted a Phase I/II clinical trial called ATB200-02 of 23 adults with LOPD, which has studied the efficacy of cipaglucosidase alfa in combination with miglustat over 4 years so far. All participants included in this trial received cipaglucosidase alfa in combination with miglustat.(30)

The effect of cipaglucosidase alfa in combination with miglustat on the ability to walk is important to many people with Pompe disease, as moving around requires a combination of muscle, lung, and heart function.(31) People who are less able to walk may require more support to move around and complete daily activities (See Section 2a). The ability to breathe is also important to measure, as people with LOPD often need support with breathing (e.g. with a ventilator).(29) Therefore, in both studies, the effect of cipaglucosidase alfa in combination with miglustat was measured in many ways:

- Change in **ability to walk**: people were instructed to walk as far as possible in 6 minutes. This is called the six-minute walk test (6MWT). The change in the distance (6MWD) they could walk between the beginning and the end of the trial was measured.
- Change in **ability to breathe**: people were instructed to take a deep breath in. Then, the amount of air they could breathe out was measured, as a proportion of the amount that a healthy person should be able to breathe out. This is called forced vital capacity (FVC) % predicted. The change in FVC % predicted between the beginning and the end of the trial was measured.
- Change in **strength**: people were instructed to hold their hip or knee at a specific point and push against gravity or a doctor pushing down to determine the strength of the muscles. This is called manual muscle testing. The change in strength at the beginning and the end of the trial was measured.

The results of each of these assessments are outlined below.

Ability to walk

In the PROPEL trial, after 52 weeks (1 year) of treatment:

- On average, individuals who received cipaglucosidase alfa in combination with miglustat saw improvements in the distance they could walk in 6 minutes. This improvement was ‘clinically meaningful’ because of the difference it could make to the lives of adults with LOPD.

- Individuals who received alglucosidase alfa saw smaller improvements in the distance they could walk in 6 minutes.
- The improvement with cipaglucosidase alfa in combination with miglustat was numerically larger than the improvement with alglucosidase alfa but not statistically significant.(29)

In the ATB200-02 trial, people were able to walk further than they could at start of the study. This improvement in the distance walked has been maintained over 4 years of treatment with cipaglucosidase alfa in combination with miglustat.(30)

Ability to breathe

In the PROPEL trial, after 52 weeks (1 year) of treatment:

- On average, individuals who received cipaglucosidase alfa in combination with miglustat saw a slight worsening in FVC % predicted.
- Individuals who received alglucosidase alfa saw more worsening in FVC % predicted.
- The worsening in FVC % predicted with cipaglucosidase alfa in combination with miglustat was significantly smaller than with alglucosidase alfa. This means that FVC % predicted did not worsen as much with cipaglucosidase alfa in combination with miglustat as it did with alglucosidase alfa.(29) This also represented a clinically meaningful benefit to patients.

In the ATB200-02 trial, FVC % predicted also increased and then remained stable throughout 4 years of treatment with cipaglucosidase alfa in combination with miglustat.(30)

Strength

In the PROPEL trial, after 52 weeks (1 year) of treatment:

- On average, individuals who received cipaglucosidase alfa in combination with miglustat saw improvements in strength (manual muscle testing).
- Individuals who received alglucosidase alfa saw smaller improvements in strength.
- The improvement with cipaglucosidase alfa in combination with miglustat was larger than the improvement with alglucosidase alfa.(29)

In the ATB200-02 trial, people's strength was higher after 4 years of treatment with cipaglucosidase alfa in combination with miglustat, compared with the start of the study.(30)

It should be noted that in both trials, the number of people taking part was small. This is common in rare diseases such as Pompe disease, but it makes it difficult to generate high-quality, reliable evidence.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

How did cipaglucosidase alfa in combination with miglustat affect individuals' quality of life?

In the PROPEL trial, quality of life was measured by asking participants to answer questionnaires at the beginning and the end of the trial. These questionnaires are called 'patient-reported outcomes'.

- Patient-Reported Outcomes Measurement Information System (PROMIS) – Physical Function score: this measures a person's ability to carry out daily activities
- Subject's Global Impression of Change (SGIC) score: this measures a wide variety of aspects of quality of life
- EQ-5D-5L: this measures a person's mobility, self-care, usual activities, pain/discomfort and anxiety/depression
- Rasch-built Pompe-specific activity (R-PAct) score: this measures a person's ability to carry out daily activities and their social participation. This questionnaire was designed specifically for Pompe disease.

On average, scores in the majority of patient-reported outcomes improved more with cipaglucosidase alfa in combination with miglustat, compared with alglucosidase alfa. This means that people's quality of life generally improved more with cipaglucosidase alfa in combination with miglustat, and they were better able to complete daily activities.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Safety of cipaglucosidase alfa in combination with miglustat

Like all medicines, cipaglucosidase alfa in combination with miglustat can cause side effects, although not everybody gets them.

In the clinical trials, cipaglucosidase alfa in combination with miglustat was generally a well-tolerated treatment. Side effects were mainly seen while people were being infused with cipaglucosidase alfa or shortly after.(22, 24)

Infusion-associated reactions: These are symptoms that occur shortly after receiving an infusion. Symptoms may include difficulty breathing, bloating, fever, chills, dizziness, skin redness, itchy skin and rash. Most infusion-associated reactions are mild or moderate. (22, 24)

Allergic reactions: Allergic reactions may include symptoms such as rash anywhere on the body, puffy eyes, prolonged difficulty breathing, cough, swelling of the lip, tongue or throat, itchy skin and hives.(22, 24)

The table below summarises the side effects which have been seen with this treatment.(22, 24)

	Cipaglucosidase alfa	**Miglustat**
Very common side effects (may affect more than 1 in 10 people)	• Headache	• Headache
Common side effects (may affect up to 1 in 10 people)	• Cough • Sudden reddening of the face, neck or upper chest • Pain in chest • Rash, itching • Rise in blood pressure • Sweating • Bloating • Passing gas or wind • Loose, runny stools • Vomiting • Nausea • Fever or chills • Hives • Swelling or pain in the body area where needle was inserted • Muscle cramps, muscle pain, muscle weakness • Involuntary shaking of one or more parts of the body • Increased sweating • Pain • Altered sense of taste • Feeling tired all the time or feeling sleepy • Shortness of breath	• Shortness of breath • Sudden reddening of the face, neck or upper chest • Rise in blood pressure • Stomach pain • Bloating • Passing gas or wind • Loose, runny stools • Trouble passing stools • Vomiting • Fatigue • Nausea • Fever • Very itchy hives (urticaria) • Itchy rash, wanting to scratch • Chills • Muscle cramps, muscle pain, muscle weakness • Involuntary shaking of one or more parts of the body • Increased sweating • Pain • Altered sense of taste
Uncommon side effects (may affect up to 1 in 100 people)	• Breathing difficult and triggers coughing, a whistling sound (wheezing) when you breathe out, and shortness of breath (asthma) • Allergic reaction • Swelling in the hands, feet, ankles, legs • Swelling of the skin • Indigestion • Belly pain • Constant feeling of being tired	• Asthma • Allergic reaction • Uneasy stomach • Indigestion • Sore or irritated throat • Painful and abnormal contractions of the throat • Feeling of uneasiness, overall feeling of being sluggish • Feeling jittery • Swelling in the hands, feet, ankles, legs • Constant feeling of being tired

	• Sore or irritated throat • Painful and abnormal contractions of the throat • Mouth irritation • Mouth pain or discomfort in the back of the mouth • Pain in the cheek, gums, lips, chin • Loss of strength and energy, feeling weak • Feeling of uneasiness, overall feeling of being sluggish • Burning sensation • Scratch or damage to the skin • Changes in body temperature • Decrease in a type of white blood cell – shown in tests • Feeling drowsy • Feeling dizzy • Pain in joints • Pain in the area between the hip and rib • Muscle fatigue • Increased rigidity of muscles • Cannot hold or maintain balance • Low blood pressure • Feeling of near fainting • Pain in one or both sides of the head, throbbing pain, aura, eye pain, sensitivity to light (migraine) • Skin discolouration	• Unusual paleness of the skin • Low blood pressure • Decrease in platelets or a type of white blood cell – shown in tests • Pain in joints • Pain in the area between the hip and rib • Muscle fatigue • Increased rigidity of muscles • Feeling drowsy • Pain in one or both sides of the head, throbbing pain, aura, eye pain, sensitivity to light (migraine) • Skin discolouration • Balance disorder

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Unmet need

Since alglucosidase alfa can sometimes work less well over time, and is not effective in some people,(13) there is a substantial unmet need for effective treatments for adults with LOPD who:

- Do not experience improvement in their symptoms using alglucosidase alfa,
- Experience a decline in the effectiveness of alglucosidase alfa over time,

- Have not yet received treatment for Pompe disease.

Benefits of cipaglucosidase alfa in combination with miglustat

Based on available data from the PROPEL and ATB200-02 studies, we have found that in comparison to people treated with alglucosidase alfa, people treated with cipaglucosidase alfa in combination with miglustat:

- Experienced an increase in ability to walk, ability to breathe and their strength.(29)
- Experienced increased or similar quality of life scores.(29)
- Experienced a similar safety profile.(29)

3i) Summary of key disadvantages of treatment for people

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration.
- What is the impact of any disadvantages highlighted compared with current treatments

Like all medications, cipaglucosidase alfa in combination with miglustat can cause side effects, although not everybody gets them. These represent the key disadvantage for people taking cipaglucosidase alfa in combination with miglustat. The main side effects that people taking cipaglucosidase alfa in combination with miglustat should look out for are listed above in Section 3g.

Cipaglucosidase in combination with miglustat must be taken on an empty stomach. People receiving treatment cannot eat for the two hours before and after taking miglustat. In contrast to other enzyme replacement therapies, cipaglucosidase alfa in combination with miglustat requires that patients take miglustat as a separate capsule, in addition to the infusion.(22)

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life

How the model reflects LOPD

In order to assess the cost-effectiveness of cipaglucosidase alfa in combination with miglustat, an economic model was developed in accordance with NICE guidelines. This model was designed to predict the costs and quality of life gains for a group of people with LOPD over their whole lifetime. The model was made up of 'health states'. These health states described the severity of someone's disease based on how much support they need with moving around and breathing. As an example, health states could be described by 'no support', 'wheelchair' or 'invasive ventilation'. Each health state was assigned with a certain level of quality of life. Experienced clinicians agreed that many aspects of the model represented the reality of Pompe disease.

The model consisted of hypothetical people with Pompe disease with certain abilities to walk and breathe. They received treatment with either cipaglucosidase alfa in combination with miglustat or alglucosidase alfa over their lifetime. Based on the treatment they received, their abilities to walk and breathe changed over their lifetime. This change was informed partly by results from the clinical trials. As their health declined, they moved through health states, meaning that they required more mobility and/or breathing support. The model calculated the amount of time each person spent in each health state. As each health state was assigned with a certain level of quality of life, the model was able to calculate the overall quality of life experienced by each person over their lifetime. The possibility of death was also factored into the model.

Modelling how the costs of treatment differ with the new treatment

Costs were assigned to each health state based on the level of mobility and breathing support a person required. For example, costs of wheelchairs or ventilation were used. The cost of each treatment was also used in the model.

Uncertainty

As mentioned before, the PROPEL trial had a small number of participants compared with trials for non-rare diseases, which means there may be uncertainty in the results of the PROPEL trial. Also, in order to develop the model, some assumptions were made where data were not available. For example, only 3 years of clinical trial data were available to use. Therefore, assumptions were made around how quickly the disease progresses after 3 years of treatment.

These assumptions have been tested in the model and the impact on the results presented in Document B of the submission. The cost-effectiveness results did not change substantially when alternative assumptions were used.

Cost-effectiveness results

Cipaglucosidase alfa in combination with miglustat was associated with a greater benefit to health at a lower cost than alglucosidase alfa.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Cipaglucosidase alfa has a modified structure compared with alglucosidase alfa. This means the body can process it in the same way as GAA.(1) Cipaglucosidase alfa is also given with miglustat – this makes the treatment innovative by improving how well cipaglucosidase alfa works. Miglustat allows cipaglucosidase alfa to stay 'active' while it is travelling through the blood stream to muscle cells. This means that more medication can be delivered to muscle cells to break down the glycogen that has built-up.(1) As a result, cipaglucosidase alfa in combination with miglustat can increase the ability to breathe, move around and muscle strength, in comparison to treatment with alglucosidase alfa.(29, 32) The effectiveness of alglucosidase alfa treatment has been shown to decline in some people with Pompe disease.(13) The design of cipaglucosidase alfa in combination with miglustat represents an innovation in treatment, as effectiveness has been demonstrated to continue over time.(32) As described in Section 2a, Pompe disease can impact an individual's ability to move and complete daily activities, which can make them more dependent on their caregivers.(4, 11) The improvement in efficacy is also expected to help patients and their caregivers have more time for work and social activities. The economic model did not capture all of the benefits of cipaglucosidase alfa in combination with miglustat. For example, it did not capture improvements in muscle strength. Also, the model did not capture the fact that cipaglucosidase alfa in combination with miglustat offers an alternative treatment option to alglucosidase alfa. This is especially important for people who cannot receive alglucosidase alfa, or no longer benefit from taking alglucosidase alfa. Cipaglucosidase alfa in combination with miglustat has been awarded a Priority Innovative Medicines (PIM) designation by the Medicines and Healthcare products Regulatory Agency (MHRA) in 2020.(33) This was because of its effectiveness in improving the ability to walk, ability to breathe, and muscle strength, based on the results of people treated with cipaglucosidase alfa in combination with miglustat in the ATB200-02 trial (See Section 3e). PIM designations are only awarded to treatments that could offer a major advantage for people with conditions where existing methods of treatment have serious limitations.(34)

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.
There are currently no widely used treatments for people who do not respond to, or whose response declines with, alglucosidase alfa. Amicus strongly believes all adults with LOPD should have access to the appropriate medicines (including cipaglucosidase in combination

with miglustat) and not be restricted by reasons of their previous treatments, disability status or how much their disease has progressed.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information about Pompe Disease

- NORD Rare Disease Database; Pompe Disease: https://rarediseases.org/rare-diseases/pompe-disease/

Patient groups

- Association for Glycogen Storage Disease UK: https://agsd.org.uk/
- Pompe Support Network: https://pompe.uk/
- International Pompe Association: https://www.worldpompe.org/

Further information about cipaglucosidase alfa in combination with miglustat

- MHRA Early Access to Medicines Scheme – Treatment protocol – Information for patients; Cipaglucosidase alfa in combination with miglustat: https://www.gov.uk/government/publications/cipaglucosidase-alfa-with-miglustat-in-the-treatment-of-late-onset-pompe-disease/cipaglucosidase-alfa-with-miglustat-treatment-protocol-information-for-patients

Further information on NICE and the role of patients

- Public Involvement at NICE: Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in health technology assessment (HTAs): Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://toolbox.eupati.eu/resources/guidance-for-patient-involvement-in-hta/EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative: https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in

Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Six-minute walk distance	The distance walked in the six-minute walk test (6MWT)
Six-minute walk test	A test in which a person is instructed to walk as far as they can in six minutes
Acid alfa-glucosidase	A protein found in muscle cells responsible for breaking down a molecule called glycogen
Active	An active enzyme is one that is working properly
Advisory board	A type of meeting in which people discuss certain predefined topics
Alglucosidase alfa	An enzyme replacement therapy for Pompe disease which is currently approved. Also called
ATB200-02	The Phase II trial of cipaglucosidase alfa in combination with miglustat
Avalglucosidase alfa	An enzyme replacement therapy that has been recently approved for the treatment of Pompe
Blood vessels	Tubes that carry blood through the body
Bloodstream	The blood circulating through the body
Cell	Muscles and organs are made of small units called cells
Cipaglucosidase alfa	One part of the treatment in this submission. It is an enzyme replacement therapy
Clinical trial	A research study that measures how well and safe a treatment is. Examples are PROPEL and
Clinically meaningful	Makes a meaningful difference to someone with the disease, their carer or doctor
Deoxyribonucleic acid (DNA)	Genetic material in cells that provide instructions for making proteins
Economic model	A 'simulation' of the disease which weighs up the costs and benefits of the disease
Efficacy/effectiveness	How well a treatment works
Eligibility criteria	Criteria which determine who can and cannot take part in a trial
Enzyme	A type of protein that causes chemical changes. An example is GAA
Enzyme replacement therapy	A treatment that replaces missing enzymes in the body
Equitable	Fair or just
Forced vital capacity	The amount of air a person can breathe out after a deep breath in
Gene therapy	A treatment which modifies a gene
Glucose	A type of sugar
Glycogen	The form of glucose stored in muscle cells, made up of many connected glucose molecules
Health state	A description of someone's health

Infantile-onset Pompe disease	A type of Pompe disease which usually starts before 1 year of age
Infusion-associated reaction	Symptoms that occur soon after receiving an infusion
Late-onset Pompe disease	A type of Pompe disease which usually starts before 1 year of age
Marketing authorisation	Approval to bring a treatment to market
Medicines and Healthcare products Regulatory Agency (MHRA)	The government body in the UK which is responsible for ensuring that medicines and medic
Miglustat	One part of the treatment in this submission. It stabilises enzymes
Myozyme®	The brand name for alglucosidase alfa
Open label extension	The continuation of a clinical trial, in which participants know what treatment they rec
Patient-reported outcomes	Measures of a person's quality of life
Phase	The stage of a clinical trial in the development process of a treatment
Physiotherapist	A professional that helps to restore movement and function when someone is affected by injury, illness or disability.
Placebo	A substance that has no effect on the body
Pompe disease	A rare condition where muscle cells do not have enough of the protein GAA
PROPEL	The Phase III trial of cipaglucosidase alfa in combination with miglustat
Protein	Large molecules that have different uses in the body. An example is an enzyme
Quality of life	the way people experience life
Respiratory support	Help with breathing, with e.g., a ventilator
Roundtable	A type of meeting in which people discuss certain predefined topics
Safety	The number and severity of side effects
Side effect	Unwanted effects of a treatment
Sleep apnoea	When breathing stops and starts during sleep
Therapy	Treatment intended and expected to alleviate a disease or disorder
Ventilator	A device which helps people breathe
x-ray	A diagnostic test which uses invisible electromagnetic energy beams to produce images of

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pompe disease - cipaglucosidase alfa

Clarification questions

December 2022

File name	Version	Contains confidential information	Date
ID3771_Cipaglucosidase alfa with miglustat clarification questions_Company response_02Dec22_redacted	1.0	Yes	02Dec22

Section A: Clarification on effectiveness data

Additional information required

A1. Please provide an update on the marketing authorisation status for cipaglucosidase alfa in combination with miglustat.

The marketing authorisation for cipaglucosidase alfa in adults with late-onset Pompe disease (LOPD) is expected in [redacted] following Committee for Medicinal Products for Human Use (CHMP) opinion as early as [redacted]. [redacted]

A2. PROPEL trial enrolment was from December 2018 to November 2019 and the open label extension is ongoing (results expected December 2023). Are there any interim results available for the open label extension study, e.g. 2 years?

Interim results from the open-label extension study of PROPEL are not yet available; these are anticipated in H1 2023. Amicus would be happy to provide these interim results to NICE when they become available.

A3. Priority Question: Please supply the appendix to the CSR for the PROPEL trial which includes the statistical analysis plan (SAP) and all of the tables and figures**.**

The full clinical study report (CSR; including appendices) and SAP for the PROPEL trial has been submitted along with this response to the evidence assessment group (EAG) clarification questions.

Systematic review

A4. In Appendix D the PRISMA flow diagram states that 36 studies are excluded because they do not report on relevant clinical outcomes, and the Amicus Indirect Treatment Comparison report states 15 studies were excluded based on outcome data. Please clarify. Just because outcomes are not reported does not mean they were not measured. Were authors contacted to ascertain if they were measured? If not, then the impact of selective reporting on this review could be substantial.

Given that the systematic reviews developed for this appraisal have been used to identify high-quality studies relevant to the decision problem, it was determined that any articles that did not report relevant clinical outcomes should not be included in the review and submission. Subsequently, any studies where the outcome assessment was not feasible to obtain were excluded from both the indirect treatment comparison (ITC) and systematic literature reviews (SLRs). In terms of the differing number of studies excluded between the SLRs and ITC, the ITC

included an additional data restriction to exclude observational studies as these were deemed not to be of sufficient quality for inclusion.

Generally, there was no indication from the reported study methodologies that any of the studies measured more outcomes than they reported; therefore, authors were not contacted.

We do not believe the impact of selective reporting, which is inherent to systematic reviews in general, to be any more substantial in our review than in other reviews which apply inclusion criteria based on outcome reporting. As added reassurance, quality assessments which assess the risk of bias associated with missing data have been conducted for all studies included within the review.

A5. Risk of bias assessments using ROBINS-I should be undertaken at the result level but they have been completed at the study level. Please complete all risk of bias assessments for each outcome in each study.

The risk of bias assessments using Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) were undertaken at a study level because any issues identified for each domain at the study level are likely to apply to all outcomes within the study in question. It is expected that this approach of undertaking risk of bias assessment at the study level should not affect the overall quality assessment rating, within reasonable resource constraints.

PROPEL trial

A6. Please present the number of patients/observations used for analysis for all outcomes reported in the company submission (in tables, line charts and bar charts). Please provide an explanation for reduced numbers for some of the analyses (e.g. GSGC).

The number of participants/observations used for analysis of all outcomes reported in tables and figures in Document B of the submission are presented in Table 1 and Table 2, respectively. The reduced number of subjects for certain assessments at certain timepoints was due to: 1) missed assessments or 2) participant discontinuation from the study.

The PROPEL study was conducted during the initial wave of the COVID-19 lockdowns which contributed to missed assessments because of travel restrictions and/or sites only allowing critical assessments to be performed. Importantly, the percentage of subjects with missing data is approximately [redacted]% for the primary (6MWD) and first key secondary (FVC) endpoints. Additionally, the percentages with missing data are similar between treatment groups, indicating that the missing at random (MAR) assumption is not violated and further supporting the robustness of these data. The greater percentage of missing assessments for GSGC may be due to the composite nature of this tool (four separate manoeuvres) – if a participant did not complete any one of the four manoeuvres, this would be considered a missed assessment. The outlier participant (described in Section B.2.4.1) is not included in the alglucosidase alfa arm (n = 37).

Table 1. Number of participants reported in outcome tables in Document B (excluding outlier participant)

Table (outcome)	Data point	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 37)
Table 17 (6MWD)	Baseline	85	37
	Change from Baseline at Week 52 (LOCF)	85	37
	MMRM parameter estimation (OBS)	[redacted]	[redacted]
Table 19 (FVC % predicted)	Baseline	85	37
	Change from Baseline at Week 52 (LOCF)	84	37
	Parameter estimation and comparison from ANCOVA (LOCF)	84	37
Table 21 (MMT lower extremity score)	Baseline	[redacted]	[redacted]
	Change from Baseline at Week 52	80	34
	Parameter estimation and comparison from ANCOVA (ITT-LOCF)	80	34
Table 23 (GSGC total score)	Baseline	74	32
	Change from Baseline at Week 52 (LOCF)	72	30
	Parameter estimation and comparison from ANCOVA (LOCF)	72	30
Table 24 (PROMIS - Physical Function Short Form)	Baseline	84	37
	Change from Baseline (LOCF)	84	37
	ANCOVA parameter estimation and comparison at Week 52 (LOCF)	84	37
Table 25 (PROMIS-Fatigue short form 8a)	Baseline	85	37
	Change from Baseline at Week 52	85	37
	ANCOVA parameter estimation and comparison at Week 52 (LOCF)	85	37
Table 26 (Biomarkers - CK)	Baseline	85	37
	Change from Baseline at Week 52 (LOCF)	85	37
	Parameter estimation and comparison from ANCOVA (LOCF)	85	37

Table 27 (Biomarkers – Hex4)	Baseline	84	37
	Change from Baseline at Week 52 (LOCF)	84	37
	Parameter estimation and comparison from ANCOVA (LOCF)	84	37

Abbreviations: 6MWD: 6-minute walk distance; ANCOVA; analysis of covariance; CK: creatine kinase; FVC: forced vital capacity; GSGC; Gait, Stairs, Gowers' manoeuvre, and Chair; Hex4: hexose tetrasaccharide; ITT: Intention-to-Treat; LOCF: last observation carried forward; MMT: manual muscle test; NA: not applicable; OBS: observed; PROMIS: Patient-reported Outcomes Measurement Information System.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Table 2. Number of participants reported in outcome figures in Document B (excluding outlier participant)

Figure (outcome)	Data point	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 37)
Figure 8 (6MWD)	Baseline (OBS)	85	37
	Week 12 (OBS)	83	37
	Week 26 (OBS)	73	34
	Week 38 (OBS)	78	35
	Week 52 (LOCF)	[redacted]	[redacted]
Figure 9 (6MWD)	Proportion of participants with change from Baseline from grouped by consolidated ranges	[redacted]	[redacted]
Figure 10 (FVC % Predicted)	Baseline (OBS)	85	37
	Week 12 (OBS)	81	37
	Week 26 (OBS)	72	32
	Week 38 (OBS)	71	32
	Week 52 (LOCF)	84	37
Figure 11 (FVC % Predicted)	Proportion of participants with change from Baseline from grouped by consolidated ranges	[redacted]	[redacted]
Figure 12 (MMT lower extremity)	Baseline (OBS)	[redacted]	[redacted]
	Week 12 (OBS)	[redacted]	[redacted]
	Week 26 (OBS)	[redacted]	[redacted]
	Week 38 (OBS)	[redacted]	[redacted]
	Week 52 (LOCF)	[redacted]	[redacted]
Figure 13 (GSGC)	Baseline (OBS)	[redacted]	[redacted]
	Week 12 (OBS)	[redacted]	[redacted]
	Week 26 (OBS)	[redacted]	[redacted]
	Week 38 (OBS)	[redacted]	[redacted]

	Week 52 (LOCF)	[redacted]	[redacted]
Figure 14 (PROMIS-Physical Function)	Baseline (OBS)	[redacted]	[redacted]
	Week 12 (OBS)	[redacted]	[redacted]
	Week 26 (OBS)	[redacted]	[redacted]
	Week 38 (OBS)	[redacted]	[redacted]
	Week 52 (LOCF)	[redacted]	[redacted]
Figure 15 (SGIC overall physical wellbeing)	Score at Week 52 compared to Baseline	[redacted]	[redacted]
Figure 16 (Biomarkers - CK)	Baseline (OBS)	85	37
	Week 2 (OBS)	[redacted]	[redacted]
	Week 4 (OBS)	[redacted]	[redacted]
	Week 6 (OBS)	[redacted]	[redacted]
	Week 12 (OBS)	82	36
	Week 26 (OBS)	78	37
	Week 38 (OBS)	77	35
	Week 52 (LOCF)	85	37
Figure 17 (Biomarkers – Hex4)	Baseline (OBS)	84	37
	Week 2 (OBS)	[redacted]	[redacted]
	Week 4 (OBS)	[redacted]	[redacted]
	Week 6 (OBS)	[redacted]	[redacted]
	Week 12 (OBS)	[redacted]	[redacted]
	Week 26 (OBS)	[redacted]	[redacted]
	Week 38 (OBS)	[redacted]	[redacted]
	Week 52 (LOCF)	85	37

Abbreviations: 6MWD: 6-minute walk distance; ANCOVA; analysis of covariance; CK: creatine kinase; FVC: forced vital capacity; GSGC: Gait, Stairs, Gowers' manoeuvre, and Chair; Hex4: hexose tetrasaccharide; ITT: Intention-to-Treat; LOCF: last observation carried forward; MMT: manual muscle test; NA: not applicable; OBS: observed; PROMIS: Patient-reported Outcomes Measurement Information System; SGIC: Subject Global Impression of Change.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

A7. Please provide details of the number of patients in each treatment arm for which LOCF was used in the analysis.

For the primary and key secondary endpoints in PROPEL, Table 3 presents the numbers of observed values and values determined by last observation carried forward (LOCF).

Table 3. Analysis populations (PROPEL)

	Cipaglucosidase alfa in combination with miglustat	Alglucosidase alfa in combination with placebo
Primary endpoint: Change from Baseline in 6MWD at Week 52		
Number of observations used for analysis	[redacted]	[redacted]

Number of values determined by LOCF, n	[redacted]	[redacted]
Total number of values used in analysis (Week 52-LOCF), n	85	37
Key secondary endpoint: Change from Baseline in FVC % predicted at Week 52		
Number of observations used for analysis	[redacted]	[redacted]
Number of values determined by LOCF, n	[redacted]	[redacted]
Total number of values used in analysis (Week 52-LOCF), n	84[a]	37

[a]One participant had baseline FVC result of 70.5% but subsequently withdrew consent due to not wanting to travel to the site and was therefore excluded from analysis.
Abbreviations: 6MWD: 6-minute walk distance; FVC: forced vital capacity; LOCF: last observation carried forward.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report) Table 14.2.2.1.1.b1 and Table 14.2.3.1.1.b1.[1]

A8. Please provide additional subgroup analysis results for ERT-experienced and ERT-naïve populations for the following outcomes: PROMIS – physical function, PROMIS – fatigue, GSGC, SGIC, PGIC and adverse effects.

[redacted], the total population considered in the pre-invitation scope, and the National Institute for Health and Care Excellence (NICE) appraisal for avalglucosidase alfa, this submission focuses on the total population of adults with LOPD without considering prior treatment status. Expert clinical opinion indicates that there is no reason to expect different efficacy results between enzyme replacement therapy (ERT)-experienced and ERT-naïve adults with LOPD, as there is no expected biological plausibility for a difference between the people in these groups.[2]

Although data from the ERT-experienced and ERT-naïve subgroups in the PROPEL clinical trial are presented in the submission and below for completeness, Amicus considers that prior ERT status should not be a factor in accessing treatment with cipaglucosidase alfa in combination with miglustat in the interests of fair and equitable access.

ERT-experienced population

PROPEL secondary efficacy endpoint in the ERT-experienced population: Change in the PROMIS-Physical Function total score from Baseline to Week 52

A numerically greater improvement in Patient-Reported Outcomes Measurement Information System (PROMIS)-Physical Function total score from Baseline to Week 52 was observed with cipaglucosidase alfa in combination with miglustat (1.76; SD: 7.179) vs. alglucosidase alfa (-0.97; SD: 11.196; Table 4; a higher score indicates better physical function). For the analysis of covariance (ANCOVA) model, the least squares (LS) mean treatment difference was 3.14 (SE: [redacted]), with a nominal 2-sided p-value of [redacted].[1] Numerical benefits in this participant-reported physical function outcome were sustained to Week 52 (Figure 1).[1]

Table 4: Summary of change in PROMIS-Physical Function Short Form 20a by visit from Baseline to Week 52 (ITT Population, excluding outlier participant) and ANCOVA model (ITT-LOCF population) – ERT-experienced population [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 65)	Alglucosidase alfa in combination with placebo (n = 30)
Baseline[a] mean (SD)	64.43 (11.379)	66.87 (12.286)
Change from Baseline at Week 52, mean (SD)	1.76 (7.179)	-0.97 (11.196)
ANCOVA parameter estimation and comparison at Week 52[a]		
n	64	30
LS mean difference (SE)	3.14 ([redacted])	
95% CI	(-0.73, 7.02)	
2-sided p-value	[redacted]	

The total score ranged from 20 to 100, with higher scores indicating less impact on physical function.
[a]Baseline was the last non-missing value prior to the administration of the first dose of study drug.
[b]All estimates were obtained from the ANCOVA model including terms for treatment, baseline PROMIS Physical Function total score, age, height, weight (all as continuous covariates), and gender.
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; ERT: enzyme replacement therapy; ITT: Intention-to-Treat; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LS: least squares; PROMIS: Patient-reported Outcomes Measurement Information System; SD: standard deviation; SE: standard error.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Figure 1: Line chart for LS mean (SE) of change from Baseline in PROMIS-Physical Function over time (ITT-LOCF population) – ERT-experienced population [PROPEL]

LS mean and SE were obtained from the analysis of covariance model.
Abbreviations: ERT: enzyme replacement therapy; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LS: least squares; PROMIS: Patient-reported Outcomes Measurement Information System; SE: standard error.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Table 5: Number of participants included in the analysis of PROMIS-Physical Function Short Form 20a each time point – ERT-experienced population (ITT-LOCF population) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 65)	Alglucosidase alfa in combination with placebo (n = 30)
Baseline	[redacted]	[redacted]
Week 12	[redacted]	[redacted]
Week 26	[redacted]	[redacted]
Week 38	[redacted]	[redacted]
Week 52	[redacted]	[redacted]

Abbreviations: ERT: enzyme replacement therapy; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; PROMIS: Patient-reported Outcomes Measurement Information System
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

PROPEL key secondary efficacy endpoint in the ERT-experienced population: Change in the PROMIS-Fatigue total score from Baseline to Week 52

The PROMIS-Fatigue scores showed a mean improvement from Baseline to Week 52 in participants treated with cipaglucosidase alfa in combination with miglustat of -1.87 (SD: 5.838) and with alglucosidase alfa of -0.27 (SD: 5.265; Table 6; a lower score indicates less fatigue). For the ANCOVA model, the LS mean treatment difference was -0.84 (95% CI:-3.16, 1.49), with a nominal 2-sided p-value of [redacted] (Figure 2).[1]

Table 6: Summary of change in PROMIS-Fatigue Short Form 8a by visit from Baseline to Week 52 (ITT population, excluding outlier participant) and ANCOVA model total score (ITT-LOCF population) – ERT-experienced population [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 65)	Alglucosidase alfa in combination with placebo (n = 30)
Baseline[a] mean (SD)	22.00 (7.924)	20.37 (5.379)
Change from Baseline at Week 52, mean (SD)	-1.87 (5.838)	-0.27 (5.265)
Parameter estimation and comparison from ANCOVA[b]		
n	65	30
LS mean difference (SE)	-0.84 ([redacted])	
95% CI	(-3.16, 1.49)	
2-sided p-value	[redacted]	

If post-Baseline scores were partially missing but ≥ 50% of items were available, the total score was calculated as the average of non-missing items multiplied by the total number of items expected.
The total score ranged from 8 to 40, with lower score indicating less impact by fatigue, and it was calculated by summing scores (1 to 5) across all 8 items.
[a]Baseline was the last non-missing value prior to the administration of the first dose of study drug
[b]All estimates were obtained from the ANCOVA model including terms for treatment, baseline PROMIS-Fatigue total score, age, height, weight (all as continuous covariates, and gender.

Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; ERT: enzyme replacement therapy; ITT: Intention-to-Treat; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LOCF: last observation carried forward; LS: least squares; PROMIS: Patient-reported Outcomes Measurement Information System; SD: standard deviation; SE: standard error.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Figure 2: Line chart for LS mean (SE) of change from Baseline in PROMIS-Fatigue total score over time (ITT-LOCF population) – ERT-experienced population [PROPEL]

LS mean and SE were obtained from the analysis of covariance model.
Abbreviations: ERT: enzyme replacement therapy; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LS: least squares; PROMIS: Patient-reported Outcomes Measurement Information System; SE: standard error.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Table 7: Number of participants included in the analysis of PROMIS-Fatigue at each time point – ERT-experienced population (ITT-LOCF population) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 65)	Alglucosidase alfa in combination with placebo (n = 30)
Baseline	[redacted]	[redacted]
Week 12	[redacted]	[redacted]
Week 26	[redacted]	[redacted]
Week 38	[redacted]	[redacted]
Week 52	[redacted]	[redacted]

Abbreviations: ERT: enzyme replacement therapy; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; PROMIS: Patient-reported Outcomes Measurement Information System
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

PROPEL key secondary efficacy endpoint in the ERT-experienced population: Change in the Gait, Stairs, Gowers' manoeuvre, and Chair *(GSGC) total score from Baseline to Week 52*

Similar to the overall ITT population, GSGC showed nominally significant improvements following treatment with cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa. Using LOCF values, a mean change from Baseline of -0.53 (SD: 2.534) was observed with cipaglucosidase alfa in combination with miglustat, compared with 0.61 (SD: 1.828) for the

alglucosidase alfa group (Table 8, Figure 8). For the ANCOVA model, the LS mean treatment difference was -1.19 (95% CI: -2.38, 0.00),[1] with a nominal 2-sided p-value of [redacted][1]

Table 8: Summary of change in GSGC total score by visit from Baseline to Week 52 (ITT Population excluding outlier participant) and ANCOVA model - ERT experienced population (ITT-LOCF population) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 55)	Alglucosidase alfa in combination with placebo (n = 25)
Baseline[a] mean (SD)	15.61 (4.073)	15.52 (4.350)
Change from Baseline at Week 52, mean (SD)	-0.53 (2.534)	0.61 (1.828)
Parameter estimation and comparison from ANCOVA[b]		
n	54	23
LS mean difference (SE)	-1.19 ([redacted])	
95% CI	(-2.38, 0.00)	
2-sided p-value	[redacted]	

Gait score is based on the 10-metre walk test; stairs score was based on the participant climbing stairs; Gowers' manoeuvre score was based on the participant lying down on the floor, then rising from the floor to get to a standing position; chair score was based on the participant arising from a sitting position in a chair to a standing position. GSGC total score was the sum of 4 tests and ranges from a minimum of 4 points (normal performance) to a maximum of 27 points (worst score).
[a]Baseline was the last non-missing value prior to the administration of the first dose of study drug.
[b]All estimates were obtained from the ANCOVA model including terms for treatment, baseline GSGC total score, age, height, weight (all as continuous covariates), and gender.
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; GSGC: Gait, Stairs, Gowers' manoeuvre, and Chair; ITT: Intention-to-Treat; LOCF: last observation carried forward; LS: least squares: SD; standard deviation.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Figure 3: Line chart for LS mean (SE) of change from Baseline over time in GSGC total score – ERT-experienced population (ITT-LOCF population)

Gait score was based on the 10-metre walk test; stairs score is based on the participant climbing stairs; Gowers' manoeuvre score was based on the participant lying down on the floor, then rising from the floor to get to a standing position; chair score was based on the participant arising from a sitting position in a chair to a standing position. GSGC total score was the sum of 4 tests and ranges from a minimum of 4 points (normal performance) to a maximum of 27 points (worst score). LS mean and SE were obtained directly from the ANCOVA model.
Abbreviations: ANCOVA: analysis of covariance; GSGC: Gait, Stairs, Gowers' manoeuvre, and Chair; ITT-LOCF: Intention-to-Treat–last observation carried forward; LS: least squares; SE: standard error
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Table 9: Number of participants included in the analysis of GSGC at each time point – ERT-experienced population (ITT-LOCF population) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 65)	Alglucosidase alfa in combination with placebo (n = 30)
Baseline	[redacted]	[redacted]
Week 12	[redacted]	[redacted]
Week 26	[redacted]	[redacted]
Week 38	[redacted]	[redacted]
Week 52	[redacted]	[redacted]

Abbreviations: ERT: enzyme replacement therapy; GSGC: Gait, Stairs, Gowers' manoeuvre, and Chair ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

PROPEL secondary efficacy endpoint in the ERT-experienced population: Analysis of Subject's Global Impression of Change *(SGIC) Overall Physical Wellbeing and Physician's Global Impression of Change (PGIC) from Baseline to Week 52*

The SGIC Overall Physical Wellbeing and PGIC Overall Status from Baseline to Week 52 are presented in Figure 4 and Figure 5, respectively. A greater percentage of participants treated with cipaglucosidase alfa in combination with miglustat had improving or stable scores at Week 52 than those treated with alglucosidase alfa.

Figure 4: SGIC overall physical wellbeing at Week 52 compared to Baseline in ERT-experienced participants (ITT population) [PROPEL]

Abbreviations: ERT: enzyme replacement therapy; SGIC: Subject's Global Impression of Change.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Table 10: Number of participants included in the analysis of SGIC overall physical wellbeing at Week 52 compared to Baseline point – ERT-experienced population (ITT-population) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 65)	Alglucosidase alfa in combination with placebo (n = 30)
n	[redacted]	[redacted]

Abbreviations: ERT: enzyme replacement therapy; ITT- intention to treat; SGIC: Subject's Global Impression of Change.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Figure 5: PGIC overall status at Week 52 compared to Baseline in ERT-experienced participants (ITT population) [PROPEL]

Abbreviations: ERT: enzyme replacement therapy; ITT: intention to treat; PGIC: Physician's Global Impression of Change.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Table 11: Number of participants included in the analysis of PGIC overall status at Week 52 compared to Baseline point – ERT-experienced population (ITT population) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 65)	Alglucosidase alfa in combination with placebo (n = 30)
n	[redacted]	[redacted]

Abbreviations: ERT: enzyme replacement therapy; ITT: intention to treat; PGIC: Physician's Global Impression of Change.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

PROPEL safety endpoint in the ERT-experienced population: Summary of treatment emergent adverse events (TEAEs)

The frequency of TEAEs was similar between the group of participants treated with cipaglucosidase alfa in combination with miglustat and alglucosidase alfa. A summary of TEAEs is presented in Table 12.

Table 12: Overall summary of TEAEs in PROPEL (ERT-experienced safety population)

	Cipaglucosidase alfa in combination with miglustat (n = 65)			Alglucosidase alfa in combination with placebo (n = 30)			Total (N = 95) n (%)
	Cipaglucosidase alfa n (%)	Miglustat n (%)	Total n (%)	Alglucosidase alfa n (%)	Placebo n (%)	Total n (%)	
Participants who had any TEAE			[redacted]			[redacted]	[redacted]
Participants who had any TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any serious TEAE			[redacted]			[redacted]	[redacted]
Participants who had any serious TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related serious TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A TEAE was defined as any event that started or changed in intensity on or after the first dose of study drug.

A study drug-related TEAE was defined as a TEAE with the corresponding relationship to study drug marked as definite, probable, or possible. For the total column under each treatment, the participant was counted only once under the category according to the worst relationship for any component of the treatment. If relationship was missing, it was classified as related.
Percentages were based on the number of participants in each treatment group for the Safety Population.
Abbreviations: TEAE: treatment-emergent adverse event
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

ERT-naive population

The results in the ERT-naïve population presented below should be interpreted considering the limitations provided by the small size (n=27), particularly in the alglucosidase alfa arm (n=7). As mentioned above, clinical experts noted that there is no reason to expect different efficacy results between ERT-experienced and ERT-naïve adults with LOPD, as there is no expected biological difference between the people in these groups.[2] For this reason, Amicus does not consider that prior treatment status should be a factor in accessing treatment with cipaglucosidase alfa in combination with miglustat in the interests of fair and equitable access.

PROPEL secondary efficacy endpoint in the ERT-naive population: Change in the PROMIS-Physical Function total score from Baseline to Week 52

Results for PROMIS-Physical Function scores showed improvement in both treatment groups. At Week 52 using LOCF values, the mean PROMIS-Physical Function score improvement was 2.50 (SD: 8.618) from Baseline for participants treated with cipaglucosidase alfa in combination with miglustat compared to the mean improvement of 5.14 (SD: 7.819) for the participants treated with alglucosidase alfa (a higher score indicates better physical function). For the ANCOVA model, the LS mean treatment difference was -5.09 (95% CI: -14.04, 3.85), with a nominal 2-sided p-value of [redacted] (Table 13, Figure 6).[1]

Table 13: Summary of change in PROMIS-Physical Function Short Form 20a by visit from Baseline to Week 52 (ITT Population) and ANCOVA model (ITT-LOCF Population, excluding outlier participant) – ERT-naïve population [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 20)	Alglucosidase alfa in combination with placebo (n = 7)
Baseline[a] mean (SD)	74.65 (11.984)	72.71 (16.317)
Change from Baseline at Week 52, mean (SD)	2.50 (8.618)	5.14 (7.819)
ANCOVA parameter estimation and comparison at Week 52[c]		
n	20	7
LS mean difference (SE)	-5.09 ([redacted])	
95% CI	(-14.04, 3.85)	
2-sided p-value	[redacted]	

The total score ranged from 20 to 100, with higher score indicating less impact on physical function.
[a]Baseline was the last non-missing value prior to the administration of the first dose of study drug.
[b]All estimates were obtained from the ANCOVA model including terms for treatment, baseline PROMIS-Physical Function total score, age, height, weight (all as continuous covariates), and gender.
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; ITT: Intention-to-Treat; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LS: least squares; PROMIS: Patient-reported Outcomes Measurement Information System; SD: standard deviation
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Figure 6: Line chart for LS mean (SE) of change from Baseline in PROMIS-Physical Function over time (ITT-LOCF Population, excluding outlier participant) – ERT-naïve population [PROPEL]

LS mean and SE were obtained from the analysis of covariance model.
Abbreviations: ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LS: least squares; PROMIS: Patient-reported Outcomes Measurement Information System; SE: standard error.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Table 14: Number of participants included in the analysis of PROMIS-Physical Function Short Form 20a each time point– ERT-naïve population [PROPEL] (ITT-LOCF Population, excluding outlier participant)

	Cipaglucosidase alfa in combination with miglustat (n = 20)	Alglucosidase alfa in combination with placebo (n = 7)
Baseline	[redacted]	[redacted]
Week 12	[redacted]	[redacted]
Week 26	[redacted]	[redacted]
Week 38	[redacted]	[redacted]
Week 52	[redacted]	[redacted]

Abbreviations: ERT: enzyme replacement therapy; Intention-to-Treat–Last Observation Carried Forward; PROMIS: Patient-reported Outcomes Measurement Information System
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

PROPEL key secondary efficacy endpoint in the ERT-naive population: Change in the PROMIS-Fatigue total score from Baseline to Week 52

PROMIS-Fatigue scores in both treatment groups showed improvement. At Week 52 using LOCF values, the mean improvement was -2.50 (SD: 5.630) from Baseline compared to a mean improvement of -7.70 (SD: 8.771) for the alglucosidase alfa group (a lower score indicates less fatigue). For the ANCOVA model, the LS mean treatment difference was 3.29 (95% CI: -3.69, 10.27), with a nominal 2-sided p-value of [redacted] (Table 6, Figure 7).[1]

Table 15: Summary of change in PROMIS-Fatigue short form 8a by visit from Baseline to Week 52 (ITT Population) and ANCOVA model total score (ITT-LOCF Population, excluding outlier participant) – ERT-naïve population [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 20)	Alglucosidase alfa in combination with placebo (n = 7)
Baseline[a] mean (SD)	23.10 (9.614)	24.13 (8.360)
Change from Baseline at Week 52, mean (SD)	-2.50 (5.630)	-7.70 (8.771)
Parameter estimation and comparison from ANCOVA[b]		
n	20	7
LS mean difference (SE)	3.29 ([redacted])	
95% CI	(-3.69, 10.27)	
2-sided p-value	[redacted]	

If post-Baseline scores were partially missing but ≥ 50% of items were available, the total score was calculated as the average of non-missing items multiplied by the total number of items expected.
The total score ranged from 8 to 40, with lower score indicating less impact by fatigue, and it was calculated by summing scores (1 to 5) across all 8 items.
[a]Baseline was the last non-missing value prior to the administration of the first dose of study drug
[b]All estimates were obtained from the ANCOVA model including terms for treatment, baseline PROMIS-Fatigue total score, age, height, weight (all as continuous covariates), and gender.
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; ITT: Intention-to-Treat; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LOCF: last observation carried forward; LS: least squares; PROMIS: Patient-reported Outcomes Measurement Information System; SD: standard deviation; SE: standard error
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Figure 7: Line chart for LS mean (SE) of change from Baseline in PROMIS-Fatigue total score over time (ITT-LOCF Population, excluding outlier participant) – ERT-naïve population [PROPEL]

LS mean and SE were obtained from the analysis of covariance model.
Abbreviations: ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LS: least squares; PROMIS: Patient-reported Outcomes Measurement Information System; SE: standard error.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Table 16: Number of participants included in the analysis of PROMIS-Fatigue at each time point – ERT-naïve population (ITT-LOCF Population, excluding outlier participant) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 20)	Alglucosidase alfa in combination with placebo (n = 7)
Baseline	[redacted]	[redacted]
Week 12	[redacted]	[redacted]
Week 26	[redacted]	[redacted]
Week 38	[redacted]	[redacted]
Week 52	[redacted]	[redacted]

Abbreviations: ERT: enzyme replacement therapy; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; PROMIS: Patient-reported Outcomes Measurement Information System
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

PROPEL key secondary efficacy endpoint in the ERT-naïve population: Change in the GSGC total score from Baseline to Week 52

At Week 52 using LOCF values, the mean change from Baseline in GSGC total score was -0.56 (SD: 2.640) from Baseline compared to a mean change of 1.3 (SD: 1.80) for the alglucosidase alfa group. For the ANCOVA model, the LS mean treatment difference was -1.32 (95% CI: -4.03, 1.39), with a nominal 2-sided p-value of [redacted](Table 17, Figure 8).[1]

Table 17: Summary of change in GSGC total score by visit from Baseline to Week 52 (ITT Population) and ANCOVA model - ERT naïve population (ITT-LOCF Population, excluding outlier participant) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 19)	Alglucosidase alfa in combination with placebo (n = 7)
Baseline[a] mean (SD)	11.32 (6.650)	10.86 (4.413)
Change from Baseline at Week 52, mean (SD)	-0.56 (2.640)	1.29 (1.799)
Parameter estimation and comparison from ANCOVA[b]		
n	18	7
LS mean difference (SE)	-1.32 ([redacted])	
95% CI	(-4.03, 1.39)	
2-sided p-value	[redacted]	

Gait score is based on the 10-metre walk test; stairs score was based on the participant climbing stairs; Gowers' manoeuvre score was based on the participant lying down on the floor, then rising from the floor to get to a standing position; chair score was based on the participant arising from a sitting position in a chair to a standing position. GSGC total score was the sum of 4 tests and ranges from a minimum of 4 points (normal performance) to a maximum of 27 points (worst score).
[a]Baseline was the last non-missing value prior to the administration of the first dose of study drug.
[b]All estimates were obtained from the ANCOVA model including terms for treatment, baseline GSGC total score, age, height, weight (all as continuous covariates), and gender.

Abbreviations: ANCOVA; analysis of covariance; CI; confidence interval; GSGC; Gait, Stairs, Gowers' manoeuvre, and Chair; ITT; Intention-to-Treat; LOCF; last observation carried forward; LS; least squares; SD; standard deviation
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Figure 8: Line chart for LS mean (SE) of change from Baseline over time in GSGC total score – ERT-naïve population (ITT-LOCF Population, excluding outlier participant)

Gait score was based on the 10-metre walk test; stairs score is based on the participant climbing stairs; Gowers' manoeuvre score was based on the participant lying down on the floor, then rising from the floor to get to a standing position; chair score was based on the participant arising from a sitting position in a chair to a standing position. GSGC total score was the sum of 4 tests and ranges from a minimum of 4 points (normal performance) to a maximum of 27 points (worst score). LS mean and SE were obtained directly from the ANCOVA model.
Abbreviations: ANCOVA: analysis of covariance; GSGC: Gait, Stairs, Gowers' manoeuvre, and Chair; ITT-LOCF: Intention-to-Treat–last observation carried forward; LS: least squares; SE: standard error
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Table 18: Number of participants included in the analysis of GSGC at each time point – ERT naïve population (ITT-LOCF Population, excluding outlier participant) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 20)	Alglucosidase alfa in combination with placebo (n = 7)
Baseline	[redacted]	[redacted]
Week 12	[redacted]	[redacted]
Week 26	[redacted]	[redacted]
Week 38	[redacted]	[redacted]
Week 52	[redacted]	[redacted]

Abbreviations: ERT: enzyme replacement therapy; ITT-LOCF: Intention-to-Treat–last observation carried forward; GSGC: Gait, Stairs, Gowers' manoeuvre, and Chair.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

PROPEL secondary efficacy endpoint in the ERT-naïve population: Analysis of SGIC Overall Physical Wellbeing and PGIC from Baseline to Week 52

The SGIC Overall Physical Wellbeing and PGIC Overall Status from Baseline to Week 52 are presented in Figure 9 and Figure 10, respectively. A greater percentage of participants treated with alglucosidase alfa had improving or stable scores at Week 52.

Figure 9: SGIC overall physical wellbeing at Week 52 compared to Baseline in ERT-naïve participants (ITT Population, excluding outlier participant) [PROPEL]

Abbreviations: ERT: enzyme replacement therapy; SGIC: Subject's Global Impression of Change.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Table 19: Number of participants included in the analysis of SGIC overall physical wellbeing at Week 52 compared to Baseline point – ERT-naïve population [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 20)	Alglucosidase alfa in combination with placebo (n = 7)
n	[redacted]	[redacted]

Abbreviations: ERT: enzyme replacement therapy; ITT: intention to treat; SGIC: Subject's Global Impression of Change.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Figure 10: PGIC overall status at Week 52 compared to Baseline in ERT-naïve participants (ITT Population, excluding outlier participant) [PROPEL]

Abbreviations: ERT: enzyme replacement therapy; ITT: intention to treat; PGIC: Physician's Global Impression of Change.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Table 20: Number of participants included in the analysis of PGIC overall status at Week 52 compared to Baseline point – ERT-naïve population (ITT population) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 20)	Alglucosidase alfa in combination with placebo (n = 7)
n	[redacted]	[redacted]

Abbreviations: ERT: enzyme replacement therapy; ITT: intention to treat; PGIC: Physician's Global Impression of Change.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

PROPEL Safety endpoint in the ERT-naïve population: Summary of TEAEs

The frequency of TEAEs was similar between the group of ERT-naive participants treated with cipaglucosidase alfa in combination with miglustat and alglucosidase alfa. A summary of TEAEs is presented in Table 21.[1]

Table 21: Overall summary of TEAEs in PROPEL (ERT-naïve Safety Population)

	Cipaglucosidase alfa in combination with miglustat (n = 20)			Alglucosidase alfa in combination with placebo (n = 8)			Total (N = 28) n (%)
	Cipaglucosidase alfa n (%)	Miglustat n (%)	Total n (%)	Alglucosidase alfa n (%)	Placebo n (%)	Total n (%)	
Participants who had any TEAE			[redacted]			[redacted]	[redacted]
Participants who had any TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any serious TEAE			[redacted]			[redacted]	[redacted]
Participants who had any serious TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any study drug-related serious TEAE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants who had any TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A TEAE was defined as any event that started or changed in intensity on or after the first dose of study drug.
A study drug-related TEAE was defined as a TEAE with the corresponding relationship to study drug marked as definite, probable, or possible. For the total column under each treatment, the participant was counted only once under the category according to the worst relationship for any component of the treatment. If relationship was missing, it was classified as related.
Percentages were based on the number of participants in each treatment group for the Safety Population.
Abbreviations: TEAE: treatment-emergent adverse event
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

A9. Please provide a line chart for change from baseline in PROMIS-Fatigue over time (as is presented for the other results) for the PROPEL trial.

The line chart for change from Baseline in PROMIS-Fatigue over time for the overall population is presented in Figure 11.[1]

Figure 11: Line chart for LS mean (SE) of change from Baseline in PROMIS-Fatigue over time (ITT-LOCF population, excluding outlier participant) [PROPEL]

LS mean and SE were obtained from the analysis of covariance model.
Abbreviations: ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; LS: least squares; PROMIS: Patient-reported Outcomes Measurement Information System; SE: standard error.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Table 22: Number of participants included in the analysis of PROMIS-Fatigue at each time point (ITT-LOCF Population, excluding outlier participant) [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 37)
Baseline	[redacted]	[redacted]
Week 12	[redacted]	[redacted]
Week 26	[redacted]	[redacted]
Week 38	[redacted]	[redacted]
Week 52	[redacted]	[redacted]

Abbreviations: ERT: enzyme replacement therapy; ITT-LOCF: Intention-to-Treat–Last Observation Carried Forward; PROMIS: Patient-reported Outcomes Measurement Information System
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

A10. Please present results for Physician's Global Impression of Change for the PROPEL trial (as is presented for SGIC in Figure 15).

PGIC results from the PROPEL trial are presented below in Figure 12.[1]

Figure 12: PGIC overall physical wellbeing at Week 52 compared to Baseline (ITT population, excluding outlier participant) [PROPEL]

Abbreviations: PGIC: Physician's Global Impression of Change.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

Table 23: Number of participants included in the analysis of PGIC overall status at Week 52 compared to Baseline point – ERT-naïve population [PROPEL]

	Cipaglucosidase alfa in combination with miglustat (n = 85)	Alglucosidase alfa in combination with placebo (n = 37)
n	[redacted]	[redacted]

Abbreviations: ERT: enzyme replacement therapy; PGIC: Physician's Global Impression of Change.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

A11. Section 9.7.3.8 of the PROPEL clinical study report states that as a result of Covid 19 the week 52 visit may have been delayed and the delayed visit assessment was used for analysis. Please report how many patients in each study arm had delayed (i.e. post-week 52) results included in the analyses and the average (and range) length of delay.

The average delay of the actual study visit from the planned visit for assessment of six-minute walk distance (6MWD) at Week 52 was small and similar between treatment groups (mean delay [range] of [redacted] days in the cipaglucosidase alfa in combination with miglustat arm, and

[redacted] days in the alglucosidase alfa arm). Early termination visits for participants who discontinued study were treated as the next scheduled visit, resulting in large negative values.

The proportions of participants with delays of at least 14 days at the Week 52 visit were also similar between treatment groups (cipaglucosidase alfa in combination with miglustat: [redacted] [redacted%]; alglucosidase alfa: [redacted] [redacted%]; percentage calculated using total number of participant-visits as denominator, where total number of participant-visits = total number of participants at each visit). Given the similar values between treatment arms, these delays were not expected to introduce bias or substantially affect results.

A12. Priority Question: Section 10.2 of the PROPEL clinical study report states that 99.2% of participants had a protocol deviation. Please provide further details (beyond those reported in the clinical study report) on the nature of these protocol deviations and comment on how these may impact the reliability of the reported results.

The majority of protocol deviations in PROPEL were categorised as study procedure deviations, such as delays in study visits or complete physical exams being conducted outside the protocol specified time points. Other deviations included accidental deviations from the window of administration between miglustat or placebo and the infusion. These deviations were minor and are not expected to affect the reliability of the results of PROPEL.

Amicus has reviewed all protocol deviations and determined that they did not meaningfully impact study data integrity or the reliability of the reported results. More than half of the protocol deviations were attributed to the Coronavirus Disease 2019 (COVID-19) pandemic, including missed or delayed administrations of study drug and/or assessments (see responses to Questions A6 and A11). Whenever possible, administrations of study drug and assessments were rescheduled rather than missed entirely. Despite these challenges, the frequency of missing data, particularly for the primary endpoint, was low. Also of note, there were very few protocol deviations that led to exclusion from the Per Protocol 1 (PP1) and Per Protocol 2 (PP2) Populations (i.e., prespecified important deviations that may have impacted the analyses of 6MWD and forced vital capacity (FVC), respectively). These are documented in CSR Appendix 16.1.9.2, Section 2.2. Finally, other types of more frequently observed deviations, such as errors in the order of performance of assessments and errors in the informed consent form (ICF) process or timing, were assessed to have negligible impact on study data integrity or reliability of reported results.

Comparison between PROPEL and ATB200-02

A13. Baseline mean FVC % predicted is considerably lower for patients in ATB200-02 than patients in PROPEL, despite baseline 6MWD (m) being slightly higher in ATB200-02 (Tables 10 and 11 of company submission), is there an explanation for

this apparent difference in severity of respiratory symptoms between trial populations?

Although the PROPEL trial demonstrated a correlation between FVC % predicted and 6MWD, clinical expert opinion confirmed that these markers of disease progression should be considered independent from each other and can present and progress at different rates.[3] As such, FVC % predicted and 6MWD were also measured and reported separately in both trials, and in a heterogenous population, the difference is not unexpected. Therefore, the higher baseline 6MWD in ATB200-02 does not indicate that there should necessarily be a higher baseline FVC % predicted score. Additionally, PROPEL and ATB200-02 had different inclusion criteria with regards to 6MWD and FVC % predicted (Table 24), accounting for the difference in baseline characteristics between the trials.

The apparent difference in severity of respiratory and/or mobility impairment is not expected to reflect a clinically significant difference between the trial populations.

Table 24: 6MWD and FVC % predicted inclusion criteria in PROPEL and ATB200-02

PROPEL inclusion criteria	ATB200-02 inclusion criteria
• Sitting FVC ≥ 30% of the predicted value for healthy adults at screening.	• Sitting FVC must have been 30% to 80% of predicted value for healthy adults
• Performed two 6MWTs at screening that were valid, as determined by the clinical evaluator, and that met all of the following criteria: ○ both screening values of 6MWD were ≥ 75 m ○ both screening values of 6MWD were ≤ 90% of the predicted value for healthy adults ○ the lower value of 6MWD was within 20% of the higher value of 6MWD	• 6MWD between 200 and 500 m

Abbreviations: 6MWD: 6-minute walk distance; FVC: forced vital capacity.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report);[1] Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[4]

Indirect treatment comparison (ITC)

A14. **Priority Question:** Please justify why the indirect comparisons have been undertaken given that they are not used in the economic model.

As requested by NICE, avalglucosidase alfa has been included as a secondary comparator in this submission as agreed in the decision problem meeting, and therefore has only been included in scenario analyses. The indirect comparison has been undertaken solely to inform the single economic scenario analysis which compares cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa, given that no head-to-head data comparing the two treatments were available. Given that avalglucosidase alfa is not included in the base case, the ITC has not been used to inform the base case model.

The indirect comparison also provided estimates of the comparative efficacy of alglucosidase alfa and placebo. These results were included in the company submission for completeness but did not inform the model since head-to-head data were available for the relevant comparison of cipaglucosidase alfa in combination with miglustat and alglucosidase alfa.

A15. **Priority Question:** Please justify use of ML-NMR rather than a straightforward indirect comparison.

Utilising all available evidence is particularly important in rare conditions such as Pompe disease, in where there is a paucity of evidence available in a small population. To capture all suitable data and evidence across a network of different studies of ERTs recommended for people with LOPD, a Multi-Level Network Meta-Regression (ML-NMR) was determined to be appropriate to assess comparative effectiveness. An ML-NMR approach adjusts for differences in participant populations, making use of both individual patient level-data and aggregate data.

A network meta-regression approach was deemed more appropriate than a simple indirect comparison such as a standard network meta-analysis (NMA), as NMAs assume homogeneity between studies, which is not appropriate in this context as the randomised controlled trial (RCT) of avalglucosidase alfa (COMET) only included ERT-naïve participants, whereas PROPEL included both ERT-naïve and ERT-experienced participants. Additionally, single-arm studies were included and matched to appropriate comparator arms, which allowed the inclusion of data from ERT-experienced participants as per the decision problem. This also increased the amount of evidence in the network, helping to addresses the limitations of small RCT sample sizes typical in the study of rare diseases (see also the response to Question A16).

A standard NMA relies on the assumption that baseline modifiers of treatment effect do not differ between trials, which was not considered an appropriate assumption for this submission, given the small trial population sizes and heterogeneous nature of Pompe disease. The matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) methods relax the assumption of homogeneity required in an NMA, but only allow adjustment for differences in potential treatment effect modifiers using data from one study. The ML-NMR method maintains the probabilistic framework provided by an NMA but allows baseline data on treatment effect modifiers to be considered from all included trials. This enables within- and between-study variation to be considered with populations that differ by prior treatment status (see also the response to Question A17). ML-NMR also is recommended by NICE as it optimally integrates all available evidence (aggregate and patient-level data).[5, 6]

A16. **Priority Question:** Please justify the inclusion of single arm trials when data from RCTs are available.

The RCT of avalglucosidase alfa (COMET) only included ERT-naïve participants by design, whereas PROPEL included both ERT-naïve and ERT-experienced participants. Incorporating single-arm trials into the evidence network allowed the incorporation of clinical evidence for ERT-experienced participants for avalglucosidase alfa, in order to minimise bias in the comparisons.

Furthermore, given that Pompe disease is a rare disease, the available RCT data are limited by small population sizes. As such, single-arm trials were also incorporated to ensure that all relevant data informed the ML-NMR, enabling as robust and complete a comparison as possible. The ML-NMR method was used to adjust for measured covariates. Additionally, single-arm

evidence was incorporated into the network by matching the single arms to RCT comparator arms with similar previous ERT duration (see explanation below), limiting the heterogeneity between the single and matched arms. Thus, the incorporation of single-arm trials into the evidence network is not expected to introduce substantial bias into the comparisons.

Comparative analyses of 6MWD and FVC % predicted using only the RCT data were conducted and are included in the ITC report (Sensitivity Analysis 2). These comparisons were associated with a high degree of uncertainty demonstrated by the wide credible intervals for each comparison, compared to the smaller uncertainty in the main base case analyses owing to the inclusion of single-arm trials into the network. Therefore, the results of the main base case analyses including the single arm trials are considered to be the most robust and appropriate for use in this submission.

Inclusion of single-arm studies

Single-arm study results were matched to appropriate comparator arms of the comparative studies to allow for inclusion into the network.[7] More precisely, for the single-arm study with treatment k, based on M covariates (participant characteristics) x_m, for all the other arms j in each study i in the network, $\Delta_{ijk}=\sum_{m=1}^{M}\left|x_{mij}-x_{mk}\right|$ was calculated and the arm j^* in study i^* with the lowest difference was chosen as the best match for treatment k.

Table 25 shows the matching of single-arm studies to an appropriate comparator arm and provides a justification for the choice of the comparator arm.

Table 25: Matching of single-arm studies to comparator arms from RCTs

Trial	Arm	Matched to	Comment
LOTS OLE/van der Ploeg, 2012[8]	Alglucosidase alfa	Placebo arm of LOTS	-
NEO-1/-EXT/ 2022[9]	Avalglucosidase alfa	Alglucosidase alfa arm of ATB200-03	Prior ERT duration similar for these two trial arms: • Avalglucosidase alfa in NEO-1/-EXT: 4.0 yrs • Alglucosidase alfa in PROPEL: 5.8 yrs
COMET OLE/CDER, 2021[10]	Avalglucosidase alfa	Alglucosidase alfa arm of COMET	Prior ERT duration similar for these two trial arms: • Avalglucosidase alfa in COMET OLE: 0.9 yrs • Alglucosidase alfa in COMET: 0.0 yrs
ATB200-02/Byrne, 2022[11]	Cipaglucosidase alfa in combination with miglustat	Alglucosidase alfa arm of PROPEL	Prior ERT duration similar for these two trial arms: • Cipaglucosidase alfa in combination with miglustat in ATB200-02: 5.0 yrs • Alglucosidase alfa in PROPEL: 5.8 yrs

The time profiles for 6MWD (m) and sitting FVC (% predicted) change from Baseline, including the matched comparator arm, are shown in Figure 13 and Figure 14, respectively.

Figure 13: 6MWD change from Baseline (m) per treatment arm per trial, including matched comparator arm

Abbreviations: 6MWD: 6-minute walk distance; SE: standard error.

Figure 14: Sitting FVC % predicted change from Baseline per treatment arm per trial, including matched comparator arm

Abbreviations: FVC: forced vital capacity; SE: standard error.

A17. **Priority Question:** Please undertake a simple indirect comparison using the Bucher method.

As discussed previously, the RCTs for avalglucosidase alfa (COMET) and alglucosidase alfa (LOTS) were conducted in ERT-naïve participants whereas the PROPEL trial included both ERT-experienced and ERT-naïve participants. The ML-NMR assessed the relative effect of cipaglucosidase alfa in combination with miglustat in comparison to alglucosidase alfa in a mixed participant population (i.e., ERT-naïve and ERT-experienced participants) as per the decision problem.

The Bucher method would be less appropriate than the ML-NMR method in this case as it assumes homogeneity between studies, which is not appropriate in this context as described in the response to Question A16 (differing trial populations). Instead, the ML-NMR method was used to adjust for population differences and to provide relative effect estimates in the mixed participant population. Amicus is currently assessing the feasibility of conducting a comparison using the Bucher method with the existing evidence base.

A18. Priority Question: Please undertake indirect comparisons for naïve participants from the RCTs only using methods documented in the submission and also a simple comparison using the Bucher method.

Amicus feels that indirect comparisons for ERT-naïve participants using only RCT data are not appropriate in this context as the population of interest (per the decision problem [redacted]) is anticipated to be adults with LOPD, regardless of previous ERT experience (see response to Question A8). In addition, the sample size of the ERT-naïve participant subgroup in the PROPEL trial is relatively small in each arm (n=7 in the alglucosidase alfa arm) and thus an indirect comparison in this subgroup would likely produce unreliable results with a large amount of uncertainty.

As described in the response to Question A16, comparative analyses of 6MWD and FVC % predicted using only the RCT data were conducted and are included in the ITC report (Sensitivity Analysis 2). Scenario analyses for Sensitivity Analysis 2 were conducted to assess the impact of setting previous ERT duration to zero; results are available in the ITC report. Results were generally similar to the results for the base case of Sensitivity Analysis 2, with a similarly large level of uncertainty.

A19. Priority Question: Please provide the data used for the indirect comparisons.

The data used for the ML-NMRs include individual patient-level data from PROPEL and ATB200-02 (Amicus sponsored studies) and available published data for other included studies. In an effort to protect the confidentiality of individual participants, the data used in the ML-NMRs cannot be provided.

A20. In Section B.2.9.4 the company states "Significance was tested using a 2-tailed Z test with significance level 0.05." Please specify:

a) significance of what exactly

b) how do they define "significance", an inherently frequentist concept, in a Bayesian context?

c) what hypothesis are they testing and why are they doing that in a Bayesian framework?

a) ‘Significance’ refers to the statistical significance of the relative treatment effect of cipaglucosidase alfa in combination with miglustat in comparison to another treatment (i.e., avalglucosidase alfa or alglucosidase alfa), assessed in the ML-NMRs.

b) In a Bayesian context, the definition of statistical significance is the same as in a frequentist context (i.e. under the null hypothesis that there is no difference between the effect of cipaglucosidase alfa in combination with miglustat and the effect of avalglucosidase alfa or alglucosidase alfa, the probability of obtaining a larger or smaller relative effect is less than 0.05), However, in the Bayesian context, the calculation was based on the posterior distribution of the parameters.

c) The null hypothesis being tested was that there is no difference between the effect of cipaglucosidase alfa in combination with miglustat and the effect of avalglucosidase alfa (or alglucosidase alfa). The Bayesian rather than frequentist framework was considered suitable for performing this ITC in Pompe disease due to the limitations and uncertainty associated with small networks and low sample sizes of the trials included in the network (as seen in rare diseases in general). Informative priors, which reflected a prior belief of the possible values of the pooled relative effect and effects of covariates, were chosen to alleviate the limitations and uncertainty that may have been observed when using a frequentist approach.

Section B: Clarification on cost-effectiveness data

Value proposition

B1. Priority Question: The value proposition for avalglucosidase alfa considered in TA821 was principally informed by a cost comparison. Please justify the use of the cost-utility model and whether you consider such an approach informative in the appraisal of cipaglucosidase alfa plus miglustat.

It is Amicus' understanding that, whilst the value proposition for avalglucosidase alfa considered in TA821 was initially principally informed by a cost comparison, the submitting company later prepared a full cost-utility analysis as requested by NICE, as this was required in order for costs and benefits to be fully evaluated.

As described in the original company submission, Amicus maintains that treatment with cipaglucosidase in combination with miglustat results in improvements for adults with LOPD when compared to alglucosidase alfa. The Phase III trial PROPEL demonstrated the improved efficacy of cipaglucosidase alfa in combination with miglustat compared to alglucosidase alfa, across a range of endpoints relevant to people with LOPD, covering motor function, respiratory function, muscle strength and patient-reported outcomes (PROs). Namely, in the overall trial population in PROPEL, participants treated with cipaglucosidase alfa in combination with miglustat demonstrated LS mean treatment improvements of 14.21 m in 6MWD and 2.66% in FVC % predicted compared to those treated with alglucosidase alfa.

Benefits and associated cost are fully captured in the cost-effectiveness analysis over the lifetime of an adult with LOPD, which cost comparison would not allow. Indeed, in the base case cost-utility analysis presented in the company submission, the health benefits observed with cipaglucosidase alfa in combination with miglustat translated into a gain of [redacted] QALYs per individual, compared with alglucosidase alfa. Amicus therefore considers it appropriate to fully demonstrate this expected benefit through the use of the cost-utility analysis.

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

Model structure and patient simulation

B2. Priority Question: The runtime for the economic model is currently very long. This may be improved by using a single random draw across all treatments per parameter. This will reduce stochastic error and speed up the processing of each iteration of the model as fewer random draws will be required. Please update the model so that a single random draw is used for all treatments per parameter.

The model has now been updated to apply a total of two randomly drawn seed values for the normal distribution of relevant baseline characteristics, combined into two groups based on likely expected general correlation:

- People with LOPD's age, height and weight
- 6MWT and FVC pred % predicted at Baseline

As per the reply to Questions B6 and B7, disease progression parameters are no longer varied as part of the first-order iterations but are instead included as part of the probabilistic sensitivity analysis (PSA) second-order iterations. However, in line with the above, the PSA has now been adjusted to apply the same random seed value for the probabilistic sampling of (likely) correlated parameters; this also includes respective disease progression parameters (e.g. initial annual change from Baseline to Year 1) across the different treatments.

Amicus can confirm that, whilst this update should indeed reduce stochastic errors, it has no substantial impact on the runtime of the model (around 40 minutes for 30,000 first-order iterations).

The results of the updated model base case are presented in Appendix 1.

B3. Priority Question: In the economic model, baseline characteristics are randomly determined using independent normal distributions rather than a joint distribution.

a) Please comment on why independent distributions were used as these characteristics are likely to be correlated e.g. older patients may be heavier.

b) Please update the economic model so that these values are generated from a joint distribution.

a) Amicus can confirm that the initially independent sampling of baseline characteristics was a pragmatic decision made during the development of the model, based on the availability of independent sets of data (i.e. average and standard deviation for each of the individual characteristics) from the PROPEL trial.

b) As outlined in the response to Question B2, the individual baseline characteristics are still sampled based on their respective normal distributions (informed by their individually available data from PROPEL). However, the distributions of parameters that could be expected to have a general correlation (e.g. person with LOPD's age, weight and height) are now informed by the same random seed value, thereby ensuring that correlated values are always taken from equivalent points of their respective distributions (e.g. a higher age will always be sampled together with a correspondingly higher weight). It should however also be noted that this may represent an oversimplification and would only be expected to reflect very general trends in the demographic of people with LOPD.

B4. The model currently permits patients to have baseline characteristics that fall outside the marketing authorisation for cipaglucosidase alfa plus miglustat. Specifically, patient age falls below 18 in a non-negligible number of iterations. Please truncate the distributions, so that baseline characteristics remain within the

market authorisation and align with those who would plausibly be treated with cipaglucosidase alfa plus miglustat.

Amicus can confirm that the model now includes truncations for the normal distribution of relevant baseline characteristics to ensure that randomly sampled values are always [redacted]

The results of the updated model base case are presented in Appendix 1.

B5. Priority Question: The model simulates the patients' characteristics for baseline 6MWT and FVC % predicted values independently. Please generate these values from a joint distribution, i.e., accounting for the correlation in these measures, as informed by PROPEL trial data.

Whilst a general correlation between 6MWT and FVC %predicted at Baseline has been observed in PROPEL, clinical expert opinion has confirmed that there is no direct link expected between the two parameters over the course of disease progression and that these should be considered separately when assessing an individual's overall status (for example, individuals may present with significant mobility impairment but mild respiratory impairment). Through patient research conducted in the UK looking at the onset of noticeable symptoms of Pompe disease, it was observed that for all individuals at some point a decline in their physical capabilities became noticeable, but for a few/a minority it was specifically respiratory symptoms that had emerged first.[12]

As such, as detailed in the response to Question B2, the two parameters are still sampled based on their individual normal distributions (informed by the available data from PROPEL) but now use a common random seed value to ensure general correlation of the individually randomly sampled parameters for each simulated patient.

B6. Priority Question: For several effectiveness parameters, variability is determined using the standard error rather than the standard deviation. This is inappropriate (and inconsistent with the approach used for other parameter inputs). Please update the economic model so that variability in parameters is determined using the standard deviation only (standard errors should only be used to inform uncertainty in parameter inputs).

In the model included in the initial submission, the mean change in 6MWT and FVC % predicted with each intervention were included in the first order iterations. In the updated model, these parameters have now been removed from the first order iterations and, instead, are included as part of the second order iterations for the probabilistic analysis. Therefore, all parameters associated with uncertainty, rather than variability, are now varied in the probabilistic analysis only. Further information on this change is included in the response to Question B7. As such, in line with the model changes related to the questions above, Amicus can confirm that standard deviation is now exclusively used for the first-order variation of baseline characteristics; standard errors are now only used for the probabilistic sampling of parameters as part of the PSA.

B7. Priority Question: The probabilistic analysis is improperly parameterised and conflates variability and uncertainty. The first-order iterations do not (should not) account for uncertainty in parameter inputs, and should account only for variability in inputs. Uncertainty is addressed by the probabilistic analysis (second-order iterations) only and should account for uncertainty in both the mean and standard deviation for each parameter.

a) Please update the economic model to correct the misspecification of the probabilistic analysis.

The model has now been amended so that only baseline characteristics (i.e. age, weight, height, baseline 6MWT and baseline FVC % predicted) are varied as part of the first-order iterations; the uncertainty around disease progression parameters (which were also varied as part of the first-order iterations for the originally submitted model) is now explored as part of the PSA.

The results of the updated model base case are presented in Appendix 1.

Comparator and model population

B8. Priority Question: The company economic analysis only considers avalglucosidase alfa (Nexviadyme®) as a secondary comparator, when it is likely to become available early in 2023 and is listed in the NICE scope.

a) Please provide further justification for this exclusion.

b) Please comment on the relevance of alglucosidase alfa as a comparator given the likely availability of avalglucosidase alfa and the likelihood that avalglucosidase alfa will be prioritised (over alglucosidase alfa) as a treatment for both ERT-naive and ERT-experienced patients.

c) Please fully document all assumptions and inputs used in the scenario analysis where avalglucosidase alfa is included as a comparator and present pairwise results between cipaglucosidase alfa plus miglustat and avalglucosidase alfa.

a) Avalglucosidase alfa received Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation in July 2022[13] and NICE guidance in August 2022 (TA821; with a 30-day implementation period)[14] for the treatment of Pompe disease of all ages. However, at the time of this submission, Amicus understands from clinicians, the NICE website and an National Health Service (NHS) formulary that avalglucosidase alfa is not commercially available in the United Kingdom (UK) for the treatment of adults with

LOPD[14, 15] and that it will likely not be available until at least Spring 2023. As agreed in the decision problem meeting, it is unlikely that avalglucosidase alfa will be widely used in clinical practice for some time even after it were to become commercially available. Additionally, it is Amicus' understanding that there was very limited, if any, uptake of the early access to medicines scheme (EAMS) for avalglucosidase alfa at UK adult Pompe disease treatment centres.

Therefore, given that avalglucosidase is not yet commercially available and healthcare decision-making based on an assumption of future use is not appropriate, Amicus believes that avalglucosidase alfa should only be considered a secondary comparator, and as such, included in scenario analyses only. To perform the comparision of cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa, the original submission included a full ITC in the absence of head-to-head data, as well as cost-utility scenario analyses.

b) Alglucosidase alfa is the current standard of care for adults with LOPD as confirmed by clinicians and, as above, avalglucosidase alfa would be unlikely to be widely used in clinical practice for some time even after it were to become commercially available in the UK following the 30-day implementation period.

c) **Scenario analyses with avalglucosidase alfa as a comparator**

Two scenario analyses (#1 and #2), which included avalglucosidase alfa as a comparator and differed with respect to assumptions around long-term disease progression (see below), were presented in the company submission. A third scenario analysis (#15) which also differs from #1 and #2 with respect to assumptions around long-term disease progression, has now been run; this is detailed below.

For these scenarios, the same general approach was taken as for the base case analysis (with alglucosidase alfa as comparator), with respect to model health states and progression through the model. However, some aspects of the modelling approach and inputs in the company base case have been amended in response to these questions from the EAG (see Appendix 1 for a summary of the updated base case analysis and results). Scenario analyses #1 and #2 have therefore been re-run with the updated base case settings and inputs; updated results are presented at the end of the response to this question. Scenario analysis #13 has been run with the updated base case settings and inputs.

A summary of where the inputs and assumptions for these scenarios were consistent, or differed, from the updated base case, are detailed below.

Baseline characteristics

For the scenario with avalglucosidase alfa, all baseline characteristics were the same as in the base case (as presented in Table 42, Section B.3.3.1 of the company submission; including updates to the normal distribution of parameters as detailed in Questions B2 and B4). It was therefore assumed that the baseline characteristics from PROPEL are generalisable to the population of adults with LOPD who would receive avalglucosidase alfa.

Health state transitions

The thresholds used for health state transitions in the scenarios with avalglucosidase alfa were the same as those used in the base case model (Table 43, Section B.3.3.1 of the company submission).

Treatment efficacy

Initial annual change (Baseline to Year 1)

Results of the ML-NMRs informed the clinical effectiveness data used in the model from Baseline to Year 1. Initial change from Baseline in 6MWD and FVC % predicted were applied from Baseline to Year 1 of the model only, as treatment efficacy data were available from the ML-NMRs at Week 52 (Table 28) also in Table 63, Section B.3.10.3 of the company submission).

Table 28: Initial annual change from Baseline to Year 1 (Scenario analyses #1, #2 and #15)

Treatment	N	Initial annual change from Baseline in 6MWD, m	Initial annual change from Baseline relative in FVC, % predicted
Cipaglucosidase alfa in combination with miglustat (from PROPEL)[1]	85	20.8 (SE: 4.639)	-0.9 (SE: 0.007)
Relative effects of comparator vs. cipaglucosidase alfa in combination with miglustat			
Avalglucosidase alfa, relative to cipaglucosidase alfa in combination with miglustat	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWD: six-minute walk distance; CrI: credible interval; FVC: forced vital capacity; SE: standard error.

Subsequent annual change (Year 1 onwards)

The ML-NMRs ITC did not explore treatment effectiveness beyond 52 weeks due to the duration of the trials informing the ML-NMR. Beyond Year 1 of the model in Scenario analyses #1 and #2, the subsequent annual change in 6MWD and FVC % predicted was based on long-term data for alglucosidase alfa from Semplicini *et al.*[16]. Two scenario analyses were therefore conducted and presented in the company submission:

- **Scenario analysis #1**: [redacted] rate between avalglucosidase alfa and alglucosidase alfa (i.e., both with [redacted] than with cipaglucosidase alfa in combination with miglustat)
- **Scenario analysis #2**: [redacted] rate with avalglucosidase alfa vs. alglucosidase alfa (i.e. [redacted] with avalglucosidase alfa than with cipaglucosidase alfa in combination with miglustat)

Clinical experts have confirmed that, given that the short-term efficacy for avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat are relatively similar, it is also reasonable to assume that long-term effectiveness is also likely to be similar.[2] Therefore, Amicus has now run and presented a third, more conservative scenario analysis to supplement #1 and #2:

- **Scenario analysis #15**: [redacted] rate between avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat (i.e., both [redacted] than with alglucosidase alfa)

Table 29 presents the rates of long-term disease progression used in Scenario analyses #1 and #2 and the new Scenario analysis #15.

Table 29: Effectiveness inputs beyond Year 1 (Scenario analyses #1, #2 and #15)

Outcome	Mean annual predicted percentage change (SE) with alglucosidase alfa	Mean annual predicted percentage change (SE) with avalglucosidase alfa		
		Scenario #1	Scenario #2	Scenario #15
6MWD % predicted	-2.3% (0.003)[16]	[redacted]	[redacted]	[redacted]
FVC % predicted	-0.9% (0.001)[16]	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWD: six-minute walk distance; FVC: forced vital capacity; SE: standard error.

Mortality

Mortality was applied in the model as a hazard ratio for each health state, independent of treatment. Therefore, no changes were made to the way that mortality was modelled in the scenarios with avalglucosidase alfa, compared with the base case (see Table 49, Section B.3.3.3 of the company submission).

Health-related quality of life

The scenarios with avalglucosidase alfa used the same health state utilities as those used in the base case (see Table 51, Section B.3.4.4 of the company submission).

As in the base case model, adverse events (AEs) were not modelled in the scenarios with avalglucosidase alfa. Cipaglucosidase alfa in combination with miglustat, and avalglucosidase alfa, were shown to have similar safety profiles to alglucosidase alfa in their Phase III trials (PROPEL and COMET, respectively). Additionally, cipaglucosidase alfa in combination with miglustat, and avalglucosidase alfa belong to the same class of medicines. Therefore, it was assumed that differences in adverse events experienced when treated with either avalglucosidase alfa or cipaglucosidase alfa in combination with miglustat would be negligible and would therefore not impact overall quality of life.

Costs and healthcare resource use

The acquisition and administration costs for cipaglucosidase alfa in combination with miglustat were unchanged in the scenarios including avalglucosidase alfa, compared with the base case.

The acquisition costs for avalglucosidase alfa are presented in Table 65, Section B.3.1.3 of the company submission. Administration costs for avalglucosidase alfa was assumed to be the same as that of cipaglucosidase alfa, using the same assumptions and unit costs. As mentioned above, Scenario analyses #1 and #2 have been re-run using the corrected inputs for nurse time (see Question B16). Therefore, the administration costs for the updated Scenarios #1 and #2 are detailed in Table 30.

Table 30: Updated administration costs used in Scenarios #1, #2 and #15

Treatment administration cost	Annual cost: First year	Annual cost: Second year onwards
Cipaglucosidase alfa/miglustat	£6,322	£6,191
Avalglucosidase alfa	£6,322	£6,191

All other costs (e.g. health state unit costs) remained the same as those used in the base case, as these were not treatment-dependent.

Assumptions

Assumptions made for the base case model were presented in Table 60, Section B.3.8.2 of the company submission. Additional assumptions made in conducting the scenarios with avalglucosidase alfa are described in Table 31.

Table 31. Summary of key assumptions used in the scenario analyses with avalglucosidase alfa, in addition to those used in the base case (Table 60, Section B.3.8.2 of the company submission)

Assumption	Justification
Scenario #1: [redacted] between avalglucosidase alfa and alglucosidase alfa Scenario #2: [redacted] with avalglucosidase alfa in combination with miglustat compared with alglucosidase alfa Scenario #15: [redacted] rate between avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat (i.e., both [redacted] than with alglucosidase alfa)	Clinical experts have confirmed that, given that the short-term efficacy for avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat are relatively similar, it is also reasonable to assume that long-term effectiveness is also likely to be similar.[2] Therefore, Scenario analysis #15 was conducted.
Baseline characteristics from PROPEL were assumed to be generalisable to the population of adults with LOPD who would receive avalglucosidase alfa	No differences are expected to exist in the populations receiving avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat, as confirmed by clinical experts. Furthermore, participants were not selected for PROPEL based on any known response to previous therapies. Clinical experts confirmed that treatment decisions between avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat would likely be determined by non-biological and practical factors, such as access to an EAMS and the ability to self-infuse at home.[2]
Differences in adverse events experienced when treated with either avalglucosidase alfa or cipaglucosidase alfa in combination with miglustat were assumed to be negligible enough not to impact overall quality of life	Clinical experts validated that, for the comparison between cipaglucosidase alfa in combination with miglustat and alglucosidase alfa, differences in adverse events experienced when treated with either alglucosidase alfa or cipaglucosidase alfa in combination with miglustat would be negligible enough not to impact overall quality of life.[2] This assumption was extended to the scenario analyses with avalglucosidase alfa, as cipaglucosidase alfa in combination with miglustat, and

	avalglucosidase alfa, were shown to have similar safety profiles to alglucosidase alfa in their Phase III trials (PROPEL and COMET, respectively). Additionally, cipaglucosidase alfa in combination with miglustat, and avalglucosidase alfa belong to the same class of medicines.
It was assumed that individuals were not required to take any alternative treatments alongside avalglucosidase alfa	According to the SmPC for avalglucosidase alfa [redacted], no alternative treatments are required to be taken.[17, 18] There is no reason that individuals would be required to take alternative treatments in clinical practice.
The cost per administration of avalglucosidase alfa was assumed to be the same as that for cipaglucosidase alfa in combination with miglustat	For both cipaglucosidase alfa and avalglucosidase alfa, the time from a nurse required for each administration was informed by the NICE appraisal of avalglucosidase alfa (TA821).[14] For the two treatments, the same assumptions were made with respect to the proportion of people who can self-infuse, number of infusions in hospital before starting self-infusion and nurse time required. Although the number of vials required per administration is expected to be slightly higher with avalglucosidase alfa (15) compared with cipaglucosidase alfa (14), this was not accounted for in this analysis in line with using a conservative approach.

Abbreviations: 6MWD: six-minute walk distance; EAMS: early access to medicines scheme; FVC: forced vital capacity; LOPD: late-onset Pompe disease; NICE: National Institute for Health and Care Excellence; SmPC: summary of product characteristics; UK: United Kingdom.

Results

Results of Scenario analyses #1, #2 and #15 are presented in Table 32, Table 33 and Table 34, respectively. In all scenarios, cipaglucosidase alfa in combination with miglustat remained dominant vs. avalglucosidase alfa.

Table 32: Results of re-run Scenario #1 ([redacted] between avalglucosidase alfa and alglucosidase alfa)

	Cipaglucosidase alfa in combination with miglustat	Avalglucosidase alfa	Incremental	
Total cost	[redacted]	[redacted]	[redacted]	
Total QALYs	[redacted]	[redacted]	[redacted]	
Total life years (discounted)	[redacted]	[redacted]	[redacted]	
Total life years (undiscounted)	[redacted]	[redacted]	[redacted]	
Cost per QALY	[redacted]	[redacted]		
Incremental cost-effectiveness ratio (ICER)			Dominant	
Willingness to pay threshold			**£20,000/ QALY**	**£30,000/ QALY**
Net monetary benefit			[redacted]	[redacted]
Net health benefit			[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 33: Results of re-run Scenario #2 ([redacted] with avalglucosidase alfa compared with alglucosidase alfa)

	Cipaglucosidase alfa in combination with miglustat	Avalglucosidase alfa	Incremental	
Total cost	[redacted]	[redacted]	[redacted]	
Total QALYs	[redacted]	[redacted]	[redacted]	
Total life years (discounted)	[redacted]	[redacted]	[redacted]	
Total life years (undiscounted)	[redacted]	[redacted]	[redacted]	
Cost per QALY	[redacted]	[redacted]		
Incremental cost-effectiveness ratio (ICER)			Dominant	
Willingness to pay threshold			**£20,000/ QALY**	**£30,000/ QALY**
Net monetary benefit			[redacted]	[redacted]
Net health benefit			[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Table 34: Results of Scenario #15 [redacted] rate between avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat (i.e. [redacted] with cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa, compared with alglucosidase alfa)

	Cipaglucosidase alfa in combination with miglustat	Avalglucosidase alfa	Incremental	
Total cost	[redacted]	[redacted]	[redacted]	
Total QALYs	[redacted]	[redacted]	[redacted]	
Total life years (discounted)	[redacted]	[redacted]	[redacted]	
Total life years (undiscounted)	[redacted]	[redacted]	[redacted]	
Cost per QALY	[redacted]	[redacted]		
Incremental cost-effectiveness ratio (ICER)			Dominant	
Willingness to pay threshold			**£20,000/ QALY**	**£30,000/ QALY**
Net monetary benefit			[redacted]	[redacted]
Net health benefit			[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

B9. Priority Question: The company base case analysis models the population recruited to the PROPEL study pooling data from both ERT-naïve and ERT-experienced populations. Please justify the pooling of these populations and comment on the relevance of both an ERT-naïve and ERT-experienced population to how the company anticipate cipaglucosidase alfa plus miglustat will be used in practice.

As agreed in the decision problem meeting, the base case analysis for cipaglucosidase alfa in combination with miglustat used data from the total PROPEL population (i.e. ERT-naïve and ERT-experienced populations) as there is no reason to expect any biological differences, and therefore different efficacy results, between these subgroups. This was confirmed during an advisory board with UK clinicians from specialist Pompe disease treatment centres with years of experience treating adults with LOPD,[2] in which clinicians noted that ERT-naïve and ERT-experienced individuals would not be treated differently. Furthermore, participants were not selected for PROPEL based on any known response to previous therapies.

The PROPEL trial was designed and powered to detect an effect size in a total population size of 99 participants. Amicus therefore feels that the word pooled is not appropriate in this context, as results in the total population are the key findings of the study (rather than being considered pooled results), and prior treatment-defined subgroups are not considered to be key analysis populations. In addition, it is statistically appropriate to include results from the total population in the model, especially given the powering of the PROPEL trial was used to minimise uncertainty.

Cipaglucosidase alfa in combination with miglustat is intended for use in [redacted], in line with clinical opinion.[2] Therefore, Amicus considers that prior ERT status should not be a factor in accessing treatment with cipaglucosidase alfa in combination with miglustat in the interests of fair and equitable access; the treatment is cost-effective in the total population.

Treatment effectiveness and extrapolation

B10. Priority Question: The treatment effect applied in year 1 to 2 and 2 to 3 for cipaglucosidase alfa plus miglustat is informed by data from the ATB200-02.

a) Please provide details of which cohorts contribute to this analysis and the number of patients contributing at each time point.

b) Please provide details of any reweighting or adjustments applied, as the values used in the economic analysis do not match those reported in the CSR.

a) Data were taken from Cohorts 1 ([redacted] years' experience of prior ERT, [redacted]) and 4 ([redacted] years' experience of prior ERT, [redacted]) for the ERT-experienced population used in this analysis. For the ERT-naïve population, data were taken from Cohort 3 (ERT-naïve, [redacted]).[11]

b) 6MWD and FVC % predicted values used in the economic analysis were directly calculated as a weighted average (based on the numbers of participants) of data in the ERT-naïve and ERT-experienced treatment groups from ATB200-02, as reported by Byrne *et al.* (2022). This publication was based on an interim CSR of ATB200-02, specific values may therefore be different when compared to the final CSR provided as part of the company submission.

B11. Priority Question: The treatment effect beyond year 1 is informed by a non-randomised comparison between ATB200-02 and data from the Semplicini *et al.*, 2020 study.

a) Please comment on the comparability of the ATB200-02 and Semplicini *et al.*, 2020 populations, the appropriateness of a naive comparison, and the feasibility of conducting a matched adjustment.

The baseline characteristics of both the ATB200-02 and Semplicini *et al.*, 2020 populations are shown in Table 35. Overall, key baseline characteristics are comparable between the two studies. Therefore, the naïve effectiveness comparison is expected to be appropriate. A matched adjustment analysis such as a MAIC to obtain a relative effect estimate would not be feasible due to the low sample size of ATB200-02 and the resulting (even lower) effective sample size when matching participants from ATB200-02 to the Semplicini *et al*. cohort.

Table 35: Baseline characteristics of ATB200-02 and Semplicini *et al.*, 2020.

Characteristic	ATB200-02 Overall population [redacted]	Semplicini *et al.* ERT-treated cohort (n = 158)
Male, n (%)	[redacted]	76 (48.1)
Age at inclusion, years, mean (SD)	[redacted]	50.9 (14.7)
Baseline efficacy outcomes		
6MWD % predicted, mean (SD)	[redacted]	56.95 (23.64)
FVC % predicted, mean (SD)	[redacted]	64.38 (26.22)

[a]Cohorts 1, 3 and 4 only (ambulatory participants).
Cohorts 1, 2, 4: ERT-experienced participants; Cohort 3: ERT-naïve participants (n=6); Cohorts 1, 3, 4: ambulatory participants; Cohort 2: non-ambulatory participants.

B12. The model has a scenario in which a constant rate of change is assumed over three years. Please comment on how the results of Semplicini *et al.*, 2020 affects the short-term rate of disease progression with alglucosidase alfa in Year 2 and Year 3.

Whilst not explicitly presented as a scenario analysis in the company submission, the submitted model includes the option to extrapolate the change from Baseline to Year 1 in 6MWD % predicted and FVC % predicted (based on data from PROPEL) up to Year 3 for alglucosidase alfa. However, the base case analysis instead uses data from Semplicini *et al.* (2020) to inform

these initial annual changes after Year 1. As seen in Table 36, this presents an overall conservative approach, due to the comparatively improved disease progression with alglucosidase alfa when modelled based on Semplicini *et al.* In the absence of long-term data, Semplicini *et al.* was determined to be appropriate for use in the model due to the large population size.

Table 36: Comparison of 6MWD % predicted and FVC % predicted initial annual change used in the model base case

Time frame	6MWD % predicted	FVC % predicted	Source
Baseline to Year 1	[redacted]	-4.0%	PROPEL[1]
Year 1 to Year 2 / Year 2 to Year 3	1.4%	-0.9%	Semplicini *et al.* (2020)

[a]Converted from absolute 6MWD based on average participant age, weight and height from PROPEL.
Abbreviations: 6MWD: six-minute walk distance; FVC: forced vital capacity.

Health related quality of life

B13. Priority Question: The Propel study collected EQ-5D data. This is not summarised in the company submission or provided in the clinical study report.

a) Please provide a summary of the EQ-5D data collected in the PROPEL trial with an analysis by health state as defined by the cut-offs for 6MWT and FVC used in the model.

In PROPEL, EuroQol 5 Dimension 5 Level (EQ-5D-5L) data were collected at repeated intervals (Screening and Weeks 12, 26, 38, and 52). These EQ-5D-5L values were mapped to EuroQol 5 Dimension 3 Level (EQ-5D-3L) values using the Van Hout cross-walk algorithm.[19] Summaries of the EQ-5D-5L data collected in the PROPEL trial, and the cross-walked EQ-5D-3L data, are provided in Table 37.

Univariable mixed regression analyses indicated that age, FVC % predicted and 6MWD were potentially associated with participant health-related quality of life (HRQoL). Multivariable analyses indicated that, after controlling for 6MWD, no other factors were significant predictors of HRQoL. Therefore, it was determined that the optimal regression model should use an equation which only considered 6MWD (Table 38). This regression model predicted the utility values based on 6MWD thresholds (Table 39).

A summary by health state (as used in the model) is provided in Table 40. Not all health states within the model had available EQ-5D utilities because participants enrolled in PROPEL did not progress to the more severe health states in the 52 weeks of the trial.

Table 37: Summary of EQ-5D data collected in the PROPEL trial and mapped to EQ-5D-3L

Treatment	EQ-5D-5L (as collected in PROPEL)			EQ-5D-3L (mapped from PROPEL EQ-5D-5L using the van Hout crosswalk algorithm)		
	Mean	SE	95% CI	Mean	SE	95% CI
Cipaglucosidase alfa in combination with miglustat (across all observations)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alglucosidase alfa (across all observations)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total population, Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total population, Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; EQ-5D-3L: EuroQol 5 Dimension3 Level; EQ-5D-5L: EuroQol 5 Dimension 5 Level; SE: standard error.
Source: PROPEL PRO Responder Analysis Report.[20]

Table 38: Final mixed regression model

Over	Regression Coefficient	SE	z-score	P>z	95% CI
6MWD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cons	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWD: six-minute walk distance; CI: confidence interval; SE: standard error.
Source: PROPEL PRO Responder Analysis Report.[20]

Table 39: Utility predictions by 6MWD

6MWD category range (min, max), m	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6MWD midpoint, m	[redacted]		[redacted]		[redacted]	
EQ-5D 3L	[redacted]		[redacted]		[redacted]	

Abbreviations: 6MWD: six-minute walk distance; EQ-5D-3L: EuroQol 5 Dimension3 Level.
Source: PROPEL PRO Responder Analysis Report.[20]

Table 40: Summary of EQ-5D data derived from different sources by health state

Health state	Amicus Vignette Study (Base Case)	Literature (Scenario #6)	PROPEL[20]	TA821 submission[14]
No wheelchair use or respiratory support (0–5 years alive from treatment initiation)	0.61 (0.12)	0.74 (0.15)[21]	-	-
No wheelchair use or respiratory support (6–15 years alive from treatment initiation)		0.70 (0.16)[21]	-	-
No wheelchair use or respiratory support (>15 years alive from treatment initiation)		0.69 (0.23)[21]	[redacted]	0.652
Intermittent mobility support	0.43 (0.19)	0.67 (0.21)[21]	[redacted]	-
Intermittent, non-invasive respiratory support	0.36 (0.19)	0.61 (0.26)[21]	-	0.614
Intermittent mobility support and intermittent, non-invasive respiratory support	0.29 (0.24)	[redacted]	-	0.545
Wheelchair dependent	0.11 (0.23)	0.146 (0.010)[22,b]	[redacted]	0.504
Wheelchair dependent and intermittent, non-invasive respiratory support	0.08 (0.22)	[redacted]	-	-
Wheelchair and invasive respiratory support dependent	-0.08 (0.22)	[redacted]	-	-

[a]Assumed values were used as no utilities for individuals that required both mobility and respiratory support were identified. These assumptions were generally viewed as appropriate for the scenario analysis by clinicians. Values were ordered to ensure logical values were produced for each iteration (i.e., the utility value of a particular health state could not be higher than an 'earlier' state). [b]Based on utilities in Duchenne muscular dystrophy. [c]Utility predictions extrapolated for severe health states (i.e. mobility dependent) from PROPEL data would be outside of sample estimates and consequently should be treated with caution.
Abbreviations: EQ-5D-5L: EuroQol 5 Dimension.

b) Please provide further justification on why it was considered “inappropriate” to use this data in the economic model.

EQ-5D-5L data from the PROPEL trial were not suitable for informing the utility of ‘later’ health states that required invasive respiratory support or a combination of mobility and respiratory support, because most included participants had not yet reached the later severe health states over the 52-week trial follow-up period. Given that these data were only able to inform the utility associated with three of the health states,[20] multiple utility sources would need to have been used to assign utilities to each health state in the base case. Amicus considered it more appropriate to use a single study to inform the health state utilities, as explained in part e) below. However, a scenario analysis using EQ-5D data from PROPEL for the health states where this was possible is provided below, supplemented with values from the vignette study and the literature.

c) Please provide scenario analysis using utility values generated from the PROPEL study; the EAG recognises it may be necessary to supplement this data with values from the TTO or published studies.

The utility values from PROPEL, supplemented with values from the Amicus vignette study, used in a new scenario analysis #16 are outlined in Table 41. The results of the Scenario analysis #16 are outlined in Table 42.

Table 41: Utility values used for Scenario analysis #16

Health state	Utility value	Source
No wheelchair use or respiratory support (0–5 years)	0.608	Amicus vignette study (EQ-5D index scores)
No wheelchair use or respiratory support (6–15 year)	0.608	Amicus vignette study (EQ-5D index scores)
No wheelchair use or respiratory support (>15 years)	[redacted]	PROPEL[1]
Intermittent mobility support	[redacted]	PROPEL[1]
Wheelchair dependent	[redacted]	PROPEL[1]
Intermittent respiratory support (non-invasive ventilation)	0.361	Amicus vignette study (EQ-5D index scores)
Intermittent mobility support and intermittent respiratory support (non-invasive ventilation)	0.289	Amicus vignette study (EQ-5D index scores)
Intermittent respiratory support and wheelchair dependent (non-invasive ventilation)	0.080	Amicus vignette study (EQ-5D index scores)
Wheelchair and respiratory support dependent (non-invasive ventilation)	0.080	Amicus vignette study (EQ-5D index scores)
Wheelchair and respiratory support dependent (invasive ventilation)	-0.078	Amicus vignette study (EQ-5D index scores)

Abbreviations: EQ-5D: EuroQol 5 Dimension.

Table 42: Scenario analysis – utility values from PROPEL

	Cipaglucosidase alfa in combination with miglustat	Alglucosidase alfa	Incremental	
Total cost	[redacted]	[redacted]	[redacted]	
Total QALYs	[redacted]	[redacted]	[redacted]	
Cost per QALY	[redacted]	[redacted]	[redacted]	
Incremental cost-effectiveness ratio (ICER)			Dominant	
Willingness to pay threshold			**£20,000/ QALY**	**£30,000/ QALY**
Net monetary benefit			[redacted]	[redacted]
Net health benefit			[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

d) Please comment on the face validity of the utility values generated from the TTO exercise compared with those obtained from i) the PROPEL trial, and ii) the published values.

It should be clarified that the utility values generated from the time trade-of (TTO) exercise were not used in the base case and were instead used in Scenario analysis #5. The base case utilised values derived from EQ-5D valuation of health state vignettes rather than using TTO, in line with the NICE hierarchy of HRQoL evidence,[23] NICE reference case[24] and Decision Support Unit (DSU) best practice recommendations.[25]

The vignettes were validated by healthcare professionals and were reviewed by individuals with LOPD who had experienced that health state, to ensure they accurately represented living with LOPD. The resulting utility values used in the base case (using EQ-5D) for each health state were validated by clinical experts.[2] Both sets of utility values derived from the vignette study conducted by Amicus (EQ-5D and TTO) showed a similar trend, with results from some participants yielding utilities worse than death for the most advanced clinical presentations of LOPD, highlighting the severity of the disease. TTO weights were marginally higher than EQ-5D utilities as observed in previous research.[26, 27] Therefore, the utility values derived from the vignette study are considered to have high face validity.

In addition to clinical validation, the use of these values in the model is supported by their similarity to those derived from the PROPEL trial and the published values from Malottki *et al.* and Kanters *et al.* The methodology of the vignette study also allowed for the generation of utility values that are more appropriate to the decision problem than currently available published values. The vignette study sampled the UK general population, while the published values were generated through studies not conducted in the UK population.

e) Please provide further justification for using the TTO values rather than the published values which by and large use preference-based measures in patients rather than values elicited from the public.

As described in part d), the utility values generated from the TTO exercise were not used in the base case and were instead used in Scenario analysis #5. However, this question has been answered to justify the use of EQ-5D-derived values from the vignette exercise conducted by Amicus.

Although the available published values used preference-based measures in people with LOPD, identified studies were determined to be insufficient for use in the economic model as they only provided utility data stratified by 'earlier' health states. No single study identified in the literature provided utilities for all health states in LOPD. In Scenario #5, Kanters *et al.*[21] provided utilities for the 'earlier' health states, and due to the absence of utilities for the 'later' health states, Duchenne Muscular Dystrophy (Landfeldt *et al.*)[22] was used as a proxy condition to inform these 'later' health states. However, these two studies together were still insufficient to inform the utility values for each health state and an assumption had to be made to complete outstanding health state utilities. Malottki *et al.*,[28] which also only provided utilities for 'earlier' health states, included both individuals receiving ERT treatment and those who were not; the use of ERT in some individuals may have impacted the estimated utility.

DSU best practice recommendations state that if insufficient EQ-5D data are available as described above, utility data can be generated using vignettes valued by the general population.[25] The vignette study was the only single study that captured the full range of severity of LOPD, and all health states were rated by the same UK group (n=100). This ensured that the value of cipaglucosidase alfa in combination with miglustat was fully and consistently captured.

Resource use and costs

B14. Priority Question: The economic model currently assumes patients will be treated until death with zero discontinuation.

a) Please comment on the clinical plausibility of patients being treated until death. The European Pompe Consortium (EPOC) consensus outlines several criteria for stopping ERT and the van Kooten et al study suggests stopping rules are applied in practice.

b) Please comment on the clinical plausibility of zero discontinuation given the non-zero rates of discontinuation observed in the PROPEL trial.

c) Please comment on the plausibility of patients' sequencing alternative ERT treatments.

a) Currently, there are no stopping rules for ERT in adults with LOPD provided by UK guidelines and subsequently, UK clinicians would not typically look to stop treatment with ERT unless discontinuation was required due to adverse events which is considered to be uncommon (please see Question B14). Therefore, it was considered reasonable to assume that individuals will be treated until death, and that it was not appropriate for Amicus to define stopping rules in the UK.

b) During an advisory board with UK clinicians from specialist Pompe disease treatment centres, it was confirmed that differences in adverse events experienced when treated with alglucosidase alfa, avalglucosidase alfa or cipaglucosidase alfa would be negligible enough not to lead to discontinuation of treatment,[2] and therefore discontinuation was assumed not to occur in the model. This approach was also used to ensure simplicity of the model, as any discontinuations would be assumed to be similar for all treatments included in the model to avoid introducing undue uncertainty.

c) Given that there is no clear treatment paradigm in LOPD, it is unclear how likely individuals are to sequence alternative ERT treatments. During the advisory board mentioned above, it was confirmed that clinicians would discourage sequencing treatments if this was based on 'trivial' reasons. Incorporating treatment switching into the model would also add uncertainty, particularly given the lack of data on post-switch efficacy and costs.

B15. Priority Question: The economic model implicitly assumes 100% compliance with the dosing schedule with no dose interruptions or alterations.

a) Please provide relevant data on compliance and relative dose intensity for PROPEL, ATB200-02 any other relevant study.

b) Please include a scenario analysis in which RDI is used to adjust acquisition/administration costs.

c) Please comment on compliance with current treatments (based on clinical experience)?

a)

PROPEL

Treatment compliance was high, with an overall mean of [redacted]% for cipaglucosidase alfa/alglucosidase alfa and [redacted]% for miglustat/placebo. No subject had compliance below [redacted]% or above [redacted]%.

Relative dose intensity (RDI) data were not available from the PROPEL trial.

Table 43: Treatment compliance in PROPEL (Safety Population)

	Cipaglucosidase alfa in combination with miglustat (n = 85)		Alglucosidase alfa in combination with placebo (n = 38)		Total (N = 123) n (%)	
	Cipaglucosidase alfa n (%)	Miglustat n (%)	Alglucosidase alfa n (%)	Placebo n (%)	Cipaglucosidase alfa/ alglucosidase alfa	Miglustat/placebo
Dose compliance[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose compliance category, n (%)						
<80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 80% to ≤80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>120%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infusion compliance[b]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infusion compliance category						
<80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 80% to ≤ 80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>120%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]Dose compliance for alglucosidase alfa and cipaglucosidase alfa = 100*(total infusion dose administered [mg] / total infusion dose planned or intended [mg]); Dose compliance for placebo and miglustat = 100*(total dose administered [mg] / scheduled or planned dose [mg]
[b]Compliance for number of infusions = 100*(number of infusions administered / number of infusions planned or intended), where the number of infusions planned is obtained as (subject's last date in study while on treatment - date of first infusion + 14) / 14. Missed infusions due to COVID-19 related policies are subtracted.
Abbreviations: SD: standard deviation; Max: maximum; Min: minimum.
Source: Amicus Therapeutics Data on File (PROPEL Clinical Study Report).[1]

ATB200-02

In ATB200-02, treatment compliance was high (mean ≥ [redacted]%) for all stages of the study for both cipaglucosidase alfa (Table 44) and miglustat (Table 45)

Table 44: Compliance with cipaglucosidase alfa – Stage 2 Period 5 + Stage 3 + Stage 4 in ATB200-02 (Safety Population)

	Total (Cohorts 1 – 4) ([redacted])
Compliance based on infusion dose (%)[a]	
Mean (SD)	[redacted]
Min, Max	[redacted]
Compliance based on infusion dose categories, n (%)[a]	
< 80%	[redacted]
80% - 120%	[redacted]
Compliance based on number of infusions (%)[b]	
Mean (SD)	[redacted]
Min, Max	[redacted]
Compliance based on number of infusions categories, n (%)[b]	
80% - 120%	[redacted]

[a]Compliance based on infusion dose is calculated as: 100 * (Total infusion dose administered [mg/kg] / total infusion dose planned or intended [mg/kg])
[b]Compliance based on the number of infusions is calculated as: 100 * (Number of infusions administered/number of infusions planned or intended)
Cohorts 1, 2, 4: ERT-experienced participants; Cohort 3: ERT-naïve participants; Cohorts 1, 3, 4: ambulatory participants; Cohort 2: non-ambulatory participants.
Abbreviations: ERT: enzyme replacement therapy; SD: standard deviation; Max: maximum; Min: minimum.
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[4]

Table 45: Compliance with miglustat – Stage 2 Period 5 + Stage 3 + Stage 4 in ATB200-02 (Safety Population)

	Total (Cohorts 1 – 4) ([redacted])
Compliance based on dose (%)[a]	
Mean (SD)	[redacted]
Min, Max	[redacted]
Compliance based on dose categories, n (%)[a]	
80% - 120%	[redacted]
Compliance based on number of doses (%)[b]	
Mean (SD)	[redacted]
Min, Max	[redacted]
Compliance based on number of dose categories, n (%)[b]	
80% - 120%	[redacted]

[a]Compliance for each subject taking miglustat will be calculated as: 100 * (total dose administered [mg] / total dose scheduled or planned dose [mg])
[b]Compliance based on the number of infusions is calculated as: 100 * (Number of infusions administered/number of infusions planned or intended)

Cohorts 1, 2, 4: ERT-experienced participants; Cohort 3: ERT-naïve participants; Cohorts 1, 3, 4: ambulatory participants; Cohort 2: non-ambulatory participants.
Abbreviations: ERT: enzyme replacement therapy; SD: standard deviation; Max: maximum; Min: minimum.
Source: Amicus Therapeutics Data on File (ATB200-02 Clinical Study Report).[4]

b) As RDI data were not available from the PROPEL trial, the requested scenario can, unfortunately, not be provided at this stage.

c) Amicus understands that the vast majority of adults with LOPD self-infuse, requiring a nurse visit at home, which naturally encourages high treatment compliance.[3, 14] According to clinical expert opinion, the primary reason for missing an infusion in clinical practice is a failed cannulation, but cannulation would be attempted again the next day.

B16. Miglustat needs to be taken an hour in advance of intravenous administration of cipaglucosidase alfa plus miglustat. This may impact on the administration costs of cipaglucosidase alfa plus miglustat compared with alglucosidase alfa and avalglucosidase alfa.

a) Please justify the current approach to modelling treatment administration costs and the omission of any additional administration costs associated with the provision of miglustat.

b) The nurse time required for reconstitution in the self-infusion group has been defined incorrectly in the model. The alglucosidase alfa time (1.38) has been used for cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa and vice versa. Please check and update as necessary.

a) It is assumed that individuals with LOPD can orally administer miglustat independently whilst the reconstitution of cipaglucosidase alfa is taking place, and therefore no additional nurse time should be required. This assumption also aims to avoid overcomplexity in the model.

b) Amicus can confirm that the nurse time associated with the different treatments has now been defined correctly as part of the updated model; the results of the updated model base case are presented in Appendix 1.

B17. The model only includes consultant neurologist appointments for all patients in the patient management costs. Please update the model to include omitted patient management costs associated with Pompe disease patients, for instance, physiotherapy and respiratory consultant costs, as included in TA821.

Amicus can confirm that, in addition to consultant neurologist appointments for all individuals, the submitted model base case also includes additional health-state dependent patient management costs in the form of non-invasive ventilation support assessments and respiratory physiology consultant appointments. In the absence of robust data to inform further treatment-related difference in healthcare resource use, Amicus consider it unlikely that the inclusion of additional non-health state dependent management cost items would substantially alter the results of the economic analysis; as such, Amicus consider the current, more simplified approach to be the most appropriate given the available data.

B18. Priority Question: The annual cost of invasive ventilation is informed by the Noyes *et al.* 2006 study.

a) Please provide further details on how this study was used to inform the £142,790 annual cost applied in the model.

b) Please comment on the appropriateness of this study given it considers a paediatric population who do not have Pompe disease, did the company consider alternative sources?

c) Please define what is meant by invasive ventilation and whether there is an expectation this will be delivered in a hospital or in an outpatient setting.

a) Annual costs associated with invasive ventilation were modelled in line with the accepted precedence presented in TA821. As described as part of the evidence review group (ERG) clarification questions for this appraisal, the annual cost of invasive ventilation (at an individual's home) was assumed to be the mean total cost in Table 6 of the Noyes *et al.* 2006 publication (£104,352; inflated to a value of £142,790).

b) Annual costs associated with invasive ventilation were assumed to be the same for paediatric and adult individuals (with the former representing the original study population from Noyes *et al.* 2006) as part of TA821; with the overall approach to costing in TA821 having been accepted as "reasonable" by the ERG, and the general paucity of robust data for the modelling of healthcare resource use in individuals with Pompe disease, the same approach to costing invasive ventilation was also adopted for this economic analysis.

c) Invasive ventilation was defined in TA821 as being "comprised of an endotracheal tube and a mechanical ventilator" in line with its description in the literature.[29] In the context of annual costs associated with invasive ventilation, in line with TA821, it was assumed that this would be performed at home and corresponding costs from Noyes *et al.* 2006 were applied. With regards to upfront one-off costs associated with invasive ventilation (£133,277), as per TA821 these were assumed to represent an initial 4-month inpatient stay in a high-dependency unit.

Section C: Textual clarification and additional points

C1. Several numbers reported in the company submission are highlighted as AIC (e.g. in Section B.2.3.5), yet are reported in the Schoser et al. publication of the PROPEL trial, please correct the AIC marking.

Confidentiality highlighting has been amended in the company submission, included alongside this response. No other changes beyond updates to confidentiality highlighting have been made in the submission documents.

C2. The key in Figures 13, 16 and 17 appears to be incorrect and contradicts the results reported in the text, please check and supply corrected figures.

We can confirm that the key was incorrect, and have provided the updated figures below, in the same order as included in the question (Figure 15, Figure 16, Figure 17).

Figure 15: Figure 13 in the company submission

Figure 16: Figure 16 in the company submission

Figure 17: Figure 17 in the company submission

C3. There appears to be an omission in the text in the first paragraph on page 93, please clarify whether it should read "… and [redacted] experienced treatment-related TEAEs."

We can confirm that the original text here was incorrect; the sentence should read: "In Stage 1 of ATB200-02, at a dose of cipaglucosidase alfa 20 mg/kg, [redacted] experienced TEAEs, and [redacted] experienced treatment-related TEAEs."

C4. On page 25 of the company submission it states that "values in the PROPEL CSR may differ slightly from those in the Schoser et al publication", please provide further explanation about why some values differ.

During the peer review of the Schoser *et al*. publication, specific additional analyses were requested that differed marginally from those in the CSR. The CSR forms the most complete data set and was used in the regulatory submission to the European Medicines Agency EMA.

The differences referred between the CSR and the Schoser et al. publication are related to Figure 2 and Supplemental Materials Section 2.3 (Figures A and B) in the Schoser *et al*. publication. These figures present mean change from Baseline values whereas the figures in the PROPEL CSR presented LS mean change from Baseline values based on the primary analysis model (mixed-effect model for repeated measures [MMRM] for the primary efficacy endpoint of 6MWD and ANCOVA for all the key secondary efficacy endpoints including FVC % predicted). Peer reviewers determined that the mean change from Baseline would be easier to understand for readers of the Schoser *et al*. publication; this analysis presents a trajectory of change from Baseline that is consistent with that using the LS mean change from Baseline. For the inferential statistics, both the Schoser *et al*. publication and the PROPEL CSR presented the LS mean changes from Baseline with the same results.

Search strategies

C5. For the indirect treatment comparison searches in the document 'Amicus Data on File 2022 Indirect Treatment Comparison Report', no search strategies or terms are provided for the conferences or grey literature searches.

A document summarising search strategies for the conferences or grey literature searches is provided alongside this response.[30]

C6. For the indirect treatment comparison searches in the document 'Amicus Data on File 2022 Indirect Treatment Comparison Report', the Embase search on page 83 seems to apply two separate date limits to line 17 and turn 620 papers into 637 papers. There is an error in this strategy somewhere in the number of hits listed. The hits for at least line 17 must be incorrect.

In order to restrict an Embase search to a specific time period, both the Date Delivered (.dd.) and Revised Date (.rd.) fields must be used. The Date Delivered (.dd.) field is available when a new record is included in the database, however this is removed and replaced by the Revised Date (.rd.) when the record is revised. In order to include both new records and those that have been revised, both the Date Delivered (.dd.) and Revised Date (.rd.) fields should be combined with the OR Boolean operator so as to capture all citations added in the time frame of interest.[31]

We can confirm that the number of hits in row 17 of the Embase search strategy should be 650 rather than 620.

Table 46: Search strategy: Embase (Indirect treatment comparison)

Database: Embase 1974 to 2022 September 14 **Search Platform**: Ovid **Date of Search**: September 15, 2022 [Last Database Update: September 14, 2022] **Date Range Searched**: 1974/01/01 to 2022/05/31		
#	**Search term**	**Hits (15th September 2022)**
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$)) or (open label adj (trial$ or stud$)) or (non blinded adj (trial$ 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	650
18	limit 17 to dd=19740101-20220531	386
19	limit 17 to rd=19740101-20220531	251
20	18 or 19	637

C7. For the indirect treatment comparison searches in the document 'Amicus Data on File 2022 Indirect Treatment Comparison Report', the PRISMA diagram on page 28 is awkward to read because the individual databases aren't listed. Why is the figure for grey literature only 144, how did you arrive at this figure? Why are hits from clinical trials registries or conference abstracts not shown in the PRISMA diagram?

The grey literature search initially identified [redacted] records, of which [redacted] were excluded (for reasons such as inconsistency with the patient/population, intervention, comparison and outcomes (PICO) framework, lack of results etc.), leaving [redacted] records included in the screening.

The number of records identified in particular sources (databases and grey literature) including total number of records in each source has been added to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram in Figure 18.

Figure 18: Updated PRISMA diagram for the ITC

^ Identified base 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 reference verification
Abbreviations: CDER: Center for Drug Evaluation and Research; DARE: Database of Abstracts of Reviews of Effects; ISRCTIN: International Standard Randomised Controlled Trial Number; ITC: indirect treatment comparison; SLR: systematic literature reviews; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: prospective register of systematic reviews.

Appendix 1: Updated model base case

The results of the updated model base case are presented in Table 47, with the results of the corresponding probabilistic and deterministic sensitivity analyses presented in Table 48 and Figure 19 to Figure 21.

In summary, the updated base case includes the following changes to the model:

- Joint random seed values for the normal distribution of likely correlated input parameters (Question B2)
- Truncation of the normal distribution of participants' age (Question B4)
- Removed disease progression parameters from the first-order iterations, with the uncertainty of these now being explored as part of the PSA (Question B7)
- Correctly implemented nurse time as part of the treatment administration cost calculations (Question B16)

As presented in Table 47, the results of the updated base case analysis are very similar to the originally submitted base case (with a net monetary benefit of [redacted] and [redacted] at willingness-to-pay thresholds of £20,000 and £30,000 per QALY, respectively).

Table 47: Updated base case results

	Cipaglucosidase alfa in combination with miglustat	Alglucosidase alfa	Incremental	
Total cost	[redacted]	[redacted]	[redacted]	
Total QALYs	[redacted]	[redacted]	[redacted]	
Total life years (discounted)	[redacted]	[redacted]	[redacted]	
Total life years (undiscounted)	[redacted]	[redacted]	[redacted]	
Cost per QALY	[redacted]	[redacted]		
Incremental cost-effectiveness ratio (ICER)			Dominant	
Willingness to pay threshold			**£20,000/ QALY**	**£30,000/ QALY**
Net monetary benefit			[redacted]	[redacted]
Net health benefit			[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 48 Updated PSA results

	Incremental costs	Incremental QALYs	ICER	NMB	
				£20,000/ QALY	£30,000/ QALY
Cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year

Figure 19: Cost-effectiveness scatter plot from PSA (WTP threshold: £20,000 per QALY)

Abbreviations: ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay.

Figure 20: Cost-effectiveness acceptability curve from PSA

Probability of cipaglucosidase alfa with miglustat being cost-effective (WTP threshold of £20,000): 95.3%
Probability of cipaglucosidase alfa with miglustat being cost-effective (WTP threshold of £30,000): 98.7%
Abbreviations: PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay.

Figure 21: Absolute change in incremental NMB in the DSA between upper and lower values in the DSA

All analyses have included the proposed PAS for cipaglucosidase alfa in combination with miglustat. Alglucosidase alfa is included at list price.
Abbreviations: 6MWT: six-minute walk test; DSA: deterministic sensitivity analysis; FVC: forced vital capacity; NMB: net monetary benefit; RR: risk ratio.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease [ID3771]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Association for Glycogen Storage Disease UK (AGSD-UK)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The charity was founded in 1986 to promote the interests of people affected by Glycogen Storage Disease. This is achieved through provision of information, support and education for people affected, their families and professions in the field. We engage widely with our 122 charity members and 1506 registered community members and work closely with other charities and professional partners to drive up standards of care. The charity receives funding from charitable donations and trusts and wide range of treatment industry organisations.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	£10k of core funding received from Amicus over the past 12 months to date £4,224 of project funding received from comparator organisation (Sanofi) in past 12 months to date with further project grant pending (£25K)

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	In July 2021 AGSD-UK issued a survey to better understand the impact of the condition in the UK. Wide distribution elicited 56 responses from people with Pompe, along with 29 from carers/family members of those affected. Of these 85 responses, 71 related to people with Late Onset Pompe Disease (LOPD).These responses have informed this submission, along with follow up interviews with a subset of adults with late onset Pompe with experience of cipaglucosidase alfa with miglustat**,** who responded to open questions about its impact, advantages and disadvantages.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Pompe is a rare, life threatening and life changing condition with variable rates of progression and age of onset. First symptoms can occur at any age from birth to late adulthood. Earlier onset is usually associated with the most rapid progression and even greater disease severity. At all ages the condition is characterised by skeletal muscle weakness causing increasingly severe respiratory and mobility problems. The most severely affected infants usually present within the first 3 months after birth. They have characteristic cardiac problems due to heart enlargement in addition to generalised skeletal muscle weakness, with a life expectancy of less than 2 years if untreated. In contrast to classic infantile-onset Pompe, late-onset generally refers to all cases in which hypertrophic cardiomyopathy did not manifest or was not diagnosed at or under the age of 1 year, as well as to all cases with symptom onset above the age of 1 year. Though people with late onset during childhood, adolescence, or adulthood rarely manifest cardiac problems, progressive muscle weakness leads to increasing dependency on mobility aids and respiratory support, affecting independence, quality of life and life expectancy. The route to diagnosis is uncertain and can be challenging. Among those with late onset only 26% were diagnosed within 12 months of symptoms such as breathing or mobility problems.14% waited over 10 years for diagnosis. The delay reflected the number and range of specialists that patients and carers reported seeing before receiving a diagnosis. Those affected expressed frustration at the impact of delayed diagnosis on their access to treatment to stave off degeneration and maintain function and independence: *"If I had an early diagnosis and been able to start ERT earlier I might have been able to continue to work. I felt better and saw some improvements after 6 months, but too much muscle damage had already occurred"...Had been very independent, travelled, I might have been able to do more without the obstacles I face now."* - LOPD patient in their 60s. More than 10 years before diagnosis from first onset of symptoms. **Use of health, welfare and social care services** The survey pointed to extensive use of health and welfare services, as well as highlighting unmet need in areas such as counselling/psychology. The overwhelming majority of respondents reported using physiotherapy services (99%) and accessing a Disability Living Allowance or Personal Independence Payment ((85%) Among those with late onset 57% had accessed dieticians and 53% occupational therapy services. 28% had accessed speech and language therapy, 26% had accessed psychology services, while 21% had used a paid carer and 21% a social worker. Access to aids and adaptations was seen as particularly important: *"… we need to be extremely careful and use appropriate supports such as a bath board, inflatable seats, rails or a bath lift to assist with getting in and out. A fall in a bath can be extremely painful and dangerous." – person with LOPD in his 30s*

	Living with Pompe For people affected, their symptoms and prognosis take a huge toll in terms of their physical and psychological wellbeing: *"My breathing and mobility are both getting worse. I feel worried that I will end up with breathing support fulltime and dread the thought that I won't be able to move around independently" – person with* LOPD in their 60s Physical symptoms reported by respondents were wide ranging. For the majority these included significant issues with pain (61%), sleep (58%) and digestive problems (62%) as well as muscle problems (93%), debilitating fatigue (88%) respiratory impairment (64%) and delayed motor skills (52%). In addition, a substantial minority of respondents reported other symptoms including: difficulty regulating temperature (41%), continence issues (40%) scoliosis (28%) cardiac symptoms (18%) problems with hearing (15%) and speech problems (8%). For people with late onset the most challenging symptoms were ranked as muscle weakness (72%) and respiratory problems (37%). These symptoms have a significant impact on the everyday lives of people affected, with most reliant on some form of respiratory support (60%) and walking aids (75%). 53% were wheelchair users Survey respondents overwhelmingly reported that they had missed out on doing activities they enjoyed in the last 12 months because of Pompe (92%): *"… can't go out and do the things I want to do without someone else to get me there and help me around"* – person with LOPD in their 20s 85% reported an impact on their ability to work, including restrictions in the types of roles possible. 40% of respondents reported having to leave work altogether or feeling incapable of working, with a knock on effect on their sense of self worth: "*[I] retired early from work as it became too difficult and I felt I couldn't do what I wanted and had done previously, which made me feel guilty as I became less and less productive*" – person with LOPD in their 50s Many respondents commented on the impact on independence: *"I cannot go anywhere alone for the fear of falling or struggling with energy levels*" – person with LOPD in their 30s "*Overwhelming fatigue and how to manage treatment has prevented him from going to uni and he's unsure what to do next*" - Mother of a teenager with LOPD *"[He worries about] how he'll earn an income and manage if he doesn't live with us*" - Mother of a teenager with LOPD The symptoms and prognosis had a significant impact on respondents' mental health and caused considerable anxiety for the future:

	"Getting worse. Being unable to look after my children. Being unable to look after myself. Needing help from others more often. Having to use a wheelchair or ending up on a ventilator 24 hours a day. Losing independence. No longer being able to work. Possibly dying." – person with LOPD in their 40s *"How fast I will decline. Lack of income if things decline quickly. Inability to be the mother my children deserve. Inability to eat food - have an NG tube at present as can't eat without vomiting"* – person with LOPD in her 40s *"Lack of independence and being left alone"* – person with LOPD in their 40s *"Being hopeless and a burden"* –person with LOPD in their 40s **What do carers experience when caring for someone with the condition?** Respondents with caring responsibilities for people living with Pompe described the impact this had on their lives. This included 88% reporting an effect on their finances and 83% on their ability to work their preferred hours or at all: *"Being a carer for my son for the last 12 years has taken a huge toll on my life. Being a single mother of 4 children (2 with Pompe) has been a massive juggling act between being there to support them and trying to earn."* - Mother of adult with LOPD "*As a single parent I left my job when my son was diagnosed to be able to attend the many appointments and infusion days*." - Mother of an under-10 living with LOPD 80% of parents or carers reported an impact on their social activities and many mentioned the effect on other family members, commenting that they missed out on attention and opportunities to do things. 71% reported an effect on their physical health: "*I now feel like I am doing two jobs and get quite tired near the end of days despite not necessarily doing what I previously would say would be strenuous. The mental and physical side of caring has been an eye-opener*" - Husband of person with LOPD An overwhelming 93% of parents and carers reported an impact on their mental health: *"[I] worry that he's still breathing all the time. Having to provide good balanced meals. Stressed as not seen a specialist since diagnosed. I went into depression over it last year. I don't sleep the night before treatment, as I'm worried about messing it up."* - Wife of person with LOPD in his 60s When asked about their hopes and concerns for the future a major concern among parents and carers was how the person they care for would cope if they were unable to continue to provide support.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Perceptions of current treatment were mixed with 16% of late onset respondents receiving the standard therapy reporting that it had little or no impact on the condition whilst 35% reported only a moderate impact: *"Was hoping to see an increase in muscle strength to make legs more stable but hasn't happened"* –person with LOPD in their 40s Just under half of respondents were more positive: *"It has definitely slowed the progression of the disease significantly*" – person with LOPD in their 50s "*After treatment his energy levels are up and his overall wellbeing is drastically improved*." - Mother of a child with late-onset Pompe. Some respondents reported side effects from treatment: "*Tiredness after infusion lasts for several days, I just recover and then I seem to be back in it... it's an endless routine*." – person with LOPD in their 40s Most were able to receive their infusions at home rather than travelling to specialist centres and this was welcomed: "*Very pleased to be able to have it at home."* – person with LOPD in their 50s However, treatment continues to have an impact on patients' day to day lives: "*I'm very grateful for the treatment but I feel limited by the nurse coming to the house which means I have to plan my whole day around this and it wipes out 2 days a month that I can't do other things*" – person with LOPD in their 40s 31% of respondents mentioned difficulties cannulating and problems with needles as a disadvantage of current treatment: "*Long days, trouble cannulating, mental effects of feeling like a patient rather than a person*." – person with LOPD in their 20s

8. Is there an unmet need for patients with this condition?	Whilst the current standard therapy has significantly improved life expectancy and quality of life, it is still the case that patients who have been responsive to treatment experience debilitating symptoms and disease progression. Meanwhile, those with a limited or waning response to standard therapy describe a desperate and urgent need for more effective treatments. One respondent described the impact of seeing their independence ebb away and expressed that: 'without more effective treatment the only thing that would improve things for me is a change in the law around assisted dying' -person with LOPD in their 60s Respondents described losing hope as a levelling off in their response to standard therapy led to increasing dependence on walking aids and assisted respiration. They expressed the feeling that their lives were 'shrinking' and that improved therapy may come too late: 'Whilst the current treatment regime has had some efficacy there is a general sense for us in the Pompe community that better treatment options are urgently needed in order to slow down the rate of disease progression and improve our quality of life.' Person with LOPD in their 40s

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	All respondents interviewed with experience of cipaglucosidase alfa with miglustat were overwhelmingly positive, citing a wide range of advantages. All but one respondent had previously taken the standard therapy alglucosidase alpha (Myozyme). They commented on the way the impact of this had waned over time, leaving them increasingly debilitated and affecting their ability to work, maintain independence and take part in family and social activities. They highlighted the difference that cipaglucosidase alfa with miglustat had made to their quality of life. A common theme related to feeling more positive and having a greater sense of well-being: "I now feel I can face the day." Person with LOPD in their 40s with previous experience of Myozyme Respondents commented on feeling more alert and better able to focus and concentrate. As one described it: 'my brain fog has lifted'. Person with LOPD in their 40s with previous experience of a trial therapy This was noted as a marked difference to respondents' experience of their former therapy. Others mentioned they no longer had morning headaches and put this down to better lung function. Respondents commonly referenced improved respiratory function, commenting they could undertake lung function tests more easily. Two of the respondents commented on having recovered from Covid without this having had a major impact on their respiration and felt the therapy might have contributed to this. Respondents generally commented on having more energy and stamina and experiencing less fatigue. They described the difference this made to their lives in terms of being able to undertake activities they could only previously manage with difficulty, if at all. These included being able to climb stairs, get in and out of a car, get up from the floor and be socially active. They spoke about having more stamina to be able to fulfil plans and get through the day and the difference this made to their quality of life:

	‘It doesn’t feel like everything is an effort any more’ Person with LOPD in their 50s with previous experience of Myozyme ‘My life doesn’t feel so limited’ Person with LOPD in their 60s with previous experience of Myozyme Respondents mentioned increased strength and mobility and referred to improved walking distances. Though some commented that the impact here had not been as marked, this was qualified by referencing their short time on the treatment or disruption of therapy due to Covid and unrelated illness which they felt meant that it was ‘too early to say’ An unanticipated benefit referred to was a reduction in pain, which for some respondents was highly significant. “It made a massive impact on my life. It was unexpected too as the thought that I would be in less pain hadn’t crossed my mind” Person with LOPD in their 60s with previous experience of Myozyme As one respondent described: “within two infusions I noticed I was much less tired and more alert. Within the next two infusions I noticed I was having much less pain and within two months of starting the new drug I was able to cut my painkillers (morphine slow release) by half. I also cut out the co codamol 30 500mg which I was also having 2-4 times most days. Person with LOPD in their 50s with previous experience of Myozyme Respondents who had previously received Myozyme commented on a more straightforward infusion process “Having the infusion in one big bag is better –time seems to pass more quickly.”

	"..it's not like the faff of Myozyme" Person with LOPD in their 50s Some also commented on feeling less tired on infusion days. None of those interviewed had experienced an adverse reaction to the new therapy. Overall respondents commented on how positive they felt about having access to a new treatment option that could make such a difference to their life: "I feel so fortunate to have been part of this trial and it's so important that everyone affected has the chance to benefit from the therapy" Person with LOPD in their 40s with previous experience of Myozyme

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Though some respondents commented on the requirement to fast for two hours before and after miglustat, all felt they had been able to adapt their routine to accommodate this, some getting up early to eat before the two hour cut off. Comments included: "It doesn't disrupt life in any way' 'It's not an issue at all.' In common with the standard therapy the need to receive treatment via fortnightly infusion was seen as a disadvantage.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	For those who have experienced an adverse reaction or lack of response to standard therapy or whose response is waning, the need for more effective treatment options is particularly urgent. All those with this debilitating, degenerative condition would benefit from the earliest possible access to the most appropriate and effective treatment for them, in order to slow progression, maintain function and independence and improve quality of life.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	For those with this rare, degenerative, life limiting condition, the absence of screening and delays in diagnosis make the need for access to effective treatment to stave off muscle wastage and dependence on respiratory support still more urgent.

Other issues

13. Are there any other issues that you would like the committee to consider?	AGSD-UK would also like to acknowledge and endorse the background evidence provided by Pompe Support Network in their submission to the consultation.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Pompe is a severe, degenerative, life limiting and life changing condition that affects every aspect of daily living. • The huge impact of Pompe on quality of life was demonstrated an AGSD-UK 2021 survey. The vast majority of respondents reported problems with muscle weakness, mobility and frequent falls, tiredness or overwhelming fatigue, pain, sleep problems, digestive issues and difficulties with respiration. A substantial minority reported a range of other symptoms including continence problems and difficulties with temperature regulation. The majority were reliant on respiratory support and mobility aids, with a substantial need for health, welfare and social care support. Over half were wheelchair users. Respondents described severe restrictions on their independence and ability to work and socialise, with a major detrimental effect on their mental wellbeing and significant anxiety about the future. • The overwhelming majority of carers for those with Pompe reported that their mental and physical health, financial security, ability to work and take part in social activities were affected and many described a significant toll on their wellbeing. • The survey also showed the limitations of the standard therapy Myozyme for those who do not tolerate it, whose response is limited or who are experiencing waning effectiveness. Just over half of those with late onset reported no, little or only moderate impact from standard therapy. Respondents articulated an urgent need for access to more effective treatments options to prevent deterioration and meet their needs. • Interviewees who had experienced Cipaglucosidase alfa with miglustat referred to a range of advantages over standard therapy, including: -increased sense of well-being -feeling more alert -fewer headaches -reduced fatigue and improved stamina -increased muscle strength -increased walking distance -improved respiration -reduced pain They commented on the positive impact of these on their day to day lives, in terms of their ability to work, maintain independence and take part in family and social activities.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease (ID3771)

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? No A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	Charity organisation representing UK neurologists, funded by members
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Stabilisation of an otherwise progressive disease and ideally improvement, although RCT data so far for the latter has not been convincingly demonstrated
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The main RCT (PROPEL) used 6 minute walking distance as the primary outcome measure (i.e. mobility) with sitting Forced Vital Capacity as a secondary measure (i.e. respiratory function), both measures compared with baseline after 52 weeks of treatment. These are the same measures used clinically to assess effect of currently available enzyme replacement therapy (ERT)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes; not all people respond to currently available ERT and at best it stabilises the condition

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Current ERT is alfa glucosidase (Myozyme®)
9a. Are any clinical guidelines used in the	Yes, European Consensus for starting and stopping ERT in PD https://pubmed.ncbi.nlm.nih.gov/28477382/

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	My experience is based in Scotland, but I think there is general consensus on treating people with Pompes Disease and most follow the above European consensus statement.
9c. What impact would the technology have on the current pathway of care?	I think this would be an option for people who have not responded well to Myozyme, I do not think the evidence yet is sufficient to suggest this therapy should replace the currently available ERT.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, it remains a fortnightly infusion as Myozyme, plus an oral component (miglustat)
10a. How does healthcare resource use differ between the technology and current care?	No difference essentially
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Infusion initiation is usually on a day case unit, evolving to home care delivery, I am assuming the same would be possible for the new therapy
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Effectively none, as this is already in place and delivery is the same, other than an additional oral component.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Based on the current RCT (PROPEL) results, it seems unlikely that this will replace currently available ERT, but it may prove a useful treatment for those people who have received standard ERT and are not/no longer responding. More data may become available in ongoing open label studies from PROPEL but the trial failed to reach significance in its primary outcome.
11a. Do you expect the technology to increase length of life more than current care?	Probably not, but no data
11b. Do you expect the technology to increase health-related quality of life more than current care?	Probably in the above selected subgroup
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not applicable

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Essentially identical

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, I would expect the same consensus guidelines to apply to this therapy; this is based on the same outcome measures as currently used.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	This is unlikely: specifically the adverse effect profile looks similar, perhaps with a trend to more with the new therapy compared to Myozyme
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It is not innovative; it is an evolution of currently available ERT
16a. Is the technology a 'step-change' in the management of the condition?	No, evolution

16b. Does the use of the technology address any particular unmet need of the patient population?	Other than being an option for people who have not responded to Myozyme, no
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Both this new and currently available therapy have a high rate of adverse effects, the new therapy looks very similar.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes (PROPEL)
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Yes, mobility and respiratory function as above
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
18d. Are there any adverse effects that were not apparent in clinical	Not that I am aware of

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No
21. How do data on real-world experience compare with the trial data?	Unknown

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No; this is a rare disease
22b. Consider whether these issues are different from issues with current care and why.	NA

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	NA

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Evolution of currently available ERT • Similar adverse effect profile • Identical delivery method (2 weekly infusions indefinitely) other than an additional oral component • Current evidence suggest it may be a useful option for people who have failed to respond to Myozyme • More data may become available in due course form ongoing open label studies

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease [ID3771]

Patient Organisation Submission

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- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Muscular Dystrophy UK (MDUK)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Muscular Dystrophy UK (MDUK) is the charity bringing individuals, families and professionals together to beat muscle-wasting conditions. Founded in 1959, we have been leading the fight against muscle-wasting conditions ever since. We bring together more than 60 rare and very rare progressive muscle-weakening and wasting conditions, affecting around 110,000 children and adults in the UK. We fund research, provide vital information, advice, resources and support for people with these conditions, their families and the professionals who work with them. We are also a member of NHS England's Paediatric Neurosciences Reference Group.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	In March 2022, MDUK received £7,500.00 in sponsorship income for the 15th UK Annual Neuromuscular Translational Research Conference from possible comparator company Sanofi.

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No links to the tobacco industry.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We wish to endorse the submission being made by the Association of Glycogen Storage Disease (AGSD-UK) They have shared their response with us and we are fully supportive of it and have nothing further to add.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	MDUK endorses the AGSD-UK submission.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**MDUK endorses the AGSD-UK submission.**
8. Is there an unmet need for patients with this condition?	MDUK endorses the AGSD-UK submission.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	MDUK endorses the AGSD-UK submission.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	MDUK endorses the AGSD-UK submission.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	MDUK endorses the AGSD-UK submission.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	MDUK endorses the AGSD-UK submission.

Other issues

13. Are there any other issues that you would like the committee to consider?	MDUK endorses the AGSD-UK submission.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	As per the AGSD-UK submission; • Pompe disease is a severe, degenerative, life limiting and life changing condition that affects every aspect of daily living. • The huge impact of Pompe disease on quality of life was demonstrated by an AGSD-UK 2021 survey. The vast majority of respondents reported problems with muscle weakness, mobility and frequent falls, tiredness or overwhelming fatigue, pain, sleep problems, digestive issues and difficulties with respiration. A substantial minority reported a range of other symptoms including continence problems and difficulties with temperature regulation. The majority were reliant on respiratory support and mobility aids, with a substantial need for health, welfare and social care support. Over half were wheelchair users. Respondents described severe restrictions on their independence and ability to work and socialise, with a major detrimental effect on their mental wellbeing and significant anxiety about the future. • The overwhelming majority of carers for those with Pompe disease reported that their mental and physical health, financial security, ability to work and take part in social activities were affected and many described a significant toll on their wellbeing. • The survey also showed the limitations of the standard therapy Myozyme for those who do not tolerate it, whose response is limited or who are experiencing waning effectiveness. Just over half of those with late onset reported no, little or only moderate impact from standard therapy. Respondents articulated an urgent need for access to more effective treatments options to prevent deterioration and meet their needs. • Interviewees who had experienced Cipaglucosidase alfa with miglustat referred to a range of advantages over standard therapy, including: -increased sense of well-being -feeling more alert -fewer headaches -reduced fatigue and improved stamina -increased muscle strength -increased walking distance

	-improved respiration -reduced pain They commented on the positive impact of these on their day to day lives, in terms of their ability to work, maintain independence and take part in family and social activities.

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About you

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2. Name of organisation	Pompe Support Network
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Pompe Support Network is a registered Charitable Incorporated Organisation (CIO), it is a network of individuals, families, scientists, and healthcare professionals who aim to improve the lives of all people living and working with Pompe disease. The network is managed by members of the Pompe community, for the benefit of the Pompe community. It aims to: • **Influence** and support research into safe, effective, and affordable therapies for Pompe Disease • **Advocate** for access to therapies or medical devices for individuals living with Pompe disease • **Facilitate and finance** community sub-groups to share experience and manage projects to improve the physical and mental wellbeing of the Pompe community. Funds are raised from individual donations, Charitable trusts and foundations, The National Lottery, and Charitable grants from companies with interests in Pompe disease (currently we receive grants from seven such companies). The organisation is not a membership organisation. The organisation has over 140 subscribers, all of whom are members of the Pompe disease community. We have over 300 followers on social media.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for	**Received grants to the value of £15,000 from Amicus Therapeutics** to support activities including: • PompAbility film project • Research to improve quality of life.

evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	• Provision of support services • Conferences and meetings • Administrative support Financial support has also been pledged by Sanofi for 2022-2023, but the amount has not been agreed at the time of submission.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We acknowledge the excellent work of the Association for Glycogen Storage Disease (AGSD-UK) in their survey of the Pompe disease community and fully endorse the conclusions they have reached and presented in their own submission to this appraisal. Each of our five Trustees have communicated with the patient community extensively since before the Standard of Care, Myozyme, was approved for Pompe disease in 2006. All trustees are either parents of Pompe patients, have Pompe disease themselves, or have partners with the condition. We (staff and Trustees) regularly meet virtually and in-person with patients and carers nationally and around the world to discuss many topics of interest to the Pompe community. We have issued several short surveys to assess the Pompe community's views on topics such as "Quality of Life", and "Future Research Priorities" In 2020 and again this year, we have received responses to a national survey of patient experiences at the NHS specialist services for Lysosomal Storage Diseases (LDSs) throughout the British Isles. This year we

	received submissions from 64 Pompe patients who responded to questions about their clinical and social care, access to therapies, and thoughts about clinical research. We have also monitored published research by academia, industry, healthcare professionals and others to fully understand the broad issues concerning rare diseases and especially Pompe disease.

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Late Onset Pompe Disease (LOPD) is a heterogenous condition that can affect patients' lives in very different ways. Some have reduced mobility, some impaired respiratory function and most have both. There are other symptoms that receive less attention but can be equally debilitating: for example, GI issues, muscle pain, headaches, speech, swallowing, fatigue, sleep disorders. Muscle weakness lies at the root of all symptoms whether it be respiratory, skeletal or the smooth muscles of the intestines.
	Diagnosis of LOPD is often very late, many years too late, and so muscle damage has accumulated that cannot be restored. But remaining muscles have sufficient limited function to allow some patients to remain mostly independent, however, many rely on partners or carers to lead their lives comfortably and in safety.
	Many ambulatory patients will be fearful of falling due to trip hazards or instability and so will not venture far from the safely of their home. In many cases they will suffer with anxiety, isolation, and loneliness. Patient groups do everything in their powers to improve the resilience and mental wellbeing of the Pompe community.
	Carers, when family members, provide the essential physical needs of patients and can lose much of their own independence and so eventually suffer from the same anxieties as the patients.
	
	Recent published evidence[1] from 27 LOPD patient interviews that Allan Muir (Chair) presented at the World Muscle Society described the emotional rollercoaster of patients and found that:
	• Most interview participants faced challenges as their condition deteriorated, with impacts on the following:
	  • Lifestyle, daily activities, social life, and holidays
	  • Ability to continue working
	  • Dependency on others, including family members and carers
	  • Family relationships.

	• In general, interview participants felt that disruptive life events, such as accidents or bereavements, added to the physical and emotional burden. • Most interview participants felt that LOPD severely affected their lives In a separate quantitative survey[2] it was shown from interviews with 37 people living with LOPD that • The mean time from symptom onset to diagnosis was 9.3 years. • Participants live with multiple diverse symptoms. Most have day-to-day living assistance and need physical aids. • 26 participants were on ERT, with half for >10 years. 77% believed their condition had deteriorated since starting treatment. • The COVID-19 pandemic has brought increased anxiety and physical deterioration with 50% of people on ERT having their treatment interrupted. [1]**Living with Pompe disease in the UK: characterising the patient journey; burden on physical and emotional quality of life; and impact of COVID-19.** Poster presented by Allan Muir (Pompe Support Network) at the World Muscle Society Annual Congress, 11-15 October 2022. [2]**Quantification of the burden, unmet needs, management, and COVID-19 impact of living with Pompe disease in the UK: results of an online patient survey.** Poster presented by Val Buxton (AGSD-UK) at the World Muscle Society Annual Congress, 11-15 October 2022.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	We have analysed the returns of 64 patients from a recent LSD Community Survey, yet to be published. Of those, 48 are receiving an approved ERT, 9 have access to Cipaglucosidase alpha through EAMS and clinical trials. Two patients had previously suffered severe reactions to therapy, three patients were waiting to start therapy. Most (50) have their ERT infusions at home but attend specialist clinics for assessments every 6 or 12 months. Most respondents (86%) were satisfied or very satisfied with their experience at the specialist centres although many would welcome additional physiotherapy and nutritional support. Many would also like the specialist facilities to be available closer to home. From our small surveys and conversations with patients it is clear that their response to current treatments is varied. Some have been stabilised by the standard of care, others have suffered slow declines across all symptoms, and a small minority have withdrawn from treatment altogether due to severe infusion reactions or total lack of benefit from ERT.
8. Is there an unmet need for patients with this condition?	There is certainly a need for improved treatments, across all stages of disease. Preservation and improved activation of whatever muscle function remains helps in so many ways: reduced risk of falls, improved quality of life, reduced muscle pain, etc. Patients often report that even with the current treatment, they fatigue very easily and cannot work effectively for a full day. Over-exerting themselves on one day will mean that they need one or more days to recover.

	Fatigue often becomes worse as the time of their next two-weekly infusion approaches. The prospect of further deterioration reduces quality of life, longevity, and imposes both physical and mental stresses on the patient, carer, family, and friends. Those who have withdrawn from treatment due to infusion reactions clearly need an alternative treatment to halt their disease progression.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We have listened to several patients who have experience the proposed technology, although they have not all had long to experience its full benefits. One patient with very advanced disease has not yet noticed any additional benefit. Other patients have reported great benefits, particularly in respect of fatigue. They report that they do not feel the increasing fatigue towards the time of the next infusion. The prospect of a reduction in future deterioration, other than the normal ageing process, gives a huge boost to the mental wellbeing of both patient, carers and close family and friends. Anecdotal evidence from the USA suggests that some patients who had reactions to the standard of care are able to tolerate and benefit from Cipaglucosidase alpha.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The period of fasting and the Miglustat pill is concerning for a small minority of patients. Those who already experience GI issues due to Pompe disease do not want those issues aggravated by Miglustat. This may be a patient education issue as patients are aware of GI distress in other LSD patient communities where the prescribed dose and frequency of Miglustat is much higher. Dietitians have advised against fasting in the past, and a small number of patients do have concerns that it may aggravate their condition. Overall, most patients are very excited to access the new treatment.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those patients with advanced disease may benefit less than others from the proposed therapy, but it could still be an improvement over the current standard of care (Alglucosidase alpha). Small improvements in clinical measures can often lead to significant functional improvements and relief in related symptoms. All Enzyme Replacement Therapies for Pompe disease require access to intact muscle fibres to restore and/or preserve functionality.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are not aware of any equality, cultural, or dietary reasons that should be accounted for. We are no longer concerned for those patients who are unable to swallow the Miglustat pill. We are aware that the drug protocol includes procedures for taking the pill contents orally, in liquid form.

Other issues

13. Are there any other issues that you would like the committee to consider?	We would always advocate for flexibility to be given in drug dose prescribing. We have had problems with Alglucosidase alpha (Myozyme) when the dose was insufficient for a small number of patients, often growing children but also for some adults. An increase in dose or frequency, at the physician's discretion, could be very beneficial for those patients. In the past the global Pompe community has suffered greatly when drug supply was interrupted by contamination in bioreactor nutrients. There is still only one production facility for the two alternative ERTs and so having a second facility for Cipaglucosidase alpha would offer drug security, should one therapy be interrupted for any reason. A globally recognised expert biochemist impressed on me how the proposed technology appreciably clears autophagic debris from muscle cells. This will help to preserve muscles, but the full effects may not be seen for several years.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There are significant unmet needs in Late Onset Pompe Disease. • Fatigue is a serious unmet need that is addressed with the proposed technology. • Treatment choice would allow more patients access a suitable and beneficial therapy. • Keeping patients' disease progression in check provides huge physical and mental health benefits for patients, their carers, friends, and family. • Additional therapies provide redundancy in manufacturing facilities, mitigating risks of supply interruption.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease ID3771

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS ENGLAND
3. Job title or position	MEDICAL ADVISOR HIGHLY SPECIALISED SERVICES

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? ~~Yes or No~~ Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? **Yes** or ~~No~~ Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? ~~Yes or No~~ An expert in treating the condition for which NICE is considering this technology? ~~Yes or No~~ An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ~~Yes or No~~ Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no NHSE clinical commissioning policies for this drug
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is a well defined care pathway and there is a nationally commissioned lysosomal storage disorders highly specialised service (HSS) for adults and paediatric patients.
8. What impact would the technology have on the current pathway of care?	If the technology were recommended this would represent an additional treatment option for this patient group.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	This technology is not currently routinely commissioned
10. Will the technology be used (or is it already used) in the same way	The technology would be administered through existing commissioning arrangements

as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	The technology would provide an additional treatment option
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology would be available only through the commissioned lysosomal storage disorders HSS
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The costs of both drugs - cipaglucosidase and miglustat - will be additional costs.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	As the drug is not currently formally commissioned there are no starting or stopping rules in place
11. What is the outcome of any evaluations or audits of the use of the technology?	There are no current evaluations or audits

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No additional issues
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

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External Assessment Group Report
Cipaglucosidase alfa with miglustat for treating Pompe disease

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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Date completed	12/01/2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR135712.

Declared competing interests of the authors

None.

Acknowledgements

Dr Chong Yew Tan, Consultant Metabolic Physician at the Lysosomal Disorders Unit, Cambridge University Hospitals NHS Foundation Trust, provided expert clinical advice and commented on a draft of the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Wade R, Deng J, Dwan K, Robertson L, Njoroge M, Uphoff E, Fulbright H, Dias S, Hodgson R, Eastwood A. Cipaglucosidase alfa with miglustat for treating Pompe disease: A Single Technology Appraisal. CRD and CHE Technology Assessment Group, University of York, 2023.

Contributions of authors

Ros Wade wrote the critique of the decision problem and contributed to the critique of the clinical effectiveness evidence. Lindsay Robertson critiqued the clinical effectiveness evidence. Eleonora Uphoff contributed to the critical appraisal of the clinical effectiveness evidence. Helen Fulbright wrote the search strategy sections. Kerry Dwan wrote the critique of the indirect comparison and performed the simple indirect comparison. Sofia Dias supported the critical appraisal of the indirect comparison and commented on a draft report. Martin Njoroge, Jasmine Deng and Robert Hodgson critiqued the company's model, and co-authored Sections 1, 4, 5, 6 and 7 of the report. Robert Hodgson took overall responsibility for cost-effectiveness sections. Alison Eastwood provided advice, commented on drafts of the report and took overall responsibility for the clinical effectiveness sections.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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List of abbreviations

6MWD	Six-minute walk distance
6MWT	Six-minute walk test
AE	Adverse event
BNF	British National Formulary
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
DES	Discrete event simulation
DICE	Discretely Integrated Condition Event
EAG	External Assessment Group
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	Standardised instrument for use as a measure of health outcome
EQ-5D-3L	EuroQol-5-Dimensions 3-Level
EQ-5D-5L	EuroQol-5-Dimensions 5-Level
ERT	Enzyme replacement therapy
FVC	Forced vital capacity
GAA	Acid α-glucosidase
GSGC	Gait, Stairs, Gowers' manoeuvre, and Chair
HRQoL	Health-related quality of life
HST	Highly specialised technology
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IOPD	Infantile-onset Pompe disease
ITC	Indirect treatment comparison
LOPD	Late-onset Pompe disease
LY	Life years
LYG	Life years gained
MHRA	Medicines and Healthcare products Regulatory Agency
ML-NMR	Multi-level network meta-regression
MMT	Manual muscle test
NHB	Net health benefit

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAS	Patient Access Scheme
PGIC	Physician's global impression of change
PROMIS	Patient-Reported Outcomes Measurement Information System
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Uni
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
SGIC	Subject global impression of change
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
TTO	Time trade-off
WTP	Willingness-to-pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report, starting at Section 2.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1: Summary of key issues

ID3711	Summary of issue	Report sections
1	The inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion from the base case analysis	2.3
2	Differences between the ERT-naïve and ERT-experienced populations	3.2.1
3	Uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat	3.2
4	Use of single arm studies in the indirect treatment comparison	3.4
5	Indirect treatment comparison including both ERT-naïve and ERT-experienced participants	3.4
6	Cost-effectiveness of comparator treatments	4.2
7	Improper parameterisation of model	4.3.2
8	Utilities generated using a non-reference case approach	4.3.7
9	Resource use for invasive home mechanical ventilation	4.3.8.4, 4.3.8.5

The EAG does not have a single base case analysis due to uncertainties in the long-term effectiveness of treatments. This issue aside, the main differences between the company and EAG base case are as follows:

- Inclusion of alglucosidase alfa as comparator
- Treatment effects are informed by the ML-NMR that includes RCT evidence only
- The utility values set is informed by the PROPEL trial
- Patient management costs included for consistency with TA821.
- Different costs of non-invasive mechanical ventilation

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Slowing disease progression and therefore maintaining mobility and respiratory function
- Reducing disease related mortality (as a consequence of slowed disease progression)

Overall, the technology is modelled to affect costs by:

- Treatment acquisition costs
- Costs of invasive mechanical ventilation.

The modelling assumptions that have the greatest effect on the ICER are:

- The data used to inform treatment effects up to 1 year.
- The rate of disease progression following year 3
- The costs of invasive mechanical ventilation

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion from the base case analysis

Report section	2.3
Description of issue and why the EAG has identified it as important	Avalglucosidase alfa was not included in the company's base case and only included in scenario analyses in the economic model. The company argue that avalglucosidase alfa is not yet commercially available in the UK for the treatment of adults with late onset Pompe disease (LOPD). However, since avalglucosidase alfa is likely to be commercially available prior to NICE's guidance for cipaglucosidase alfa in combination with miglustat, it is a relevant comparator for this appraisal. The exclusion of avalglucosidase alfa from the base case analysis is inconsistent with the NICE scope and current NICE guidance (TA821). The EAG considers avalglucosidase alfa to be the primary comparator for the economic analysis, as it is likely to replace alglucosidase alfa as the preferred first-line treatment option in ERT-naïve patients with LOPD. In ERT-experienced patients, it is expected that patients will only switch treatments if they experience a decline in health outcomes on alglucosidase alfa; the primary alternative treatment in this scenario will be avalglucosidase alfa.
What alternative approach has the EAG suggested?	The EAG considers that assessment of the clinical and cost-effectiveness of cipaglucosidase alfa with miglustat should consider avalglucosidase alfa as a relevant comparator.
What is the expected effect on the cost-effectiveness estimates?	Cost-effectiveness results including avalglucosidase alfa as a comparator are presented as part of the EAG additional analysis.
What additional evidence or analyses might help to resolve this key issue?	None.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Differences between ERT-naïve and ERT-experienced populations

Report section	3.2.1
Description of issue and why the EAG has identified it as important	There are several important differences in the baseline characteristics of ERT-naïve and ERT-experienced patients recruited to the PROPEL trial. [redacted] Response to treatment may differ between ERT-naïve and ERT-experienced patients. Clinical advice provided to the EAG indicates that a larger, but delayed, treatment effect is expected for the ERT-naïve population compared to the ERT-experienced population who would already have an improved clinical status from previous treatment. Moreover, the PROPEL trial population primarily consists of ERT-experienced patients, while the COMET trial exclusively recruited ERT-naïve patients. This creates uncertainty in any indirect comparison between avalglucosidase alfa and cipaglucosidase alfa as relative effectiveness estimates are drawn from distinctly different populations. The EAG considers it important to appropriately reflect this uncertainty; this is most transparently done by considering the ERT-naïve and ERT-experienced populations separately.
What alternative approach has the EAG suggested?	The EAG considers that the comparison of a combined ERT-naïve and ERT-experienced population is not appropriate and that these subgroups should be considered separately.
What is the expected effect on the cost-effectiveness estimates?	The impact of considering ERT-naïve and ERT-experienced populations depends on the ML-NMR used. Specifically, whether single-arm studies are included in the ML-NMR analysis (see Issue 5). Using the EAG's preferred approach which includes RCTs only, Cipaglucosidase alfa in combination with miglustat remains the most cost-effective option in both the ERT-naïve and ERT-experienced population assuming a WTP of £20,000.
What additional evidence or analyses might help to resolve this key issue?	Resolving uncertainty regarding how treatment effects differ across ERT-naïve and ERT-experienced patients would require additional comparative trial evidence in these populations. The ML-NMR implemented by the company helps mitigate the need for this evidence but is limited by the lack of data (see Issue 6). Additional evidence on the proportion of ERT-Naïve and ERT-experienced patients would help inform the relative size of these populations.

Issue 3 Uncertainty over long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat

Report section	3.2, 4.3.6
Description of issue and why the EAG has identified it as important	There is significant uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat. PROPEL trial data are only available for up to 52 weeks follow-up. Longer term data are available from the ATB200-02 study, however, this was an uncontrolled study, therefore, no long-term comparative data are available.
What alternative approach has the EAG suggested?	There is limited evidence to inform long-term relative effectiveness estimates. The EAG considers that this uncertainty should be appropriately explored in scenario and sensitivity analysis.
What is the expected effect on the cost-effectiveness estimates?	The impact of long-term treatment effects is counter-intuitive with increased effectiveness leading to a deterioration in cost-effectiveness metrics. The EAG explores a range of scenarios exploring uncertainty in long-term treatment effects. In some comparisons with alglucosidase alfa, reducing the rate of long-term disease progression for cipaglucosidase alfa with miglustat to 30% of that modelled for alglucosidase alfa (HR of 0.3 applied to cipaglucosidase alfa in combination with miglustat) patients leads to NHB (£20,000 WTP) estimates less than zero for cipaglucosidase alfa in combination with miglustat.
What additional evidence or analyses might help to resolve this key issue?	Long-term comparative data on the clinical effectiveness of cipaglucosidase alfa in combination with miglustat would help resolve this issue. However, this is unlikely to be feasible in view of the rarity of this condition, which adds to the general uncertainty relating to the different treatments for this condition.

Issue 4 Inclusion of single arm studies in the indirect treatment comparison

Report section	3.4
Description of issue and why the EAG has identified it as important	The EAG do not agree with the company's approach to include single arm studies in their indirect treatment comparison; this approach may be appropriate when single arm studies are needed to connect a network, but in this case RCT data are available although the numbers are very small. The EAG consider that the inclusion of single arm studies may increase precision but with a high risk of bias which cannot be quantified.
What alternative approach has the EAG suggested?	The EAG suggests that the results from the indirect treatment comparison including RCTs only should be considered.
What is the expected effect on the cost-effectiveness estimates?	The main impact of using the EAG's preferred ML-NMR which includes RCT evidence only is to increase the relative effectiveness of comparator treatments. In the whole population analysis using the EAG ML-NMR leads to avalglucosidase alfa becoming the most effective option. However, cipaglucosidase alfa in combination with miglustat remains the most cost-effective option assuming a WTP of £20,000; NHB of [redacted] QALYs vs alglucosidase alfa and [redacted] QALYs vs avalglucosidase alfa.
What additional evidence or analyses might help to resolve this key issue?	Focus on the sensitivity analysis that includes RCTs only.

Issue 5 Indirect treatment comparison including both ERT-naïve and ERT-experienced participants

Report section	3.4
Description of issue and why the EAG has identified it as important	The company use a multi-level network meta-regression to adjust for differences in the populations of included studies. However, only 27 ERT-naïve participants are included in PROPEL and used to inform the meta-regression. One of the scenario analyses presented by the company is for previous ERT duration (none, short, medium and long term). ML-NMR may correct for population differences and estimate effects in each specific population, although with only few ERT-naïve patients included to inform the meta-regression, results in this subgroup may not be very reliable. The clinical advisor to the EAG suggested that combining ERT-naïve and ERT-experienced patients as a mixed population is not meaningful.
What alternative approach has the EAG suggested?	The EAG suggest comparing the results from the company's scenario analysis of ML-NMR including RCTs only setting previous ERT duration to zero, to the results from a simple indirect comparison for ERT-naïve participants only. The EAG has undertaken the simple indirect comparison in ERT-naïve participants and this is presented in section 3.5.1. It was not possible to do this for ERT-experienced participants as the COMET trial (which the PROPEL trial is being indirectly compared to) only includes ERT-naïve participants.
What is the expected effect on the cost-effectiveness estimates?	Using the simple indirect comparison in the economic analysis reduces NHB at a WTP of £20,000 from [redacted] to [redacted]. The impact of this issue on cost-effectiveness estimates is also explored in issues 3 and 5.
What additional evidence or analyses might help to resolve this key issue?	Ideally, further trial evidence for the relevant groups would reduce the uncertainty but this is unlikely given the rarity of the condition. Clinical validation of assumptions made in the ML-NMR may also increase confidence in this analysis.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 6 Cost-effectiveness of comparators

Report section	4.2
Description of issue and why the EAG has identified it as important	While alglucosidase alfa is standard care for the treatment of patients with Pompe disease, the EAG understands that alglucosidase alfa underwent no formal public assessment of cost-effectiveness through either the single technology appraisal (STA) or the highly specialised technology (HST) pathways. The acquisition costs of alglucosidase alfa are very high and the EAG considers it highly likely that alglucosidase alfa is not a cost-effective treatment. Any comparison to alglucosidase alfa or other comparators whose cost-effectiveness has been estimated relative to alglucosidase alfa is therefore likely to generate misleading estimates of cost-effectiveness and to significantly overestimate the value of that treatment to the NHS. Therefore, the company's economic evaluation, while consistent with the NICE scope and the previous TA of avalglucosidase alfa, is flawed and does not represent the additional value of cipaglucosidase alfa in combination with miglustat to the NHS.
What alternative approach has the EAG suggested?	An appropriate assessment of the cost-effectiveness of cipaglucosidase alfa with miglustat would require a broader scope that considered the clinical and cost-effectiveness of all ERT including alglucosidase alfa.
What is the expected effect on the cost-effectiveness estimates?	The EAG has not conducted a formal analysis to examine the cost-effectiveness of treatments relative to best supportive care but considers it likely that ICERs would be well above typically accepted willingness to pay thresholds.
What additional evidence or analyses might help to resolve this key issue?	This cannot be resolved in the scope of this appraisal.

Issue 7 Improper parameterisation of model

Report section	4.3.2
Description of issue and why the EAG has identified it as important	The economic model uses an individual patient simulation in which several model parameters including baseline characteristics and treatment effects are drawn from a distribution (similar to probabilistic analysis normally considered by the committee). The economic model has been parameterised such that the model uses independent distributions for each parameter, this is despite the acknowledgement that model parameters may be correlated. At the clarification stage the EAG requested the company fix the model to address this issue. However, the fix was not properly implemented and does not appropriately address this issue.
What alternative approach has the EAG suggested?	To properly account for the correlation of model parameters assuming they are generated from a joint distribution.
What is the expected effect on the cost-effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Correction of the economic model will allow this issue to be fully addressed. This will require information on the covariance matrix for the relevant parameters.

Issue 8 Use of a non-reference case approach to elicit utility values

Report section	4.3.7.1
Description of issue and why the EAG has identified it as important	While the company collected data on HRQoL in the PROPEL trial and identified several sources of published utility values, these were not used in the economic model. The company instead used values generated by an elicitation study commissioned by the company. This approach was justified on the basis that the PROPEL trial and published literature could not populate utility values applied in all health states. The EAG considers that the approach adopted by the company is inconsistent with the NICE reference case and that the utility values generated are unfit for decision making. The resulting value set captures only public preferences and includes no explicit consideration of the quality of life of patients themselves. The EAG notes a number of issues with the values generated from the elicitation study which are significantly lower than utility values generated using PROPEL trial data and values identified in the literature.
What alternative approach has the EAG suggested?	The EAG recommends using the utility values set generated from the PROPEL trial data supplemented by data from the published literature.
What is the expected effect on the cost-effectiveness estimates?	Alglucosidase alfa comparison: Using a utility value set sourced from the published literature reduces NHB at a WTP threshold of £20,000 from [redacted] QALYs to [redacted] QALYs. Using a utility value set based on the PROPEL trial increases NHB to [redacted] QALYs. Avalglucosidase alfa comparison: Using a utility value set sourced from the published literature increases NHB at a WTP threshold of £20,000 from [redacted] QALYs to [redacted] QALYs. Using a utility value set based on the PROPEL trial reduces NHB to [redacted] QALYs.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence on utility values in more severe health states would be informative. The EAG is, however, satisfied that all relevant sources of evidence have been identified by the company.

Issue 9 Cost of invasive mechanical ventilation

Report section	4.3.8.44.3.8.5
Description of issue and why the EAG has identified it as important	In the most severe health state modelled, patients are assumed to be dependent upon invasive mechanical ventilation. The economic model includes a cost for this based on the Noyes et al. study which was used in TA821. The EAG is concerned about the generalisability of the Noyes et al. study; this study is old and based on a paediatric population who do not have Pompe disease. The values generated by this study are also substantially higher than those from two international studies identified by the EAG suggesting the cost of invasive mechanical ventilation may have been over costed.
What alternative approach has the EAG suggested?	The EAG considers there to be significant uncertainty associated with this cost and note it is a major model driver in the alglucosidase alfa comparison. In the absence of more appropriate estimates, the EAG considers that a conservative approach based on data from either international study to be most appropriate.
What is the expected effect on the cost-effectiveness estimates?	Alglucosidase alfa comparison: Using costs reported in Nonoyama et al. leads to a reduction in NHB at WTP of £20,000 from [redacted] QALYs to [redacted] QALYs. Using costs reported in Gajdoš et al. NHB is reduced to [redacted] QALYs. Avalglucosidase alfa comparison: Using costs reported in Nonoyama et al. leads to a reduction in NHB at WTP of £20,000 from [redacted] QALYs to [redacted] QALYs. Using costs reported in Gajdoš et al. NHB is reduced to [redacted] QALYs.
What additional evidence or analyses might help to resolve this key issue?	Further evidence on the costs of invasive mechanical ventilation.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Given the high level of uncertainty associated with the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat, the EAG has presented a series of analyses to represent its base case. These consider a range of hazard ratios applied exploring long-term disease progression rates relative to alglucosidase alfa. Results presented are inclusive of commercial arrangements for cipaglucosidase alfa but do not include PAS discounts for avalglucosidase alfa. Please refer to the confidential appendix to this report for results inclusive of all available commercial pricing arrangements. The results of the EAG's alternative base-case analyses are presented in Table 2.

Table 2: EAG Exploratory Scenario Analyses on the EAG base case (whole population)

Assumptions	Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/QALY)
1. HR applied to Cipaglucosidase alfa w. miglustat and avalglucosidase alfa	Alglucosidase alfa	[redacted]	[redacted]	[redacted]					
	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
a) HR of 0.3									
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c) HR of 0.85	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. HR applied to Cipaglucosidase alfa w. miglustat	Alglucosidase alfa	[redacted]	[redacted]	[redacted]					
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
a) HR of 0.3	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
3. HR applied to avalglucosidase alfa	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
a) HR of 0.3	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
a) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2 Introduction and background

2.1 Introduction

This report presents a critique of the company's submission (CS) to NICE from Amicus Therapeutics on the clinical effectiveness and cost effectiveness of cipaglucosidase alfa (Pombiliti®) in combination with miglustat [redacted] for treating Pompe disease.

Cipaglucosidase alfa with miglustat consists of intravenous enzyme replacement therapy (ERT); cipaglucosidase alfa, with an orally administered enzyme stabiliser; miglustat (CS p12). On 15 December 2022, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for cipaglucosidase alfa, intended for the treatment of Pompe disease.[1]

2.2 Background

The current treatment pathway of people with late onset Pompe disease (LOPD) presented in Section B.1.3.3 of the CS reflects UK clinical practice. The EAG's clinical advisor noted that, whilst there are currently no UK-specific guidelines for LOPD, clinical practice is broadly consistent with European Pompe Consortium 2017 guidelines.[2] Patients meeting certain criteria, such as being symptomatic (i.e. having skeletal muscle weakness or respiratory muscle involvement observed using clinical assessments), having residual skeletal and respiratory muscle function (which is considered functionally relevant and clinically important for the patient to maintain or improve), and not having another life-threatening illness at an advanced stage (where treatment to sustain life is inappropriate), are eligible for ERT.[2]

The current commercially available ERT for LOPD patients is alglucosidase alfa (Myozyme®), which has been available since 2006 (CS p21). Avalglucosidase alfa (Nexviadyme®) was approved by NICE in August 2022, however, there are supply issues meaning that it is not yet commercially available; it is likely to become available early in 2023. The mechanisms of action of alglucosidase alfa, avalglucosidase alfa and cipaglucosidase alfa are similar, the key difference between the therapies relates to pharmacokinetics, as described in Table 2 of the CS, particularly with the addition of miglustat to cipaglucosidase alfa.

The EAG's clinical advisor suggested that patients who are currently receiving alglucosidase alfa are unlikely to be switched to a different ERT unless there are tolerance issues or lack of efficacy. Patients need to remain on ERT for around 18 months to two years in order to determine whether it is beneficial; the European Pompe Consortium guidelines recommend an initial treatment period of two years, after which the effect of treatment will be evaluated. There are specific reasons for stopping

treatment listed in the European Pompe Consortium guidelines, such as the patient suffering from severe infusion-associated reactions that cannot be managed properly, no indication that skeletal muscle function and/or respiratory function have stabilised or improved in the first two years after the start of treatment, or the patient wishing to stop ERT.[2] The EAG's clinical advisor stated that patients are anticipated to have an initial slight improvement in symptoms with ERT, followed by an eventual return to the gradual rate of deterioration. Patients are likely to remain on treatment for as long as they have residual skeletal and respiratory muscle function which is considered functionally relevant and clinically important for the patient to maintain or improve. Few patients discontinue ERT due to adverse events or intolerance.

There are approximately [redacted] in England who could be eligible for treatment with cipaglucosidase alfa with miglustat.[3]

2.3 Critique of company's definition of decision problem

Table 1 of the CS presents the decision problem, including a description of the final scope issued by NICE, the decision problem addressed within the submission and the rationale for any differences between the two. This information, along with the EAG comments on the rationale provided, is presented in Table 3 below.

EAG comments

[redacted]. The EMA CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for cipaglucosidase alfa, intended for the treatment of Pompe disease, in December 2022. In their factual accuracy check, the company clarified that the CHMP opinion for cipaglucosidase alfa states "Pombiliti (cipaglucosidase alfa) is a long-term enzyme replacement therapy used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency)." [redacted]

Avalglucosidase alfa was not included in the company's base case and only included in scenario analyses in the economic model. The company argue that avalglucosidase alfa is not yet commercially available in the UK for the treatment of adults with late onset Pompe disease (LOPD). However, since avalglucosidase alfa is likely to be commercially available prior to NICE's guidance for cipaglucosidase alfa in combination with miglustat, it is a relevant comparator for this appraisal. The exclusion of avalglucosidase alfa from the base case analysis is inconsistent with the NICE scope and

current NICE guidance (TA821). The EAG considers avalglucosidase alfa to be the primary comparator to cipaglucosidase alfa in combination with miglustat for the economic analysis. In ERT-naïve patients, avalglucosidase alfa is likely to replace alglucosidase alfa as the preferred first-line treatment option. In ERT-experienced patients, it is expected that patients will only switch treatments if they experience a decline in health outcomes on alglucosidase alfa; the primary alternative treatment in this scenario will be avalglucosidase alfa.

Table 3: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with Pompe disease.	Adults with a confirmed diagnosis of LOPD (GAA deficiency).	Only adults with LOPD aged 18 years and older are considered in this submission. This aligns with the population in the pivotal trial (PROPEL), data from which support this appraisal [redacted]	The EAG considers that the narrower population addressed in the CS is appropriate, as this population reflects the population in the pivotal trial [redacted] The clinical evidence submitted reflects the characteristics of the patient population in England and Wales eligible for treatment. LOPD is a very rare condition and it is unclear how many patients in the PROPEL and ATB200-02 trials were from the UK. However, the majority of patients were from Europe, Australia and America, therefore, it is likely that the trial populations are representative of patients in England and Wales.
Intervention	Cipaglucosidase alfa in combination with miglustat.	As per NICE final scope.	Not applicable.	The intervention described in the CS is in line with the NICE scope. However, in the company's response to the EAG's points for clarification, they stated that [redacted]
Comparator(s)	• Alglucosidase alfa • Avalglucosidase alfa	• Primary comparator: Alglucosidase alfa • Secondary comparator: Avalglucosidase alfa	Avalglucosidase alfa (Nexviadyme®) received Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation in July 2022[4] and NICE guidance in August 2022 (TA821; with a 30-day implementation period)[5] for the treatment of Pompe disease of all ages. However, at the time of this submission, Amicus understands that avalglucosidase	Since avalglucosidase alfa is likely to be commercially available prior to NICE's guidance for cipaglucosidase alfa in combination with miglustat, it is a relevant comparator for this appraisal. In view of the lack of direct comparative data on avalglucosidase alfa versus cipaglucosidase alfa in combination with

			alfa is not commercially available in the United Kingdom (UK) for the treatment of adults with LOPD,[5, 6] and, as agreed in the decision problem meeting, that it would be unlikely to be widely used in clinical practice for some time even after it were to become commercially available. Therefore, avalglucosidase alfa has been included as a secondary comparator and therefore has only been included in scenario analyses in this submission.	miglustat, it was appropriate for the company to undertake an indirect comparison between these two enzyme replacement therapies (ERTs) (presented in Section B.2.9 of the CS and appraised in Section 3.4 of this report).
Outcomes	The outcome measures to be considered include: • change in respiratory function • change in motor function • change in muscular function • mortality • immunogenicity response • adverse effects of treatment • health-related quality of life (HRQoL)	The outcome measures to be considered include: • change in motor function (assessed using the six-minute walk test [6MWT]) • change in respiratory function (assessed using sitting forced vital capacity [FVC] % predicted) • change in muscular function (assessed using manual muscle testing and the Gait, Stairs, Gowers' manoeuvre, and Chair [GSGC] assessments) • HRQoL • immunogenicity response • adverse effects of treatment	In line with the NICE final scope, except that mortality was not assessed as part of the Phase III PROPEL study. This was due to the low number of expected events over the one-year timeframe of the clinical trial. Assessment of mortality in Pompe disease is inherently difficult due to rate of disease progression and wide range of ages and stages of progression within the population. Given the lack of long-term data available, it was assumed that cipaglucosidase alfa in combination with miglustat would not impact mortality until adults with LOPD transitioned into a health state where they required ventilation or mobility support, which is reflected in the model.	The EAG considers that the company's justification for excluding mortality as an outcome measure appears acceptable. The CS reports results for 6MWT, FVC % predicted, manual muscle test (MMT), GSGC, Patient-Reported Outcomes Measurement Information System (PROMIS)-physical function and PROMIS-fatigue, adverse effects and subject global impression of change (SGIC). Other outcomes assessed in the PROPEL trial, but not reported in the submission were physician's global impression of change (PGIC) and EuroQol-5-Dimensions 5-Level (EQ-5D-5L); these results were provided by the company in response to the EAG's clarification questions.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	Avalglucosidase alfa is not included as a comparator in the company base case. Results inclusive of avalglucosidase alfa, are however, presented in scenario analysis.	Avalglucosidase alfa was not commercially available in the UK at the time of the company submission and hence not considered established practice.	The economic analysis is largely in line with the reference case. Utilities used in the base case analysis were generated using a non-reference case methodology. See Table 19 for details. Confidential commercial arrangements for comparator treatments have not been

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			accounted for in the company's analysis. The EAG presents analyses inclusive of these commercial arrangements in a confidential appendix to this report.
Subgroups	If the evidence allows the following subgroups will be considered: • people who have received prior treatment with alglucosidase alfa • people who have not received prior treatment with alglucosidase alfa	The population considered in this submission is the total population in the PROPEL trial, adults with LOPD.	[redacted], and as discussed and agreed in the decision problem meeting, this submission focuses on the total population of adults with LOPD, which is comprised of treatment-naïve and treatment-experienced people. During an advisory board, clinicians noted that they would not treat enzyme replacement therapy (ERT)-experienced	Results for the subgroups described in the NICE scope (ERT-experienced and ERT-naïve populations) were presented for 6MWT, FVC % predicted, MMT and biomarkers in the CS Appendix E. Whilst ERT-experienced and ERT-naïve adults with LOPD are unlikely to be treated differently, the relative effectiveness of cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa is likely to be affected by prior exposure to ERT, with ERT-naïve patients likely to

			and ERT-naïve adults with LOPD differently.[7] Therefore, Amicus believes that prior ERT status should not be a factor in accessing treatment with cipaglucosidase alfa in combination with miglustat in the interests of fair and equitable access. Therefore, clinical and economic results are presented for the total population of adults with LOPD. ERT-experienced and ERT-naïve data from the PROPEL clinical trial are presented in Appendix E for completeness, in line with the study design. These data are impacted by the small participant numbers for the ERT-naïve arm (ERT-naïve: n=28; ERT-experienced: n=95),[8] as is expected in a rare disease with low incidence. Thus, as discussed and agreed in the decision problem meeting, the total cohort is the most reliable and meaningful source of data in PROPEL and for the cost-effectiveness analysis.	respond better to alglucosidase alfa than ERT-experienced patients, whose treatment effect may be waning. ERT-experienced patients recruited to the trial may also be dissatisfied with their current treatment, potentially creating a selection bias against alglucosidase alfa. In addition, ERT-naïve patients are likely to have a larger, but delayed, treatment effect compared to the ERT-experienced population, who would already have an improved clinical status from previous treatment. Therefore, despite the limitations relating to small participant numbers, the subgroup analysis results are informative for this appraisal. Additional subgroup analysis results for ERT-experienced and ERT-naïve populations were provided by the company in response to the EAG's clarification questions.

Abbreviations: 6MWT: six-minute walk test; CS: company submission; EAG: External Assessment Group; EMA: European Medicines Agency; EQ-5D-5L: EuroQol-5-Dimensions 5-Level; ERT: enzyme replacement therapy; FVC: forced vital capacity; GAA: acid α-glucosidase; GSGC: Gait, Stairs, Gowers' manoeuvre, and Chair; HRQoL: health-related quality of life; LOPD: late-onset Pompe Disease; MHRA: Medicines and Healthcare products Regulatory Agency; MMT: manual muscle test; NICE: National Institute for Health and Care Excellence; PGIC: physician's global impression of change; PROMIS: Patient-Reported Outcomes Measurement Information System; SGIC: subject global impression of change.

3 Clinical effectiveness

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify all relevant clinical evidence relating to the efficacy and safety of treatments for adults with Pompe disease. Details of the SLR are reported in Appendix D of the CS.

3.1.1 Searches

The CS included searches to identify clinical evidence for adult patients with Pompe disease. A detailed description of the searches and all search strategies were included in CS Appendix D (pages 7 to 19).

Additional clinical searches were performed to identify indirect treatment comparisons (ITC), which are reported in the document 'Amicus Data on File 2022 Indirect Treatment Comparison Report'. A description of the searches and most of the search strategies were included in the ITC report. In response to the EAG's points for clarification, a further document was provided by the company, which included additional strategies and corrections to errors identified by the EAG.

The EAG appraisal of the literature searching is presented in Table 4 and Table 5.

Table 4: EAG appraisal of evidence identification for clinical evidence searches

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	Extremely comprehensive. The EAG's only criticism is that the Centre for Reviews and Dissemination (CRD) databases are no longer updated. The report of Database of Abstracts of Reviews of Effects (DARE) being searched up until 14th June 2022 (Appendix D, page 7) is inaccurate as this database has not been updated since March 2015. The list of databases for Table 3 that follows the search of DARE (Appendix D, page 13) is a bit misleading as it looks like Health Technology Assessment (HTA) and NHS Economic Evaluation Database (EED) were also searched, but perhaps this is because the records are only limited to DARE on the final line.
Were appropriate sources searched?	YES	An excellent range of relevant databases, conference proceedings, grey literature sources and trials registry databases were used. Although it can be useful to search HTA sources for clinical evidence, the EAG is confident that no relevant studies would have been missed due to the limited research into the drug and disease.
Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy. The only use of date limits was to remove conference abstracts published before 2020 which was justified and explained by the company.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study types.
Were appropriate search terms used?	YES	Search terms are extremely comprehensive and designed very carefully. Systematic reviews and network meta-analyses are not searched for with the other study types, despite being part of the inclusion criteria. However, supplementary searching of reference lists was performed, Cochrane Database of Systematic Reviews (CDSR) was searched for systematic reviews, and the additional clinical searches for the indirect treatment comparison did search for systematic reviews and network meta-analyses for reference checking.
Were any search restrictions applied appropriate?	YES	Yes, animal studies and irrelevant paper types are removed appropriately.
Were any search filters used validated and referenced?	YES	Various search filters were used and referenced, although there was no mention of whether filters were validated.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Table 5: EAG appraisal of evidence identification for indirect treatment comparisons in 'Amicus Data on File 022 Indirect Treatment Comparison Report'

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	No search strategies or search terms were provided for the conference or grey literature searches. This was raised in the EAG's points for clarification and the company sent satisfactory additional strategies in response. The Embase search contained an error in the number of hits listed for line 17. This was raised in the EAG's points for clarification and as a result the company corrected the 620 hits for line 17 to 650 hits. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram on page 28 was vague as individual databases weren't listed and hits from clinical trials registries and conference abstracts were not shown. It also wasn't clear how the figure for grey literature came to be 144. This was raised in the EAG's points for clarification and as a result the company sent a more detailed PRISMA diagram clearly showing the hits by each source. Figures throughout the PRISMA diagram were updated. However, there is a minor error in the number of references obtained from the clinical trials registry WHO International Clinical Trials Registry Platform (ICTRP). Although the database found 247 records for 166 trials as noted, reference management software only imports records of the 166 trials rather than the 247 records. However, the ITC report has treated this as 247 records and factored this into both its totals and the PRISMA diagram.
Were appropriate sources searched?	YES	An excellent range of relevant databases, conference proceedings, grey literature sources and trials registry databases were used.
Was the timespan of the searches appropriate?	YES	However, the date limits on many of the searches are unnecessary. On Medline and Embase, the years of coverage of the database segments have also been applied as a date limit, which seems unnecessary.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study types. However, in the search strategy for Cochrane Central Register of Controlled Trials it is unnecessary to enter terms to search for trials as this is already a database of trials.
Were appropriate search terms used?	YES	Search terms are extremely comprehensive and designed very carefully.
Were any search restrictions applied appropriate?	YES	No restrictions other than those already discussed (date, study type) were applied.
Were any search filters used validated and referenced?	PARTLY	Various search filters were used but not referenced. There was no mention of whether filters were validated. Inbuilt database limits (rather than validated search filters) were used to limit the Medline and Embase searches to systematic reviews and meta-analyses.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

3.1.2 Inclusion criteria

The eligibility criteria used to select studies for inclusion in the SLR of clinical effectiveness evidence were presented in Table 7 in Appendix D of the CS. The eligibility criteria were broader than the

decision problem addressed in the company submission; the population was adults with Pompe disease, the intervention included cipaglucosidase alfa in combination with miglustat, alglucosidase alfa and avalglucosidase alfa, the comparator was any or no comparator and a broad range of outcomes of interest were listed. The CS states that studies investigating other ERT interventions (other than cipaglucosidase alfa in combination with miglustat, alglucosidase alfa and avalglucosidase alfa) were originally included in the search strategy, but were excluded *post-hoc*, which appears acceptable, since all relevant interventions and comparators listed in the company's decision problem were included. Only studies reported in English were eligible for inclusion.

Study selection was undertaken independently by two reviewers, with disagreements resolved via discussion or, where necessary, the final decision was made by a third reviewer; this minimises the possibility of errors or bias affecting the study selection process. The EAG has reviewed the table of publications excluded at the full text review stage of the SLR (Table 9 in Appendix D of the CS); whilst there are a few discrepancies relating to the stated reason for exclusion, the EAG did not identify any studies that were incorrectly excluded. In their points for clarification, the EAG queried the exclusion of 36 studies for not reporting on relevant clinical outcomes (in the absence of contacting authors to ascertain whether relevant outcomes were measured). The company responded that since the systematic reviews were used to identify high-quality studies relevant to the decision problem, it was determined that articles that did not report relevant clinical outcomes should not be included and that any studies where the outcome assessment was not feasible to obtain were excluded. Generally, there was no indication from the reported study methodologies that any of the studies measured more outcomes than they reported; therefore, authors were not contacted.

Twenty-seven unique studies were included in the SLR, six of which were considered pivotal; two assessed cipaglucosidase alfa in combination with miglustat (PROPEL and ATB200-02), two assessed avalglucosidase alfa (COMET and NEO1/-EXT) and two assessed alglucosidase alfa (LOTS and LOTS open label extension (OLE)). The other 21 studies assessed alglucosidase alfa in non-RCTs and observational studies. The CS focused on the two trials assessing cipaglucosidase alfa in combination with miglustat in adults with LOPD; PROPEL and ATB200-02.

A similar but separate search was undertaken to identify studies for inclusion in the indirect treatment comparison (see CS Section B.2.9.1). This was presented in a separate report referenced in CS Appendix D (see Section D.1.4, p96). From this, 8 studies were assessed and 7 included in the indirect treatment comparison (see CS Table 27). In addition to PROPEL and ATB200-02, COMET (including OLE), NEO1/-EXT and LOTS (including OLE) are included and critiqued in the indirect treatment comparison (Section 3.3).

An additional registry study by Semplicini et al.,[9] identified in the SLR, was included in the economic model.[9] This study was not described in the CS, therefore it has been summarised and critiqued in Section 3.5.2.

3.1.3 Critique of data extraction

Data were extracted into pre-specified data extraction tables by one reviewer and checked by a second reviewer. Discrepancies were resolved via discussion or, where necessary, in consultation with a third reviewer; this minimises the possibility of errors or bias affecting the data extraction process. Detailed information on the PROPEL and ATB200-02 trials was presented in the CS and Appendices, although the EAG requested additional information for some outcomes (and subgroup analyses) from the company. The additional data requested was provided in the company's response to the EAG's points for clarification.

3.1.4 Quality assessment

The quality assessment of the PROPEL and ATB200-02 trials reported in the CS was performed using the CRD checklist and criteria adapted from the CASP checklist respectively (as per recommendations from NICE).[10, 11] Other studies included in the systematic review were quality assessed using the CRD checklist (for RCTs) and the ROBINS-I tool for interventional non-RCTs and observational studies (see CS Appendix D3).[10, 12] Where ROBINS-I was used (for studies included in the indirect treatment comparison), it was completed at the study level, rather than the outcome level; the EAG requested that the company complete all risk of bias assessments for each outcome in each study, but the company stated that any issues identified for each domain at the study level are likely to apply to all outcomes within the study and that it is expected that this approach of undertaking risk of bias assessment at the study level should not affect the overall quality assessment rating. Quality assessment was performed by one reviewer and checked by a second reviewer, minimising the possibility of errors or bias affecting the quality assessment process.

3.1.5 Evidence synthesis

Since PROPEL is the only comparative study of cipaglucosidase alfa in combination with miglustat for the treatment of adults with LOPD, it was not possible for the company to undertake a direct evidence synthesis. A critique of the indirect treatment comparison undertaken by the company is presented in Section 3.4**Error! Reference source not found.**.

EAG comments

The SLR was reasonably well conducted and whilst the EAG has a few concerns relating to the stated reason for exclusion of some studies and the completion of ROBINS-I at the study level, rather than

the outcome level, the EAG do not have any major concerns about missing studies or the quality of the included studies.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The CS included two studies of cipaglucosidase alfa in combination with miglustat in adult patients with LOPD. One was a phase III, double-blind RCT (PROPEL) and one was an open-label, ascending-dose, single-arm study (ATB200-02).

3.2.1 PROPEL Trial (NCT03729362)

3.2.1.1 Study characteristics

The PROPEL trial is a phase III, prospective, double-blind, head-to-head superiority RCT comparing cipaglucosidase alfa in combination with miglustat against alglucosidase alfa in combination with placebo. It is an international, multicentre trial conducted across 62 neuromuscular and metabolic medical centres in 24 countries. PROPEL is the first trial in LOPD to include adults who have previously been treated with alglucosidase alfa at the licensed dose, reflective of clinical practice in the UK, with a median of 7.4 years of prior ERT, as well as ERT-naïve participants.

Details of the PROPEL trial are presented in Section B.2 of the CS. Figure 3 of the CS presents an overview of the study design. Table 5 of the CS provides a summary of the study design, methodology, eligibility criteria and a list of the permitted and disallowed concomitant medication. The clinical advisor to the EAG agreed that the eligibility criteria and the list of permitted and disallowed concomitant medication in the PROPEL trial appear appropriate and likely to reflect UK clinical practice.

Method of study drug administration

The interventional arm received cipaglucosidase alfa 20 mg/kg every 2 weeks as a 4-hour IV infusion plus miglustat (195 mg for participants weighing ≥ 40 kg to < 50 kg or 260 mg daily for participants weighing ≥ 50 kg, administered as oral capsules). The control arm received alglucosidase alfa 20 mg/kg every 2 weeks as a 4-hour IV infusion plus placebo (195 mg for participants weighing ≥ 40 kg to < 50 kg or 260 mg daily for participants weighing ≥ 50 kg, administered as oral capsules) (CS p36).

Randomisation

Participants were randomly assigned in a 2:1 ratio to either the intervention arm or the control arm. Randomisation was stratified by 6MWD (baseline distance 75 to < 150 m, 150 to < 400 m, or ≥ 400 m) and ERT status (ERT-experienced or ERT-naïve). Participants continued treatment in both arms for 52 weeks, at which point they were given the option to continue in the open-label extension (NCT04138277) to be treated with cipaglucosidase alfa plus miglustat, regardless of the treatment received in PROPEL. The open-label extension study is ongoing; in response to the EAG's clarification request, the company stated that interim results are anticipated in H1 2023.

Outcomes

Outcomes assessed included:

- Change in motor function (6MWD assessed using 6MWT and the Gait, Stairs, Gowers' manoeuvre, and Chair (GSGC) assessments)
- Change in respiratory function (assessed using sitting FVC % predicted)
- Change in muscular function (assessed using manual muscle testing (MMT))
- Health-related quality of life (HRQoL)
    - Change in PROMIS - Physical Function
    - Change in PROMIS - Fatigue
    - Subject Global Impression of Change (SGIC)
    - Physician's Global Impression of Change (PGIC)
- Change in serum CK level, a biomarker for muscle injury
- Change in urinary Hex4, a biomarker for disease substrate
- Adverse effects
- Rasch-built Pompe-specific Activity (R-PAct) Scale (not presented in CS)
- EuroQol 5 Dimensions-5 Levels instrument (EQ-5D-5L) (not presented in CS but provided in response to points for clarification)

Efficacy assessments were completed at baseline and at weeks 12, 26, 38 and 52 or end of study. Adverse events were assessed at all infusion visits (every 2 weeks) and follow-up visits.

The PROPEL clinical study report (CSR) states that as a result of COVID-19 the week 52 visit may have been delayed and the delayed visit assessment was used in the analysis. Therefore, the EAG requested information on the number of patients in each study arm who had delayed (post-week 52) results included in the analyses and the length of delay. The company stated that the average delay of the actual study visit from the planned visit for assessment of 6MWD at week 52 was small and similar between treatment groups (mean delay [range] of [redacted] days in the cipaglucosidase alfa + miglustat arm and [redacted] days in the alglucosidase alfa + placebo arm). The proportion

of participants with delays of at least 14 days at the week 52 visit was similar between treatment groups [redacted] in the cipaglucosidase alfa + miglustat arm and [redacted] in the alglucosidase alfa + placebo arm). Therefore, the EAG is not overly concerned about delays in the week 52 assessment, since delays were reasonably small and similar between treatment groups. Although these data were only provided for the primary outcome 6MWD.

Definitions for key outcomes are presented in Table 6 of the CS. The advisor to the EAG stated that the assessments used and timings of assessments appear appropriate: in clinical practice most patients will be assessed using the 6MWT and FVC % predicted at least once per year. The patient reported outcomes (PROs) are likely to capture outcomes important to patients. Predefined thresholds for clinically relevant changes in outcomes (based on established thresholds for other neuromuscular and chronic respiratory diseases) are presented in Table 7 of the CS and appear appropriate.

Subgroup analyses

Subgroup analyses were conducted for the primary endpoint of change in 6MWD, and change in FVC % predicted, at week 52 by age group, gender, race, ERT status, ERT duration, baseline 6MWD, baseline FVC, region and history of infusion associated reactions (IARs). These appear appropriate.

3.2.1.2 Participants' baseline characteristics

Participants' demographics, baseline disease characteristics, and baseline mobility and respiratory function are presented in Tables 8 to 10 of the CS. There were some minor imbalances between the treatment groups in terms of sex and race (Table 8 of the CS). The clinical advisor to the EAG considered that these are unlikely to be important and more a reflection of the small participant numbers, owing to the rarity of this condition. Included participants are likely to be representative of patients with LOPD eligible for ERT in clinical practice.

Differences in baseline characteristics were more pronounced in the subgroup of ERT-naïve participants (presented in Appendix E, Tables 41 to 43). ERT-naïve participants were generally slightly older than ERT-experienced patients at diagnosis (although age at informed consent date was similar between treatment groups), less likely to be using assistive devices ([redacted] vs [redacted]%), have a history of falls ([redacted] vs [redacted] and infusion-associated reactions (IARs; [redacted] vs [redacted]), and had a higher mean 6MWD ([redacted] vs [redacted]) and mean pulmonary function ([redacted] vs [redacted]) at baseline.

3.2.1.3 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The required sample size of PROPEL is reported on page 51 of the CS. Assuming a 10% dropout rate (after randomisation), approximately 110 participants were planned to be randomised to ensure 99 evaluable participants. Figure 5 of the CS shows the CONSORT diagram of participant flow in PROPEL: 125 participants were randomised and 117 completed the study so the target sample size

was achieved. The analyses excluded one patient who deliberately underperformed at baseline in order to be included in the trial. The statistical analysis was provided and appears to be appropriate.

The results presented in the CS did not include the number of patients/observations used for analysis, therefore, the EAG requested this information in their points for clarification request. The company provided tables showing the number of participants reported in each of the outcome tables and figures. The company explained that the PROPEL trial was conducted during the initial wave of the COVID-19 lockdowns, which contributed to missed assessments because of travel restrictions and/or sites only allowing critical assessments to be performed. However, the proportion of participants with missing data was acceptably small for the primary and key secondary outcomes and was similar between treatment groups. Therefore, the EAG has no significant concerns regarding missing outcome data. The EAG also requested details of the number of patients in each treatment arm for which last observation carried forward (LOCF) was used in the analysis; the company provided this information for the primary and key secondary endpoints in PROPEL (A6 in Points for clarification response).

3.2.1.4 Risk of bias

The risk of bias assessment for PROPEL is presented in Table 15 of the CS. The company used the University of York's Centre for Reviews and Dissemination (CRD) checklist. The company stated that randomisation, concealment of allocation and blinding were adequate and treatment groups were similar at baseline. There were no unexpected imbalances in drop-outs between treatment groups, there was no evidence to suggest selective outcome reporting and analysis was undertaken for the ITT population. The company deemed PROPEL to be of high quality with a low risk of bias. The EAG also assessed the risk of bias using the same checklist and agrees with the company's risk of bias assessment.

3.2.1.5 Protocol deviations

Protocol deviations were not reported in the CS but Section 10.2 of the CSR stated that [redacted] of the participants had a protocol deviation. The CSR states that [redacted] of protocol deviations were due to the COVID-19 pandemic and in their response to the EAG's points for clarification, the company confirmed this.

Other common reasons for protocol deviations include a deviation in study procedures [redacted] of cipaglucosidase alfa + miglustat group versus [redacted] of alglucosidase alfa + placebo group), a deviation in investigational product ([redacted] of cipaglucosidase alfa + miglustat group versus [redacted] alglucosidase alfa + placebo group) and issues around informed consent ([redacted] of cipaglucosidase alfa + miglustat group versus [redacted] alglucosidase alfa + placebo group). The clinical advisor to the EAG did not envisage that the reasons for protocol deviations would affect the study results.

Points for clarification – company response:

'More than half of the protocol deviations were attributed to the Coronavirus Disease 2019 (COVID-19) pandemic, including missed or delayed administrations of study drug and/or assessments. Whenever possible, administrations of study drug and assessments were rescheduled rather than missed entirely. Despite these challenges, the frequency of missing data, particularly for the primary endpoint, was low. Also of note, there were very few protocol deviations that led to exclusion from the Per Protocol 1 (PP1) and Per Protocol 2 (PP2) Populations (i.e., prespecified important deviations that may have impacted the analyses of 6MWD and forced vital capacity (FVC), respectively). These are documented in CSR Appendix 16.1.9.2, Section 2.2. Finally, other types of more frequently observed deviations, such as errors in the order of performance of assessments and errors in the informed consent form (ICF) process or timing, were assessed to have negligible impact on study data integrity or reliability of reported results.'

3.2.1.6 Efficacy results

The primary outcome was change in 6MWD from baseline to week 52. The six key secondary outcomes were change in sitting FVC (% predicted) from baseline to week 52, change in the MMT lower extremity score from baseline to week 52, change in 6MWD from baseline to week 26, change in the PROMIS-Physical Function total score from baseline to week 52, change in the PROMIS-Fatigue total score from baseline to week 52 and change in the GSGC total score from baseline to week 52.

Whilst 6MWD and FVC are objective assessments used in clinical practice, the patient reported outcomes are likely to capture outcomes important to patients.

The NICE scope specified that ERT-experienced and ERT-naïve subgroups should be considered, if the evidence allows. Whilst the company argue that these two populations would not be treated differently in clinical practice, the relative effect of cipaglucosidase alfa + miglustat versus alglucosidase alfa + placebo may be different between the two groups. Subgroup analysis results for 6MWD, FVC % predicted, % predicted SVC and adverse events were presented in Appendix E of the CS. It should be noted that the number of participants in the ERT-naïve group receiving alglucosidase alfa + placebo was small (N=7).

6MWD

Table 6 presents change in 6MWD results from baseline to week 52 for the total population, ERT-experienced and ERT-naïve subgroups. Results for change in 6MWD from baseline to week 52 are reported in Table 17 and Figure 8 of the CS. In the total PROPEL population, cipaglucosidase alfa in combination with miglustat was associated with a greater improvement from baseline to week 52 but

it did not demonstrate statistical superiority. The mean improvement of [redacted] in 6MWD with cipaglucosidase alfa in combination with miglustat in PROPEL represents approximately a [redacted] increase from baseline, which indicates a clinically meaningful improvement according to the thresholds presented in Table 7 of the CS. The mean improvement relative to alglucosidase alfa in combination with placebo did not reach this threshold.

Subgroup analysis of 6MWD by ERT-status was reported in Appendix E of the CS. However, these results are for the ANCOVA model. For consistency with the MMRM analysis data presented in Table 17 of the CS for the total PROPEL population, the MMRM analysis data on ERT-experienced participants are presented in Table 30 of the CSR. Data on ERT-naïve participants are presented in Table 37 of the CSR.

Table 6: Summary of change in 6MWD (m) by visit from baseline to week 52 (ITT-LOCF population) for total population and ERT-experienced and ERT-naïve subgroups

	6MWD			
	Change from baseline, mean (SD)	LS mean difference (SE)	95% CI	2-sided p-value
Total PROPEL population Cipaglucosidase alfa + miglustat (n=85) Alglucosidase alfa + placebo (n=37)	20.79 (42.77) 7.24 (40.28)	[redacted]	[redacted]	[redacted]
ERT-experienced Cipaglucosidase alfa + miglustat (n=61) Alglucosidase alfa + placebo (n=29)	16.89 (40.39) -0.02 (39.34)	[redacted]	[redacted]	[redacted]
ERT-naïve Cipaglucosidase alfa + miglustat (n=20) Alglucosidase alfa + placebo (n=7)	33.44 (48.70) 38.34 (29.32)	[redacted]	[redacted]	[redacted]

FVC % predicted

Table 7 presents change in sitting FVC % predicted results from baseline to week 52 for the total population, ERT-experienced and ERT-naïve subgroups. Results for the change in sitting FVC % predicted from baseline to week 52 are presented in Table 19 and Figure 10 of the CS. There was a greater improvement in respiratory function in participants receiving cipaglucosidase alfa + miglustat than participants receiving alglucosidase alfa + placebo. The company stated that the approximate 3% (2.66[redacted] improvement met the clinically relevant threshold of 3% (range 2 to 6%) for chronic respiratory diseases. This difference vs. alglucosidase alfa was sustained through to Week 52 (Figure 10 of CS).

Subgroup analysis for sitting FVC % predicted by ERT-status is reported in Appendix E of the CS. Data on ERT-experienced participants is presented in Table 45 on page 114 of Appendix E. Data on ERT-naïve participants are presented in Table 49 on page 119 of Appendix E.

Table 7: Summary of change in sitting FVC % predicted by visit from baseline to week 52 (ITT-LOCF population) for total population and ERT-experienced and ERT-naïve subgroups

	SITTING FVC % PREDICTED			
	Change from baseline, mean (SD)	LS mean difference (SE)	95% CI	2-sided p-value
Total PROPEL population Cipaglucosidase alfa + miglustat (n=85) Alglucosidase alfa + placebo (n=37)	-0.93 (6.23) -3.95 (4.89)	2.66 [redacted]	0.37 to 4.95	0.02
ERT-experienced Cipaglucosidase alfa + miglustat (n=65) Alglucosidase alfa + placebo (n=30)	0.05 (5.84) -4.02 (5.01)	3.51 [redacted]	1.03 to 5.99	0.01
ERT-naïve Cipaglucosidase alfa + miglustat (n=20) Alglucosidase alfa + placebo (n=7)	-4.10 (6.53) -3.64 (4.71)	-1.95 [redacted]	-8.93 to 5.03	0.57

From the results of the subgroup analyses presented in Table 6 and Table 7 above, ERT-naïve patients appear to respond slightly better to alglucosidase alfa + placebo compared with cipaglucosidase alfa + miglustat, whereas ERT-experienced patients who have been on alglucosidase alfa for an average of 7.1 years respond better to cipaglucosidase alfa + miglustat.

Other outcomes

MMT lower extremity score

The summary of change in MMT lower extremity score from baseline to week 52 is presented in Table 21 of the CS. This improvement was observed from week 12 and sustained to week 52, although the difference at week 52 is not statistically significant (Figure 12 of the CS).

Subgroup analysis for MMT lower extremity by ERT-status is reported in Appendix E of the CS. Data on ERT-experienced participants is presented in Table 46 on page 115 of Appendix E. Data on ERT-naïve participants are presented in Table 50 on pages 120 and 121 of Appendix E.

Table 8: Summary of change in MMT lower extremity score by visit from baseline to week 52 (ITT-LOCF population) for total population and ERT-experienced and ERT-naïve subgroups

	MMT LOWER EXTREMITY			
	Change from baseline, mean (SD)	LS mean difference (SE)	95% CI	2-sided p-value
Total PROPEL population Cipaglucosidase alfa + miglustat (n=85) Alglucosidase alfa + placebo (n=37)	1.56 (3.78) 0.88 (2.58)	0.96 [redacted]	-0.48 to 2.40	[redacted]
ERT-experienced Cipaglucosidase alfa + miglustat (n=65) Alglucosidase alfa + placebo (n=30)	1.63 (4.13) 0.85 (2.81)	0.70 [redacted]	-1.08 to 2.49	[redacted]
ERT-naïve Cipaglucosidase alfa + miglustat (n=20) Alglucosidase alfa + placebo (n=7)	1.36 (2.55) 1.00 (1.53)	0.78 [redacted]	-1.79 to 3.34	[redacted]

GSGC

Results for change in the Gait, Stairs, Gowers' manoeuvre, and Chair (GSGC) total score from baseline to week 52 support the improvement in motor function observed using the 6MWT in PROPEL (presented in Table 23 of the CS). This improvement in motor function was observed from the first assessment at Week 12 and sustained to Week 52 (Figure 13 of CS).

The CS did not report subgroup analysis results by ERT-status but these data were provided in their response to the EAG's points for clarification (sub-group analysis for ERT-experienced participants in Table 8 and Figure 3 of points for clarification response, sub-group analysis results for ERT-naïve participants in Table 17 and Figure 8 of points for clarification response).

Table 9: Summary of change in GSGC total score by visit from baseline to week 52 (ITT-LOCF population) for total population and ERT-experienced and ERT-naïve subgroups

	GSGC total score			
	Change from baseline, mean (SD)	LS mean difference (SE)	95% CI	2-sided p-value
Total PROPEL population Cipaglucosidase alfa + miglustat (n=85) Alglucosidase alfa + placebo (n=37)	-0.53 (2.54) 0.77 (1.81)	-1.414 [redacted]	-2.46 to -0.36	[redacted]
ERT-experienced Cipaglucosidase alfa + miglustat (n=55) Alglucosidase alfa + placebo (n=25)	-0.53 (2.53) 0.61 (1.83)	-1.19 [redacted]	-2.38 to 0.00	[redacted]
ERT-naïve Cipaglucosidase alfa + miglustat (n=19) Alglucosidase alfa + placebo (n=7)	-0.56 (2.64) 1.29 (1.80)	-1.32 [redacted]	-4.03 to 1.39	[redacted]

PROMIS - Physical Function

A numerically greater improvement in PROMIS-Physical Function total score from baseline to Week 52 was observed with cipaglucosidase alfa in combination with miglustat versus alglucosidase alfa (presented in Table 24 of CS). Numerical benefits in this participant-reported physical function outcome were sustained to Week 52 (Figure 14 of CS).

The CS did not report subgroup analyses by ERT-status but these data were provided in their response to the EAG's points for clarification (sub-group analysis for ERT-experienced participants in Table 4 and Figure 1 of points for clarification, sub-group analysis for ERT-naïve participants in Table 13 and Figure 6 of points for clarification).

Analysis showed that, in ERT-naïve participants, there appeared to be a greater improvement in PROMIS - Physical Function total score from Baseline to Week 52 with alglucosidase alfa versus cipaglucosidase alfa in combination with miglustat.

Table 10: Summary of change in PROMIS – Physical Function by visit from baseline to week 52 (ITT-LOCF population) for total population and ERT-experienced and ERT-naïve subgroups

	PROMIS – Physical Function			
	Change from baseline, mean (SD)	LS mean difference (SE)	95% CI	2-sided p-value
Total PROPEL population Cipaglucosidase alfa + miglustat (n=85) Alglucosidase alfa + placebo (n=37)	1.94 (7.50) 0.19 (10.82)	1.87 [redacted]	-1.51 to 5.25	[redacted]
ERT-experienced Cipaglucosidase alfa + miglustat (n=65) Alglucosidase alfa + placebo (n=30)	1.76 (7.18) -0.97 (11.20)	3.14 [redacted]	-0.73 to 7.02	[redacted]
ERT-naïve Cipaglucosidase alfa + miglustat (n=20) Alglucosidase alfa + placebo (n=7)	2.50 (8.62) 5.14 (7.82)	-5.09 [redacted]	-14.04 to 3.85	[redacted]

PROMIS – Fatigue

The PROMIS – Fatigue scores showed similar mean improvement from baseline to week 52 between cipaglucosidase alfa in combination with miglustat and alglucosidase alfa (Table 25 of the CS). The CS did not present a line chart for this outcome but it was provided in Figure 11 of the company's response to the EAG's points for clarification.

The CS did not report subgroup analyses by ERT-status but these data were provided in the company's response to the EAG's points for clarification (sub-group analysis for ERT-experienced participants in Table 6 and Figure 2 of points for clarification response, sub-group analysis for ERT-naïve participants in Table 15 and Figure 7 of points for clarification response).

Analysis showed that, in ERT-naïve participants, a greater improvement in PROMIS – Fatigue total score from baseline to Week 52 was observed with alglucosidase alfa in combination with placebo versus cipaglucosidase alfa in combination with miglustat.

Table 11: Summary of change in PROMIS – Fatigue by visit from baseline to week 52 (ITT-LOCF population) for total population and ERT-experienced and ERT-naïve subgroups

	PROMIS – Fatigue			
	Change from baseline, mean (SD)	LS mean difference (SE)	95% CI	2-sided p-value
Total PROPEL population Cipaglucosidase alfa + miglustat (n=85) Alglucosidase alfa + placebo (n=37)	-2.02 (5.76) -1.67 (6.62)	0.04 [redacted]	-2.12, 2.20	[redacted]
ERT-experienced Cipaglucosidase alfa + miglustat (n=65) Alglucosidase alfa + placebo (n=30)	-1.87 (5.84) -0.27 (5.26)	-0.84 [redacted]	-3.16 to 1.49	[redacted]
ERT-naïve Cipaglucosidase alfa + miglustat (n=20) Alglucosidase alfa + placebo (n=7)	-2.50 (5.63) -7.70 (8.77)	3.29 [redacted]	-3.69 to 10.27	[redacted]

Subject's Global Impression of Change (SGIC)

In all eight domains, a greater percentage of participants treated with cipaglucosidase alfa in combination with miglustat reported improvement and a lower percentage reported worsening, compared with participants treated with alglucosidase alfa. Results are shown in Figure 15 of the CS for the SGIC overall physical wellbeing-domain.

The CS did not report subgroup analyses by ERT-status but these data were provided in their response to the EAG's points for clarification (sub-group analysis for ERT-experienced participants in Figure 4 of points for clarification response, sub-group analysis for ERT-naïve participants in Figure 9 of points for clarification response).

In the ERT-naïve participants, a greater percentage treated with alglucosidase alfa reported improvement compared with those treated with cipaglucosidase alfa plus miglustat, and none reported worsening.

Table 12: Summary of SGIC overall wellbeing by visit from baseline to week 52 (ITT-LOCF population) for total population and ERT-experienced and ERT-naïve subgroups

	SGIC OVERALL WELLBEING		
	IMPROVING	STABLE	DECLINING
Total PROPEL population Cipaglucosidase alfa + miglustat [redacted] Alglucosidase alfa + placebo [redacted]	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]
ERT-experienced Cipaglucosidase alfa + miglustat [redacted] Alglucosidase alfa + placebo [redacted]	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]
ERT-naïve Cipaglucosidase alfa + miglustat [redacted] Alglucosidase alfa + placebo [redacted]	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]

Physician's Global Impression of Change (PGIC)

Results for PGIC in the PROPEL trial were not presented in the CS. PGIC results for the PROPEL trial were reported in Figure 12 of the company's response to the EAG's points for clarification. Sub-group analysis for ERT-experienced and ERT-naïve participants are reported in Figure 5 and Figure 10 of points for clarification response, respectively.

Consistent with the SGIC results, a slightly greater percentage of ERT-naïve participants treated with alglucosidase alfa reported improvement, compared with ERT- naïve participants treated with cipaglucosidase alfa plus miglustat, and none reported worsening.

Table 13: Summary of PGIC by visit from baseline to week 52 (ITT-LOCF population) for total population and ERT-experienced and ERT-naïve subgroups

	PGIC		
	IMPROVING	STABLE	DECLINING
Total PROPEL population Cipaglucosidase alfa + miglustat [redacted] Alglucosidase alfa + placebo [redacted]	[redacted]	[redacted]	[redacted]
ERT-experienced Cipaglucosidase alfa + miglustat [redacted] Alglucosidase alfa + placebo [redacted]	[redacted]	[redacted]	[redacted]
ERT-naïve Cipaglucosidase alfa + miglustat [redacted] Alglucosidase alfa + placebo [redacted]	[redacted]	[redacted]	[redacted]

Creatine kinase (CK)

Reductions in CK were significantly greater with cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa, with a nominal $p < 0.001$ (Table 26 of CS). The improvements vs. alglucosidase alfa were observed from as early as Week 2 with levels continuing to decrease throughout 52 weeks of treatment (Figure 16 of CS).

Change in absolute values for serum CK from baseline to week 52:

Cipaglucosidase alfa in combination with miglustat: -130.5 (SD: 231.18)

Alglucosidase alfa in combination with placebo: 60.2 (SD: 159.49)

LS mean difference (95% CI): -176.0 (-244.4 to -107.6)

2-sided p-value: < 0.001

Hex4

Reductions in Hex4 were significantly greater with cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa, with a nominal $p < 0.001$ (Table 26 of CS). The improvements vs. alglucosidase alfa were observed from as early as Week 4, with levels continuing to decrease throughout 52 weeks of treatment (Figure 17 of CS).

Change in absolute values for serum Hex4 from baseline to week 52:

Cipaglucosidase alfa in combination with miglustat: -1.88 (SD: 2.38)

Alglucosidase alfa in combination with placebo: 1.22 (SD: 4.43)

LS mean difference (95% CI): -2.49 (-3.66, -1.32)

2-sided p-value: < 0.001

Rasch-built Pompe-specific Activity (R-PAct) Scale
Results were not presented in the CS.

Health-related quality of life (HRQoL)
EQ-5D-5L results were not presented in the CS, but were provided in response to the EAG's points for clarification request (Table 37 in points for clarification response).

Table 14: Summary of EQ-5D data collected in the PROPEL trial

	EQ-5D-5L		
Treatment	**Mean**	**SE**	**95% CI**
Cipaglucosidase alfa + miglustat (across all observations)	[redacted]	[redacted]	[redacted]
Alglucosidase alfa + placebo (across all observations)	[redacted]	[redacted]	[redacted]
Total population, baseline	[redacted]	[redacted]	[redacted]
Total population, week 52	[redacted]	[redacted]	[redacted]

Adverse events
Results for adverse events in the safety population of PROPEL are presented in Table 32 of the CS.

Subgroup analysis by ERT-status is not presented in the CS but this was provided in the company's response to the EAG's points for clarification (subgroup analysis for ERT-experienced participants is presented in Table 12 of points for clarification response, subgroup analysis for ERT-naive participants is presented in Table 21 of points for clarification response).

Table 15: Summary of adverse events by visit from baseline to week 52 (ITT-LOCF population) for total population and ERT-experienced and ERT-naïve subgroups

	ADVERSE EVENTS		
	Any TEAE	Serious TEAE	TEAE leading to death
Total PROPEL population			
Cipaglucosidase alfa + miglustat (n=85)	95.3%	9.4%	0%
Alglucosidase alfa + placebo (n=38)	97.4%	2.6%	0%
ERT-experienced			
Cipaglucosidase alfa + miglustat (n=65)	[redacted]	[redacted]	[redacted]
Alglucosidase alfa + placebo (n=30)	[redacted]	[redacted]	[redacted]
ERT-naïve			
Cipaglucosidase alfa + miglustat (n=20)	[redacted]	[redacted]	[redacted]
Alglucosidase alfa + placebo (n=8)	[redacted]	[redacted]	[redacted]

More detailed results of TEAEs occurring in at least 10% of participants were presented in Table 34 of the CS and details of study drug-related TEAEs [redacted] were presented in Table 35 of the CS. The most commonly reported TEAEs in the cipaglucosidase alfa in combination with miglustat group were falls, headache, nasopharyngitis and myalgia. The most commonly reported TEAEs in the alglucosidase alfa in combination with placebo group were falls, headache, nausea and back pain.

A summary of TEAEs reported to be infusion-associated reactions (IARs) is reported in Table 37 of the CS. The proportion of participants who had any IAR-TEAE was similar between treatment groups (24.7% and 26.3%), [redacted]

3.2.2 ATB200-02 Study (NCT02675465)

The ATB200-2 was a phase II, open-label, fixed-sequence, ascending-dose, single-arm study.

3.2.2.1 Study characteristics

Details of ATB200-02 are presented in Section B.2 of the CS. Treatment assignment and outcomes for Stages 1 to 4 are presented in Table 4 of the CS. Table 5 summarises the study design, methodology and eligibility criteria. Figure 4 provides an overview of the study stages for ATB200-02.

ATB200-02 was conducted in four stages and four cohorts with stages 1 and 2 only for Cohort 1, and stages 3 and 4 for all cohorts, eligibility criteria differed for the different cohorts:

Inclusion criteria:

- Aged ≥ 18 years
- Diagnosis of LOPD based on documentation of a deficiency in the GAA enzyme or GAA genotyping
- 6MWD between 200 and 500 m
- Upright FVC between 30% and 80% of the predicted value for healthy adults at screening
- Cohort 1: received ERT for two to six years prior to enrolment and were able to walk at least 200 m in the 6MWT
- Cohort 2: received ERT for two to six years prior to enrolment, required use of a wheelchair and were unable to walk unassisted
- Cohort 3: never received treatment with ERT, or received no more than one dose of ERT more than six months before the baseline visit in the study (Australian study centres only) and were able to walk at least 200 m in the 6MWT
- Cohort 4: received ERT for at least seven years prior to enrolment and were able to walk at least 75 m in the 6MWT

Method of study drug administration

As described in Table 4 of the CS, patients in Cohort 1 received cipaglucosidase alfa (without miglustat) in ascending doses from 5 mg/kg to 20 mg/kg during periods 1-3 (Stage 1; 6 weeks). Stage 2 (12 weeks) of the study consisted of period 4, in which patients received 3 doses of cipaglucosidase alfa 20 mg/kg in combination with miglustat 130 mg (6 weeks), and period 5, in which patients received 3 doses of cipaglucosidase alfa 20 mg/kg in combination with miglustat 260 mg (6 weeks). All four cohorts received cipaglucosidase alfa 20 mg/kg in combination with miglustat 260 mg during stages 3 (2 years) and 4 (ongoing) of the study. Cipaglucosidase alfa was administered every 2 weeks as an approximate 4-hour IV infusion (± 15 minutes). Miglustat was administered as oral capsules.

Outcomes

Outcomes assessed included:

- Change in motor function (6MWD assessed using 6MWT and GSGC)
- Change in respiratory function (assessed using sitting FVC % predicted)
- Change in muscular function (assessed using MMT)
- HRQoL
- Immunogenicity response
- Adverse effects

Efficacy assessments were performed at baseline, every 3 months in Stage 3 and every 6 months in Stage 4. Stage 4 of the trial is ongoing. 48-month efficacy and safety data are presented in the CS. However, owing to time constraints, 36-month data were used in the model.

3.2.2.2 Participants' baseline characteristics

Participants' baseline characteristics are presented in Table 11 of the CS.

3.2.2.3 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

No inferential statistics were calculated in the ATB200-02 study. Continuous variables were summarised using the mean and change from baseline at month 48 was presented with 95% CIs. Categorical variables were summarised using frequencies and percentages. All efficacy analyses were conducted on the efficacy population (described in Table 14 of the CS). No formal sample size calculation was performed. A sample size of between 18 to 34 participants was considered adequate.

Thresholds for clinically relevant changes in 6MWD and FVC were not pre-specified in the statistical analysis plan for ATB200-02. However, the CS states that the same thresholds as presented in Table 7 of the CS are relevant to ATB200-02 participants given the similarities in the population with those in PROPEL, although they were not used for analysis of 6MWD given the data are presented as change in distance as opposed to % improvement. The threshold for clinically relevant changes in FVC % predicted used in PROPEL was used in the *post-hoc* analysis for ATB200-02.

3.2.2.4 Risk of bias

The risk of bias assessment for ATB200-02 is presented in Table 16 of the CS. Quality assessment was performed using the Critical Appraisal Skills Programme (CASP) checklist. The company states that participants were recruited in an acceptable way, exposures and outcomes were accurately measured to minimise bias, study authors identified and took confounding factors into account and precise results were reported. The company judged that, overall, ATB200-02 is considered to be of high quality with a low risk of bias. The EAG agrees with the company's risk of bias assessment using the CASP checklist. However, the non-RCTs and observational studies included in the indirect treatment comparison (reported in Section 3.3 below) were assessed using the ROBINS-I tool whereas ATB200-02 was assessed using the CASP checklist. Using the ROBINS-I tool the EAG considered that the ATB200-02 study is at a low risk of bias.

3.2.2.5 Protocol deviations

Protocol deviations were not reported in the CS but are presented in Table 10 of the CSR. All participants experienced at least one protocol deviation. The most common reasons for protocol deviations included issues related to laboratory/endpoint data [redacted] visit window [redacted], study drug [redacted] and assessment safety [redacted].

3.2.2.6 Efficacy results

The primary outcome was change in motor function, assessed by the 6MWD. Key secondary outcomes were change in respiratory function (assessed using the sitting FVC% predicted), change in manual muscle testing (MMT) score, change in Gait, Stairs, Gowers' manoeuvre, and Chair (GSGC) score, change in Subject's Global Impression of Change (SGIC) score, change in Physician's Global Impression of Change (PGIC) score, and adverse events.

Whilst 6MWD and FVC are objective assessments used in clinical practice, the patient reported outcomes are likely to capture outcomes important to patients.

6MWD

Results for change in 6MWD from baseline to month 36 and month 48 for ambulatory participants (Cohorts 1, 3 and 4) are reported in Table 18 of the CS. Improvements were observed in 6MWD from baseline at month 36 (mean [redacted] and month 48 (mean [redacted]

FVC % predicted

Results for change in sitting FVC % predicted from baseline to month 36 and month 48 for ambulatory participants (Cohorts, 1, 3 and 4) are reported in Table 20 of the CS. The mean change from baseline to month 36 was [redacted] and [redacted] at month 48, representing an improvement in respiratory function from baseline.

Other outcomes

MMT score

Change in MMT from baseline is presented in Table 22 of the CS for ambulatory participants (Cohorts 1, 3 and 4). At month 36, mean change from baseline was [redacted] and at month 48, the mean change from baseline was [redacted] Cipaglucosidase alfa in combination with miglustat resulted in improvements and general stable MMT scores from baseline to month 48.

GSGC

The CS reported that participants treated with cipaglucosidase alfa in combination with miglustat also demonstrated improvement in GSGC, which was maintained above the baseline value up to month 48 of treatment, although results were not presented in the CS.

Change in Subject's Global Impression of Change (SGIC) and Physician's Global Impression of Change (PGIC)

Improvements in overall physical wellbeing were observed as early as 6 months after treatment initiation in the majority of participants in all cohorts. At month 48, the majority of participants from Cohorts 1 and 4 and all participants in Cohort 2 had either no change or reported improvement from baseline in overall physical wellbeing. All participants in cohort 3 reported improvement from

baseline at month 48. PGIC results indicated improvement or stability for all cohorts and supported the results observed for the other efficacy parameters.

Creatine kinase (CK)

Overall serum CK values decreased over the first 3 months. CK values remained stable at this lower level through to month 48, with expected visit-to-visit variability. (Results are presented in Table 14.4.1.1 in version 2 of the clinical studies report).

Hex4

Hex4 levels decreased from baseline and remained lower than baseline in stage 3 and stage 4 for all cohorts (Results are presented in Table 14.4.1.1 in version 2 of the clinical studies report).

Adverse events

The number of adverse events in ATB200-02 are reported in Table 33 of the CS. [redacted] of participants experienced a TEAE but only [redacted] were serious and [redacted] adverse events led to death. The most frequently reported treatment-related TEAEs were fatigue, headache and diarrhoea. [redacted] participants had an infusion-associated reaction (IAR); [redacted]

3.2.3 Key differences in study populations between PROPEL and ATB200-02

The mean participant age was similar in the PROPEL trial and the ATB200-02 study, [redacted] and [redacted] respectively. A higher proportion of participants in ATB200-02 were male (55.2% versus 45.5%). Data on race/ethnicity was missing for over 40% of participants in ATB200-02, although the majority of participants in both trials were white. Participants in ATB200-02 had a higher mean 6MWD (mean [redacted] versus [redacted] but lower FVC % predicted (mean [redacted] versus [redacted] than in PROPEL.

In their points for clarification request, the EAG asked the company whether there was an explanation for the lower mean FVC % predicted in ATB200-02 participants, despite a slightly higher 6MWD, in comparison with PROPEL trial participants. The company responded that these markers of disease progression should be considered independent from each other and can present and progress at different rates. In addition, PROPEL and ATB200-02 had different inclusion criteria with regards to 6MWD and FVC % predicted, accounting for the difference in baseline characteristics between the trials. They stated that the apparent difference in severity of respiratory and/or mobility impairment is not expected to reflect a clinically significant difference between the trial populations. This is consistent with information provided by the EAG's clinical advisor.

EAG comments

Whilst eligibility criteria for the PROPEL trial appear appropriate and likely to reflect UK clinical practice, there are several important differences in the baseline characteristics of the ERT-naïve and ERT-experienced patients recruited. [redacted] Response to treatment may differ between ERT-naïve and ERT-experienced patients. Clinical advice provided to the EAG indicates that a larger, but delayed, treatment effect is expected for the ERT-naïve population compared to the ERT-experienced population who would already have an improved clinical status from previous treatment. Therefore, the EAG considers that the comparison of a combined ERT-naïve and ERT-experienced population is not appropriate and that these subgroups should have been considered separately.

There is uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat. PROPEL trial data are only available for up to 52 weeks follow-up. Longer term data are available from the ATB200-02 study, however as this was an uncontrolled study, no long-term comparative data are available.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Section B.2.9 of the CS reports the details on the indirect treatment comparison undertaken by the company and full details are presented in Appendix D of the CS. Eight studies were identified, as described in Table 27 of the CS and Section 3.1.2 of the EAR, seven of which were included in the indirect treatment comparison. Only three of which were RCTs (PROPEL, COMET, LOTS)[13-15], two were open label extensions (COMET-OLE, LOTS-OLE)[16, 17] and two were single arm studies (ATB200-02, NEO-1/-EXT)[18, 19]. One further study (EMBASSY)[20] was not considered eligible for inclusion because it was exploratory and had short follow up.

Inclusion criteria for PROPEL[13] and ATB200-02[18] are described in Section 3.2 and for COMET[14], LOTS[15] and NEO[21] they are described in Table 16. Inclusion criteria was generally comparable across studies.

Table 16: Inclusion criteria

Trial	Inclusion criteria[1]	Exclusion criteria
COMET[14]	• Age ≥ 3 years old • Confirmed diagnosis of Pompe disease (GAA deficiency and/or 2 confirmed GAA mutations) • Treatment naïve • Upright FVC 30-85% predicted • Walk ≥ 40 metres without stopping and without assistive devices	• Pompe-specific cardiac hypertrophy • Requiring invasive ventilation • Wheelchair dependent • Clinically significant organic disease • Previous/current immune tolerance induction therapy • Positive pregnancy test or unwilling/ unable to test if of childbearing potential • Breastfeeding
LOTS[15]	• Age ≥ 8 years old • Confirmed diagnosis of Pompe disease (GAA deficiency and 2 GAA gene mutations) • Lower limbs muscle weakness <80% of predicted value • Able to undergo and produce reproducible muscle and pulmonary function tests • Upright FVC 30-79% predicted • Walk ≥ 40 metres in 6 minutes on 2 consecutive days (assistive devices allowed) • Postural drop in FVC ≥10% from upright to supine position. • Testable muscle in bilateral knee flexors and knee extensors.	• Requiring invasive ventilation • Requiring non-invasive ventilation whilst awake and upright • Positive pregnancy test or female of childbearing potential not protected by highly effective contraception or unwilling or unable to test for pregnancy • Enzyme replacement therapy with GAA received • Investigational product used within 30 days prior to enrolment or enrolled in another study with clinical evaluations. • Medical condition or major congenital anomaly which may interfere with compliance.
NEO[21]	• Age ≥ 18 years old • Confirmed diagnosis of Pompe disease (GAA enzyme deficiency and/or confirmed GAA gene mutation) • Walk ≥ 50 metres without stopping and without assistive devices (assistive device for walking outdoors is allowed) • Upright FVC ≥ 50% predicted • Negative pregnancy test if woman is of childbearing potential GROUP 2 (ERT-experienced) only: • Previously treated with alglucosidase alfa for ≥ 9 months.	• Cardiac hypertrophy • Wheelchair dependent • Requiring invasive ventilation • Unable to adhere to study protocol • Significant organic disease • MRI exam not possible GROUP 1 (ERT-naive) only: • Previous treatment with ERT for Pompe disease GROUP 2 (ERT-experienced) only: • High risk of severe allergic reaction to neoGAA

1. All three studies required signed, informed consent from participants or guardians prior to inclusion in the study.

Table 28 in the CS presents the baseline data from these studies and the CS states that there is some variation in baseline age, gender distribution, ERT duration and 6MWD and FVC % predicted and that most participants were white. However, for the purpose of LOPD in adults, the population studied would reflect UK population.

Appendix D.3 of the CS presents the critical appraisal of the included studies. COMET[14] and LOTS[15] were at low risk of bias in the majority of domains. LOTS OLE[16] and NEO-1[19] were of serious risk of bias and moderate risk of bias respectively. However, no details were included to justify these assessments. The EAG independently assessed LOTS OLE and NEO-1 using ROBINS-I for 6MWD and FVC (% predicted) and generally agree with the company's assessment although this may not be the most appropriate tool to use given these are single arm studies.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company undertook an indirect treatment comparison between cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa, as there were no head to head comparisons. This was done via a third intervention alglucosidase alfa. The indirect comparison has not been used to inform the base case economic model which does not include avalglucosidase alfa. However, it informs a single economic scenario analysis which compares cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa.

A multi-level network meta-regression (ML-NMR)[22] was undertaken by the company for change from baselines in 6MWD and FVC % predicted and is depicted in Figure 18 of the CS. This included both ERT-naïve and ERT experienced participants and adjusted for the following baseline characteristics: age, gender, ethnicity, previous ERT duration, visit time, and baseline 6MWD and baseline FVC % predicted (depending on the endpoint considered) using individual patient data from the PROPEL trial[13]. The EAG asked for justification of the use of ML-NMR rather than a straightforward indirect comparison (see clarification question A14). The company's justification was that it is important to use all available evidence in rare conditions and where there is a paucity of evidence available in a small population. The company state that NMAs assume homogeneity between studies which is not appropriate in this context as the RCT of avalglucosidase alfa (COMET)[14] only included ERT-naïve participants, whereas PROPEL[13] included both ERT-naïve and ERT-experienced participants. ML-NMR is therefore used to adjust for differences in the populations of included studies. The company also undertake several scenario analyses, varying previous ERT duration and other covariates, which generate relative effect estimates relevant to different target populations. The PROPEL trial[13] is similar to what would be expected in NHS practice.

The company also included single arm studies by matching them to appropriate comparator arms. The EAG asked for justification of inclusion of single arm studies when data from RCTs are available (see clarification question A16). The company states this was done in order to include further data from ERT-experienced participants for avalglucosidase alfa as COMET[14] only included ERT-naïve participants giving more robust results. The single-arm studies were matched based on previous ERT duration in order to limit heterogeneity between the single and matched arms. The company state that the incorporation of single arm studies into the evidence network is not expected to introduce substantial bias into the comparisons. A pooled model where different data are not distinguished (i.e. the matched data are treated the same as RCTs) was used.[23] In addition, random matching is recommended as a sensitivity analysis[23] which does not seem to have been undertaken. It is also not clear if participants in the matched arm are duplicated in the analysis. The results from the ML-NMR including single arm studies are presented in Table 30 and 31 of the CS.

EAG comments

The EAG do not agree that it is appropriate to include the single arm studies when a connected network of RCT data is available.[24] This approach may be appropriate when single arm studies are needed to connect a network, which is not the case in this scenario. Leahy et al also state that there is a high risk of bias and considerable uncertainty arising from incorporating single-arm evidence into an NMA.[23] Therefore, the EAG do not agree with the company's statement that results including single arm studies will be more robust as they are likely to also be biased. Furthermore, covariate values taken from the NHS population should be used to define the target population. However, these values were not available and the company have not carried out these analyses.

The EAG considers that the results from sensitivity analysis 2 for 6MWD and FVC[25], replicated in Table 17 below, are the most appropriate; this is an ML-NMR of RCTs only using the PROPEL[13] trial as the target population (mixed population).

The EAG note that although a fixed effects and a random effects approach were undertaken, the random effects was selected as most appropriate due to the DIC being slightly lower. However, due to the small number of studies included for each comparator there is insufficient information to estimate the heterogeneity parameter the EAG would recommend that informative priors are used.[26] The EAG could not undertake this approach as data used by the company for the ML-NMR approach was not supplied, therefore the fixed effect approach is preferred.

Table 17: ML-NMR relative effects Sensitivity analysis 2(Amicus Therapeutics Data on File 2022), based on RCTs only including both ERT-naïve and ERT experienced participants. Using the PROPEL trial(Schoser, Roberts et al. 2021) as the target population

Outcome	6MWD change from baseline (m)	FVC change from baseline (% predicted)
Treatment	ML-NMR relative effect Mean difference (95% credible interval)	ML-NMR relative effect Mean difference (95% credible interval)
Cipaglucosidase alfa + miglustat vs. Alglucosidase alfa	[redacted]	[redacted]
Cipaglucosidase alfa + miglustat vs. Avalglucosidase alfa	[redacted]	[redacted]
Cipaglucosidase alfa + miglustat vs. Placebo	[redacted]	[redacted]
Avalglucosidase alfa vs. Alglucosidase alfa	[redacted]	[redacted]
Avalglucosidase alfa vs. Placebo	[redacted]	[redacted]
Alglucosidase alfa vs. Placebo	[redacted]	[redacted]

1. FVC % predicted was taken from upright in COMET[14] and sitting in PROPEL[13]

3.5 Additional work on clinical effectiveness undertaken by the EAG

3.5.1 Simple indirect comparison

The EAG asked for the data used for the indirect comparisons in clarification question A19 but the company stated that the data used in the ML-NMRs could not be provided as it was individual participant data and the confidentiality of individual participants should be protected. Therefore no additional EAG work could be carried out to explore the ML-NMR models.

The EAG also requested that the company undertake a simple indirect comparison using the Bucher method[27] without adjusting for baseline characteristics (see clarification question A17) and also to undertake a simple indirect comparison in the naïve participants only using data from RCTs (see clarification question A18). The company responded that the Bucher method would be less appropriate as it assumes homogeneity between the studies and did not provide the comparison. However, the EAG believes this is a useful simple method that can be used to compare to the adjusted results to understand the potential impact of the covariate adjustment on the relative effects.

The company also think that only considering naïve participants using RCT data alone is not appropriate in this context as the population of interest is adults with LOPD, regardless of previous ERT experience. In addition, the sample size of ERT-naïve participants in the PROPEL[13] subgroup is small (n=7 in the alglucosidase alfa arm) which would result in unreliable results with a large amount of uncertainty. However, the EAG believes that this would also be a useful simple comparison to show the extent of uncertainty in the estimated relative effects for ERT-naïve patients.

The EAG undertook simple indirect comparisons in ERT-naïve participants for 6MWD, FVC and GSGC (as a patient important outcome) using the Bucher method.[27] The results are shown in Table 18 along with the company's scenario analysis using RCT data only and setting previous ERT duration to zero which extrapolates results to an ERT-naïve population.[25] The company include previous ERT duration as continuous data in the model rather than dichotomous, so participants aren't simply categorised as ERT-naïve or ERT experienced. There is a large amount of variability in all results. All ML-NMR estimates are within the Bucher 95% CIs but the latter are generally more uncertain which is expected as they have data on fewer patients, whereas ML-NMR uses the full population to adjust for ERT-naïve status. However, caution should be applied when interpreting results from ML-NMR as estimates have been extrapolated from a regression model based on data from few participants.

Table 18: ERT-naïve participants

Outcome	6MWD change from baseline (m)		FVC change from baseline (% predicted)		GSGC
Treatment	ML-NMR relative effect Mean difference (95% credible interval)[1]	Non covariate adjusted Mean difference (95% confidence interval)	ML-NMR relative effect Mean difference (95% credible interval)[1]	Non covariate adjusted Mean difference (95% confidence interval)	Non covariate adjusted Mean difference (95% confidence interval)
Cipaglucosidase alfa + miglustat vs. Alglucosidase alfa	[redacted]	-9 (-46.50, 34.95)[2]	[redacted]	-1.95 (-8.93, 5.03)[2]	-1.32 (-3.85, 1.21)[2]
Cipaglucosidase alfa + miglustat vs. Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cipaglucosidase alfa + miglustat vs. Placebo	[redacted]	NA	[redacted]	NA	NA
Avalglucosidase alfa vs. Alglucosidase alfa	[redacted]	30·01 (1·33, 58·69)[5]	[redacted]	2·43 (-0·13, 4·99)[5]	-1·31 (-0·37, -2·25)[5]
Avalglucosidase alfa vs. Placebo	[redacted]	NA	[redacted]	NA	NA
Alglucosidase alfa vs. Placebo	[redacted]	NA	[redacted]	NA	NA

1. Sensitivity analysis 2 scenario with previous ERT duration set to 0[25], based on RCTs only.
2. Taken from PROPEL[13] ERT-naïve participants. There is some concern with the mean difference used here as the Wilcoxon rank test was used so data must have been skewed, although this is to be expected with the small number of participants.
3. Based on the Bucher method[27]
4. FVC % predicted was taken from upright in COMET[14] and sitting in PROPEL[13]
5. Taken from COMET[14]. There is some concern with this value as it is the same as the LSmean in one arm according the appendix of the manuscript so there may be an error.

EAG comments

The EAG do not agree with the company's reasoning regarding undertaking separate analyses on ERT-naïve and ERT-experienced participants as the subgroups were pre-specified in the NICE final scope and data are available for ERT-naïve participants. The clinical advisor also suggests that combining these participants in mixed population meta-analyses is not meaningful. However, ML-NMR may correct for population differences and estimate effects in each specific population,

although with only few ERT-naïve patients included to inform the meta-regression, results in this subgroup may not be very reliable.

3.5.2 Additional study critique

The study by Semplicini et al.[9] is mentioned in the CS in Section B.3.3.3 (p. 127) and results from the study are used to estimate annual change in FVC and 6MWD % in the economic model. This study was identified in the company SLR, but details of the study are not reported in the clinical effectiveness section of the CS. Therefore, the EAG have summarised and critiqued the study below. In 2004, the French national Pompe Registry was set up to collect clinical and biological data on patients with Pompe disease. The registry is sponsored by Genzyme-Sanofi, Myology Institute, and INSERM. This is an uncontrolled observational study with patients on the registry. Outcomes included 6MWT, Motor Function Measurement (MFM) including sub-scores, sitting and supine FVC, difference between sitting and supine FVC, and Maximal Inspiratory/ Expiratory Pressures (MIP/MEP). All data are expressed as % of predicted values.

6MWT showed an initial significant increase (1.4% ±0.5/year, $P < .01$) followed by a progressive decline after 2.2 years (−2.3%/year; change of slope: -3.7 ± 0.6, $P < .001$). A slight increase of patients requiring non-invasive ventilation was observed after 3 years of ERT. Sitting and supine FVC slowly declined over time.

Twenty-six patients (17.3%) discontinued treatment. The study included 197 adult participants; 158 ERT-experienced (alglucosidase alfa 20 mg/kg) and 39 treatment-naïve. Reasons for absence of treatment in the ERT-naïve group included hyper-CKemia, mild symptoms, advanced age, or refusal of treatment. Untreated patients were less severely affected by the disease on various outcome measures.

The company assessed risk of bias using ROBINS-I across outcomes (CS Appendix D). Risk of bias in selection of participants was judged to be 'low'. There is no information in the study report on participants who declined to take part, or whether the study population is representative of the total population of patients with Pompe disease in France.

Risk of bias due to missing data was judged to be 'low'. In the study report, there is no explanation of missing data. Reasons for drop-out are not provided. Adverse event data appears to be based on 150/158 participants. Fewer participants are included in outcome data relating to 6MWT (N=120), sitting FVC (N=143), and supine FVC (N=50).

Risk of bias due to selective outcome reporting was judged to be 'low'. As a study protocol has not been made available, this cannot be assessed properly.

3.6 Conclusions of the clinical effectiveness section

The CS describes a SLR undertaken to assess the efficacy and safety of treatments for adults with LOPD. The SLR included two studies that assessed cipaglucosidase alfa in combination with miglustat; one double-blind RCT comparing cipaglucosidase alfa in combination with miglustat against alglucosidase alfa in combination with placebo (PROPEL) and a small phase II single-arm ascending-dose study of cipaglucosidase alfa in combination with miglustat (ATB200-02).

Included trials

The PROPEL RCT appears to have been well conducted with a low risk of bias. The results suggest that in ERT-experienced LOPD patients (and the full cohort of ERT-experienced and ERT-naïve patients) cipaglucosidase alfa + miglustat was associated with a greater improvement in physical function (6MWD) and less respiratory decline (sitting FVC % predicted) from baseline to week 52, compared to alglucosidase alfa + placebo. The [redacted] improvement in 6MWD from baseline was considered to be clinically meaningful, as was the [redacted] difference in FVC % predicted change from baseline between cipaglucosidase alfa + miglustat and alglucosidase alfa + placebo. Results for other outcomes also favoured cipaglucosidase alfa + miglustat; MMT lower extremity score, GSGC total score, PROMIS-Physical Function, PROMIS-Fatigue, SGIC and PGIC.

In ERT-naïve patients, there appeared to be a slightly greater improvement in 6MWD and less respiratory decline with alglucosidase alfa + placebo compared to cipaglucosidase alfa + miglustat. The CS only reported subgroup analysis results for the primary and key secondary outcomes, but additional results were provided in response to the EAG's clarification request (patients who had received/had not received prior treatment with alglucosidase alfa were specified subgroups in the NICE scope). Similar results were seen for some of the other outcomes assessed, suggesting more favourable results for PROMIS-Physical Function, PROMIS-Fatigue, SGIC and PGIC in the alglucosidase alfa + placebo group. However, the number of ERT-naïve patients in the analysis was very small, resulting in very wide confidence intervals. In addition, there were some differences in baseline characteristics between the alglucosidase alfa + placebo group and the cipaglucosidase alfa + miglustat group [redacted]. There were also baseline differences between the ERT-naïve and ERT-experienced patients in the trial [redacted].

The adverse event profile was similar between cipaglucosidase alfa + miglustat and alglucosidase alfa + placebo, although a higher proportion of patients reported a serious TEAE with cipaglucosidase alfa + miglustat compared with alglucosidase alfa + placebo and a small number of patients had a serious

IAR-TEAE or a study-drug related IAR-TEAE leading to study drug discontinuation, compared with [redacted] the alglucosidase alfa + placebo group.

The single-arm ATB200-02 study reported improvements from baseline in 6MWD and FVC % predicted at month 36 and month 48 (in ambulatory cohorts 1, 3 and 4), suggesting that the effects persist beyond the 52 weeks assessed in the PROPEL trial. Improvements in MMT lower extremity score and GSGC were also seen up to month 48, compared to baseline values. However, as this was an uncontrolled study, there is uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination in miglustat compared with alglucosidase alfa.

Indirect treatment comparisons

The EAG do not agree with the company's approach to include single arm studies in their indirect treatment comparison; this approach may be appropriate when single arm studies are needed to connect a network, but in this case RCT data are available although the numbers are very small. The EAG consider that the inclusion of single arm studies may increase precision but with a high risk of bias which cannot be quantified.

When considering the ML-NMR scenario analysis undertaken by the company including RCTs only in the mixed population (ERT-experienced and ERT-naïve), cipaglucosidase alfa + miglustat is favoured compared to alglucosidase alfa, for both 6MWD and FVC. All other results have wide confidence intervals and conclusions are uncertain. However, the EAG considers that the two groups of participants should be considered separately.

For the ML-NMR scenario when previous ERT duration is set to zero (including RCTs only), all interventions are favoured compared to placebo and avalglucosidase alfa is favoured compared to alglucosidase alfa for both 6MWD and FVC. Avalglucosidase alfa also shows a numerically favourable effect compared to cipaglucosidase alfa + miglustat for 6MWD. Results for cipaglucosidase alfa + miglustat compared to alglucosidase alfa had wide confidence intervals so no conclusions could be drawn.

The EAG also undertook Bucher's[27] simple indirect comparison for ERT-naïve participants, which showed a large amount of uncertainty in all results. All ML-NMR estimates are contained within the Bucher 95% CIs but the latter are generally more uncertain which is expected as data is only available for a small number of patients, whereas ML-NMR uses the full population to adjust for ERT-naïve status. However, caution should be applied when interpreting results from ML-NMR as estimates have been extrapolated from a regression model based on data from few participants. It was not possible to perform Bucher's[27] simple indirect comparison for ERT-experienced participants as the COMET[14] trial only includes ERT naïve participants.

4 Cost effectiveness

4.1 EAG comment on company's review of cost-effectiveness evidence

The company undertook an SLR to identify relevant economic evaluations, literature relating to health-related quality of life (HRQoL), and costs and healthcare resource use data for adults with Pompe disease. The company provided a detailed report of the methods and results of the SLRs in Appendices G, H, and I of the CS.

4.1.1 Search strategy

The CS included searches to identify cost-effectiveness evidence, cost and healthcare resource use measurement and valuation, and HRQoL for adult patients with Pompe disease. A detailed description of the searches and most of the search strategies were included in CS Appendix G (pages 138 - 149).

The EAG is satisfied with the search strategy adopted by the company. A detailed appraisal of evidence identification methods is provided in Appendix 1.

4.1.2 Study eligibility criteria

Study eligibility criteria applied by the company were described in CS Appendix G for the review of economic evaluations (Table 66), CS Appendix H for the quality of life studies (Table 71) and CS Appendix I for the cost and healthcare resource studies (Table 74). The population of interest in all cases was adults aged ≥18 years of age with Pompe disease. Additionally, for both quality of life studies and cost and healthcare resource studies the population of interest also included caregivers/family of patients with Pompe disease. Studies including children <18 years of age with Pompe disease were excluded for all reviews. No specific inclusion criteria in terms of interventions and comparators were defined in the review. Language restrictions were applied in all reviews and required that studies were published in English. The original searches were not limited by date in the strategy, however, economic evaluations published more than 5 years ago (i.e., 2017) were excluded *post-hoc*. Conference abstracts published before 2020 were also excluded.

Selection was based on two reviewers independently evaluating eligibility, with discrepancies resolved by a third reviewer.

The EAG considered the eligibility criteria and the company's assessment of identified studies against them to be generally appropriate. The EAG notes that the date restriction for economic evaluations *post-hoc* may have omitted older cost-effective evidence.

4.1.3 Identified studies

Based on titles and/or abstracts, the SLR identified [redacted] novel records with [redacted] full publications screened against inclusion and exclusion criteria. [redacted] article with potential relevance to the UK setting (summarised in Table 40 of the CS) met the economic evaluations eligibility criteria, [redacted] the HRQoL eligibility criteria, and [redacted] the cost and healthcare resource use measurement and valuation eligibility criteria.

Whilst the company only included one article in the cost-effectiveness review and justified this based on scarcity of relevant economic evaluations in LOPD, they also considered three economic evaluations in the Infantile-onset Pompe disease (IOPD) population.[28-30] The latter studies were ultimately excluded as they did not incorporate the primary or secondary outcomes from the PROPEL trial. All four studies found that although alglucosidase alfa provided substantial health gains in both LOPD and IOPD populations, it was not cost-effective with ICERs far above any conventional cost-effectiveness thresholds.

Another potentially relevant study excluded from the cost-effectiveness review was a NIHR commissioned study considering the effectiveness and cost of ERT.[31] This study considers a range of lysosomal storage disorders including Pompe disease, and while it does not present a formal cost-effectiveness analysis it does present a range of threshold analyses that consider the magnitude of benefits necessary for ERT to be considered cost-effective. The study concludes that ERT (alglucosidase alfa) would need to generate substantial additional QALYs to be considered cost-effective at accepted willingness to pay thresholds.

While the EAG acknowledges that the majority of these studies were not based on a UK NHS perspective and thus are not fully relevant to the UK setting, the EAG considers that these studies provide evidence that alglucosidase alfa is not cost-effective. This has important consequences for the appraisal of cipaglucosidase alfa combined with miglustat which are discussed in Section 4.2 below.

4.1.4 Interpretation of the review

The EAG considered the methods of the company's SLR sufficient to identify any existing cost-effectiveness analyses, HRQoL, or costing studies conducted in a relevant population and setting. The EAG is therefore satisfied that the model presented by the company represents the most relevant analysis for decision making.

4.2 Comparator cost effectiveness

The EAG understands that alglucosidase alfa is used routinely in NHS practice for the treatment of Pompe disease and is listed as a comparator in the NICE scope. However, the EAG considers any

comparison with alglucosidase alfa to be problematic due to the unique circumstances in which it entered commissioning in the NHS. The EAG understands that alglucosidase alfa underwent no formal public assessment of cost-effectiveness through either the single technology appraisal (STA) or the highly specialised technology (HST) pathways. The cost-effectiveness of alglucosidase alfa is therefore unknown. Based on the list price of alglucosidase alfa, the plausible benefits of ERT and evidence identified in the cost-effectiveness review, the EAG considers it highly likely that alglucosidase alfa is **not** cost-effective. Any comparison to alglucosidase alfa or other comparators whose cost-effectiveness has been estimated relative to alglucosidase alfa is therefore likely to generate misleading estimates of cost-effectiveness and to significantly overestimate the value of that treatment to the NHS. The economic evaluation presented by the company, therefore, while consistent with the NICE scope and the previous STA of avalglucosidase alfa, is flawed and does not represent the additional value of cipaglucosidase alfa in combination with miglustat to the NHS.

4.3 Summary and critique of the company's submitted economic evaluation by the EAG

4.3.1 NICE reference case checklist

Table 19: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Heath effects from both patients and carers were included.
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model had a lifetime horizon of up to 106 years. No patients were expected to be alive beyond this period.
Synthesis of evidence on health effects	Based on a systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes. The utility study elicited utilities for all health states based on a EQ-5D evaluation.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No, utilities applied to health states were elicited using vignettes describing each health state.

Source of preference data for valuation of changes in health-related quality of life	A representative sample of the UK population	Utilities were elicited directly from members of the public.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes. Scenario analysis also explored a 0% and 1.5% discount rate.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.3.2 Model structure

The company developed a patient-level simulation model in Microsoft Excel to assess the lifetime cost-effectiveness of cipaglucosidase alfa in combination with miglustat for the treatment of adult patients with Pompe disease. Modelled patients were allocated to receive either cipaglucosidase alfa in combination with miglustat or an alternative ERT; alglucosidase alfa (base case) and avalglucosidase alfa (scenario analysis). The model uses a one-year cycle length and applies a half-cycle correction.

The company justified the use of a patient simulation model highlighting its ability to separately capture progression in respiratory and mobility symptoms and permits greater granularity than a Markov model. The company further notes that the structure adopted is similar to that accepted by the NICE committee in the recent appraisal of avalglucosidase alfa (TA821).

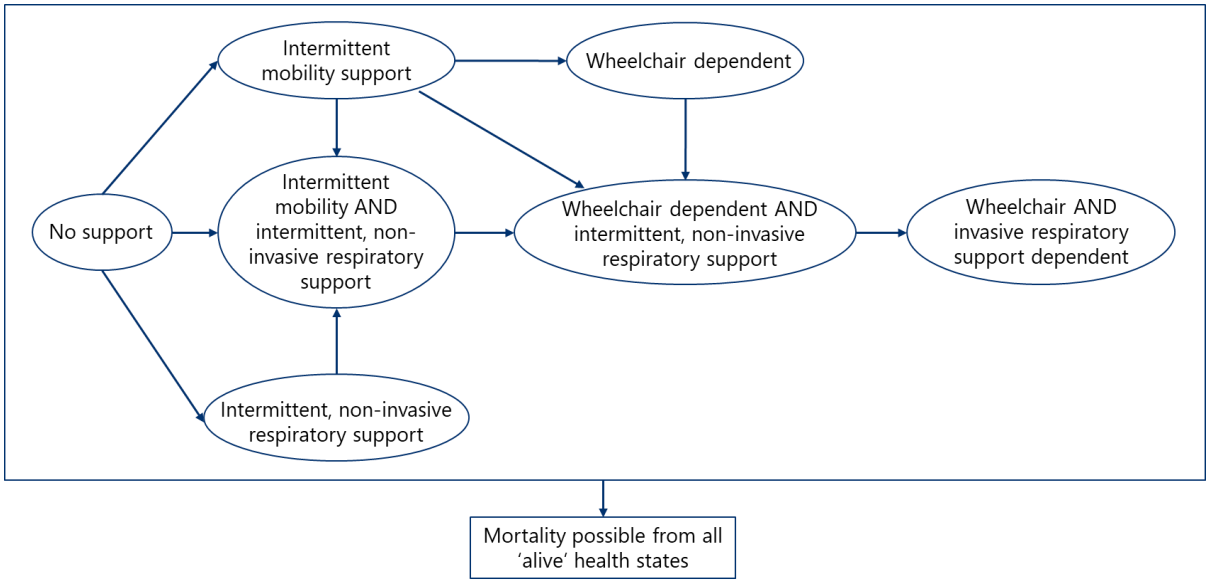
This model structure is depicted graphically in Figure 1 and comprises seven ‘alive’ health states which defined requirements for respiratory and/or mobility support. Support was classified into three levels: no support, intermittent support and wheelchair-dependent/invasive respiratory support dependant. The seven alive health states were as follows:

- No support (i.e. no requirement for ventilation or mobility support);
- Intermittent mobility support (no respiratory support)
- Wheelchair-dependent (no respiratory support)
- Intermittent respiratory support (no mobility support)
- Intermittent mobility and intermittent respiratory support
- Wheelchair-dependent and intermittent respiratory support

- Wheelchair-dependent and invasive respiratory support dependant

In addition to the alive heath states an absorbing death health state was modelled, which patients could transition to from any of the alive health states.

Figure 1: Model structure (from CS Figure 21).



All patients start in the model without ventilation or wheelchair use and begin ERT with either cipaglucosidase alfa combined with miglustat, alglucosidase alfa or avalglucosidase alfa (scenario analysis only). In each cycle, a patient can stay in the current health state or transition to a worse health state. Progression through the model was dependent upon on FVC % predicted and/or 6MWD, with thresholds applied to define the level of support required such that if FVC % predicted falls below a given threshold, patients are assumed to start ventilation (first non-invasive and then invasive) while patients start using intermittent mobility support or a wheelchair after a specified decline in 6MWD. Threshold values applied to define each health state are described in Table 20.

Table 20: Thresholds required for support (adapted from Table 43 of CS)

Support	Threshold
Intermittent mobility support (max m in 6MWD)	***
Wheelchair dependent (max m in 6MWD)	**
Intermittent respiratory support (FVC % predicted)	***
Respiratory support dependent (FVC % predicted)	***

For each iteration of the model, average time in each health state was simulated over the modelled time horizon and applied costs and QALYs recorded. These were then aggregated across the simulated cohort (30,000 patients in the base case) to estimate mean values for the cohort.

EAG comments

4.3.2.1 Appropriateness of individual patient simulation approach

As stated above, the company's economic model uses an individual patient simulation approach where, assessment of outcomes (costs and benefits) are evaluated by simulating the target group of patients individually i.e. one patient at a time. This contrasts with a cohort model, where patient outcomes for the target group of patients are evaluated without explicitly considering the outcomes of each individual patient (i.e. all patients together). The advantage of individual patient simulations is that they offer greater flexibility than cohort models, and in the case of the presented model it permits changes in mobility (6MWD) and respiratory function (FVC % predicted) to be modelled independently of one another.

The approach adopted by the company is specifically a state transition individual patient simulation in which a discrete set of mutually exclusive health states is used to capture the flow of patients through the model over time. A distinct feature of a state transition individual patient simulation is that outcomes are evaluated at every time interval, this increases computation burden as outcomes are evaluated even when no changes occur. For example, if changes in 6MWD and FVC % predicted do not result in a transition to another health state. An alternative would have been to use a discrete event simulation (DES) where evaluation of model outcomes only occurs on the occurrence of the next event. Such an approach is likely to have provided a more efficient and parsimonious solution than that offered by the adopted state transition approach and would have significantly reduced computational burden. A DES would also have reduced bias associated with multiple transitions occurring in the same cycle. Nonetheless, the EAG considers that the presented approach is appropriate for decision making.

4.3.2.2 Differences to TA821

The model structure and approach adopted by the company is largely consistent with previous appraisals, namely TA821. There are however, several noteworthy differences.

Firstly, in TA821 the economic model used the Discretely Integrated Condition Event (DICE) methodology. DICE is technically not a type of model but rather a way of implementing a model that uses proprietary DICE software. The DICE approach is, however, frequently associated with individual patient simulation models, consequently the presented approach is consistent with the model used in TA821. The EAG does not consider there to be any specific advantage or disadvantage of an individual patient simulation model verses a DICE model; validation exercises have found that both model types produce near identical results when similarly specified.[32]

Secondly, the model uses two additional health states not present in the TA821 model. These are: i) Intermittent mobility support, and ii) Intermittent mobility support and intermittent non-invasive

respiratory support. The addition of these health states allows for greater granularity in mobility to be evaluated in the economic analysis. The EAG considers the addition of the health states appropriate and consistent with clinical reality.

4.3.2.3 Dependency between model parameters

In the original economic model provided by the company, all parameter inputs were drawn from independent normal distributions and consequently did not account for correlations between parameter inputs. Such correlation may be important as outputs from the model are not a linear function of inputs. Specific examples of where such correlation may be important are baseline characteristic, response to treatment, and long-term rates of change for 6MWD and FVC % predicted. At the clarification step the EAG requested that the economic model be revised to appropriately account for correlations between model parameters. The company's response acknowledged that correlations between parameters are likely and revised the economic model. However, these changes did not address the underlying issue. For the baseline characteristics the model was revised such that values were assumed to be perfectly correlated. This is equally as inappropriate as assuming values are independent of one another and may similarly lead to bias in model outcomes. For treatment effects and changes in both 6MWD and FVC % predicted, modelling of variability was completely removed such that only average mean effects are used. Again, the EAG considers this inappropriate and fails to leverage one of the prime advantages of an individual patient simulation. Namely, that it allows heterogeneity in patient experience to be fully reflected. Because of the limited data available to the EAG, it is not possible for the EAG to correct the model, and the EAG recommends that the company further revises this model at technical engagement.

4.3.3 Population

The company's analysis focuses on adults with LOPD. This population fully aligns with the anticipated marketing authorisation for cipaglucosidase alfa in combination with miglustat, however, it is a narrower population than defined in the NICE scope which included all people with Pompe disease i.e., included both IOPD and LOPD populations.

In line with the narrower focus of the base case analysis, the modelled population is based upon the PROPEL trial and included a pooled population of ERT- naïve and ERT-experienced patients. The baseline characteristics of the modelled population are presented in Table 21 and include age, sex, weight, height, baseline 6MWD (a measure of functional exercise capacity i.e., the mean distance a patient covers walking six minutes) and baseline sitting FVC % predicted (a measure of respiratory function). Means and standard deviations were drawn from the PROPEL trial. In line with the patient simulation approach, these values were used to generate baseline characteristics for each iteration of

the model. Values for each baseline characteristic were drawn using the same random seed value. This implies that baseline characteristics are perfectly correlated.

Table 21: Baseline characteristics (adapted from Table 42 of CS)

Baseline demographics	Mean	Standard deviation
Percentage male	[redacted]	[redacted]
Average age (years)	[redacted]	[redacted]
Average weight (kg)	[redacted]	[redacted]
Average height (cm)	[redacted]	[redacted]
Baseline 6MWD	[redacted]	[redacted]
Baseline FVC % predicted (sitting)	[redacted]	[redacted]

Abbreviations: 6MWD = 6-minute walk distance; FVC = forced vital capacity.

Within the economic analysis, sex and age inform per cycle mortality as well as age-related utility adjustments applied to health state utility values. Baseline weight and height are used to calculate the dosing throughout the model; alglucosidase alfa, avalglucosidase alfa, cipaglucosidase alfa and miglustat all use weight-based dosing.

The NICE scope listed two subgroups of relevance: i) people who have not received prior treatment with alglucosidase alfa (ERT-naive), and ii) people who have received prior treatment with alglucosidase alfa (ERT-experienced). These subgroups were not explored by the company and only a mixed naive and experienced population was explored as per the base case analysis. The company's justification for not considering the subgroups was that prior ERT status should not influence access to treatment to allow fair and equitable access. In addition, the company argued that the total cohort is the most reliable and meaningful source of data for the cost-effectiveness analysis due to comparatively small patient numbers for the ERT-naïve subgroup in the PROPEL trial (n=28).

EAG comments

4.3.3.1 Exclusion of people with IOPD

The EAG is satisfied with the company's focus on adults with LOPD aged 18 years and older. LOPD refers to all patients with symptom onset over the age of 1 year, and unlike IOPD, is not characterised by manifestation of cardiac alterations e.g., hypertrophic cardiomyopathy. However, the EAG recognises heterogeneity in the different subgroups of late-onset i.e., juvenile, and late-presenting LOPD. Clinical advice provided to the EAG indicates that the disease will progress over time across all LOPD patients, with the impression that an earlier diagnosis translates to higher disease severity. It is noted that a proportion of "juvenile" onset LOPD patients would become eligible for therapy at the age of 18 years.

4.3.3.2 Pooling of ERT-naïve and ERT-experienced populations

The EAG questions the rationale for pooling the ERT-naïve and ERT-experienced populations. Typically, an economic analysis will consider each alternative position in the pathway separately. This approach allows for differences in the patient population, comparators, and ultimately cost-effectiveness to be fully reflected in each analysis. The use of a pooled population implies that the analysis cannot reflect this heterogeneity and prevents exploration of any uncertainty in the composition of the modelled population, e.g., the proportion of naive vs experienced patients.

As described in Section 3.3 there are several important differences in the baseline characteristics of ERT-naive and ERT-experienced patients recruited to the PROPEL study. Specifically, age at diagnosis, baseline 6MWD and baseline FVC % predicted differ substantially across subgroups. There is also an expectation that response to treatment will differ between ERT-naïve and ERT-experienced patients. Clinical advice provided to the EAG indicates that a larger, but delayed, treatment effect is expected for the ERT-naïve populations compared to the ERT-experienced population who would already have an improved clinical status from previous treatment.

In addition to the arguments above, there also several important technical reasons why the ERT-naïve and ERT-experienced populations should be considered separately, even if the decision problem is defined with respect to the whole population.

Firstly, one of the advantages of an individual patient simulation is that it better accounts for heterogeneity in the patient experience and the impact of individual characteristics on outcomes (benefits and costs). One way this can be done is by reflecting the correlation between baseline characteristics and the treatment effect. This can be done in several ways but given our expectation that baseline characteristic and the treatment effects differ across ERT-naïve and ERT-experienced population this could be achieved by using a model averaging approach in which the model is run separately for ERT-naïve and ERT-experienced patients, with final outcomes (for the whole population) generated by weighting model results by the proportion of ERT-naïve and ERT-experienced patients.

Secondly, the PROPEL trial population primarily consists of an ERT-experienced population (77% of participants are ERT-experienced) while the COMET trial exclusively recruits patients from an ERT-naïve population. This creates uncertainty in any indirect comparison between avalglucosidase alfa and cipaglucosidase alfa as relative effectiveness estimates are drawn from distinctly different populations. The EAG considers it important to appropriately reflect this uncertainty and that this is most transparently done by considering the ERT-naïve and ERT-experienced populations separately.

Specifically, the available trial evidence is better able to inform the relative effectiveness of avalglucosidase alfa and cipaglucosidase alfa in an ERT-naïve population than it is in an ERT-experienced population. Consideration of these populations separately therefore allows uncertainties in treatment effects for the ERT-experienced population to be more appropriately explored.

For the reasons outlined above, the EAG advises that the comparison of a combined ERT-naïve and ERT-experienced population is not appropriate and these subgroups should have been considered separately.

4.3.4 Interventions and comparators

In line with the PROPEL trial, the modelled intervention is cipaglucosidase alfa in combination with miglustat. In the primary (base case) analysis this is compared to alglucosidase alfa only. Secondary scenario analysis also considers avalglucosidase alfa as an alternative comparator. The modelled intervention comprises the co-administration of a next-generation intravenous ERT, cipaglucosidase alfa, with miglustat, an orally administered enzyme stabiliser. The comparators, alglucosidase alfa and avalglucosidase alfa, are administered as monotherapies (i.e. without miglustat) and are alternative ERTs that work in a similar way to cipaglucosidase alfa.

Dosing for each of the three ERTs was modelled in line with the relevant SmPCs, which for all three treatments is an intravenous infusion of 20mg/kg of body weight every two weeks. Miglustat dosing (applied in the cipaglucosidase alfa arm of the model) is also dependent upon patient weight with a dose of four 65 mg capsules (260 mg) used in patients weighing ≥50 kg, and three capsules of 65 mg (195 mg) in patients weighing ≥40 kg to <50 kg. At the clarification stage, the company stated that [redacted] As stated above, avalglucosidase alfa was not considered in the primary analysis and is only addressed in scenario analyses. The company's reasoning for excluding avalglucosidase alfa from the primary analysis is that it only received marketing authorisation in July 2022 and NICE guidance in August 2022 (TA821; with a 30-day implementation period[5]). It is therefore not commercially available in the UK for treatment of all individuals with Pompe disease. Therefore, it is not regarded in the CS as established NHS practice.

Treatment with all three alternative ERT is assumed to continue throughout a patient's lifetime, with no discontinuation or stopping rules applied.

EAG comments

4.3.4.1 Consideration of avalglucosidase alfa as a secondary comparator

The EAG does not agree with the company's exclusion of avalglucosidase alfa from the base case analysis. This is inconsistent with the NICE scope and current NICE guidance. The company's justification for excluding avalglucosidase alfa as the main comparator is that it is not commercially available in the UK and is unlikely to be used widely in clinical practice for a period after commercial availability. The EAG disagrees with this reasoning. Avalglucosidase alfa is expected to become commercially available in the UK from January 2023 and therefore will be widely available as a treatment option by the time any guidance on cipaglucosidase alfa in combination with miglustat comes into force.

Importantly, the EAG considers avalglucosidase alfa to be the primary comparator for the economic analysis. Clinical advice to the EAG suggests that is widely accepted that avalglucosidase alfa will replace alglucosidase alfa as the preferred first-line treatment option in patients with LOPD. All ERT-naive patients initiating therapy will therefore now begin on avalglucosidase alfa. Moreover, in ERT-experienced patients it is expected that patients will only switch treatments if they are experiencing a decline in health outcomes on alglucosidase alfa, the primary alternative treatment in this scenario will be avalglucosidase alfa given the clinical expectation that it is superior to, and will likely be prioritised over, alglucosidase alfa as a treatment for adults with LOPD.

4.3.4.2 Treatment sequencing of alternative ERT treatments

The model assumes that all patients will remain on the same ERT throughout their lifetime and does not consider treatment sequencing i.e., treatment switching owing to clinical reasons such as loss of treatment efficacy. Clinical advice to the EAG highlights that while haphazard switching between ERTs is not envisaged, switching is considered where patients are intolerant to treatment or experience lack of treatment efficacy. Patients are expected to remain on an ERT for a sufficient period to observe treatment efficacy, typically 18 months to 2 years.

In a full economic analysis, it is appropriate not only to consider active therapies as direct comparators, but also to consider the comparative cost-effectiveness of alternative treatment sequences. This allows the optimum positioning of active treatments to be established. For example, it may be more cost-effective to use cipaglucosidase alfa as a 2nd line treatment following use of avalglucosidase alfa. At the clarification step the EAG requested the company comment on the plausibility of patients' sequencing alternative ERT treatments. The company's response outlined that there is no clear treatment paradigm in LOPD, it is therefore unclear how individuals will sequence alternative ERT treatments. The company further highlights that incorporating treatment switching into the model would increase uncertainty, due to the lack of data on post-switch efficacy.

While the EAG agrees there is limited clinical experience of sequencing ERT, this does not imply that this will not occur in the future and the EAG notes that the modelled population from the available data for ERT-experienced patients is predicated on the idea that patients will sequence ERT treatments. The EAG considers this to be a potentially important omission that ideally should be explored in an appropriate scenario analysis. However, the EAG is cognisant of the lack of evidence to inform the comparative effectiveness of alternative ERTs and the complexities of appropriately capturing the impact of sequencing on both benefits and costs. Given these complexities, the EAG does not present analysis including sequencing but considers that the committee should be aware sequencing of ERTs is likely in clinical practice and may impact significantly on cost-effectiveness estimates.

4.3.4.3 Treatment stopping rules

Treatment stopping rules are not considered in the model. The European Pompe Consortium guidelines recommend that stopping treatment is considered where a patient experiences no improvement or stabilisation in muscle and/or respiratory function in the first 2 years of treatment, and can be restarted if faster deterioration is experienced after stopping than during treatment.[2] There has been an indication in long-term follow up data of the relevance of the EPOC stopping criteria, where a rapid decline after treatment discontinuation was not observed in some patients.[33] Stabilisation or improvement of clinical symptoms after restarting ERT has also been seen in some patients.[34] Clinical advice to the EAG also suggests that stopping rules are applied in practice where patients on ERT experience a continuous decline to the point they require ventilatory support, or where treatment does not add further to the patient's QoL. These stopping rules help to ensure treatment is used in patients who experience meaningful benefits thus optimising cost-effectiveness of treatment.

The EAG queried the company's reasoning for not including ERT stopping rules as per the EPOC consensus at the clarification stage. The company's response was that this exclusion is based on the lack of formal guidelines in the UK on stopping rules and that clinicians would typically only consider discontinuation due to adverse events which were considered negligible enough across the three treatment options.

4.3.5 Perspective, time horizon and discounting

Consistent with the NICE reference case,[5] the company's analysis adopted an NHS and Personal Social Services perspective and discounted costs and benefits at a rate of 3.5%. Alternative discount rates of 0% and 1.5% (applied to both costs and benefits) were also explored in scenario analysis.

In the base case analysis, a lifetime horizon of up to 106 years, was chosen to capture all relevant differences in costs and benefits between comparators in the executable model. Due to the patient

simulation approach, it is not possible to verify directly the proportion of patients alive beyond the modelled time horizon, but given the mortality rates applied beyond 100 years of age the EAG is satisfied that no simulated patients will remain alive. Scenario analysis also explored the impact of considering a 20-year time horizon.

4.3.6 Treatment effectiveness and extrapolation

As described in Section 4.3.2 the disease course of LOPD was captured through changes in FVC % predicted and 6MWD which determine transitions between the modelled health states. Changes in FVC % predicted and 6MWD associated with each alternative ERT were informed by evidence from several sources. The model time horizon was split into three periods: i) baseline to year 1; ii) years 1 to 3 (further split into years 1-2 and 2-3); and iii) year 3+. The modelled treatment effect is therefore the cumulation of changes in FVC % predicted and 6MWD across all three periods. Details of data assumptions made across each period are discussed in each of the subsequent sections. In line with the EAG's assertion that avalglucosidase alfa is a relevant comparator, assumptions made regarding the relative effectiveness of avalglucosidase alfa are also considered in detail. Table 22 summarises the change in FVC % predicted and 6MWD applied for each of the three time periods and the sources used to inform each comparison.

Table 22: Initial change from Baseline in FVC % predicted and 6MWD, Mean (SE)

	Cipaglucosidase alfa + miglustat			**Alglucosidase alfa**		
	FVC % predicted	**6MWD, m**	**Source**	**FVC % predicted**	**6MWD % predicted**	**Source**
Baseline to Year 1	-0.93% (0.007)	20.79 (4.639)	PROPEL	-3.95% (0.008)	7.24 (6.621) (absolute m)	PROPEL
Year 1 to Year 2	[redacted]	[redacted]	Weighted average of data ERT-experienced and ERT-naïve groups from ATB200-02	-0.9% (0.001)	1.4% (0.003)	Semplicini et al.[9]
Year 2 to Year 3	[redacted]	[redacted]		-0.9% (0.001)	1.4% (0.003)	
Beyond Year 3	Assumed [redacted] of progression than with alglucosidase alfa			-0.9% (0.001)	-2.3% (0.003)	
	Avalglucosidase alfa relative to cipaglucosidase alfa + miglustat					
	FVC % predicted		**6MWD**		**Source**	
Baseline to Year 1	[redacted]		[redacted]		ML-NMR ITC	

Beyond Year 1			Semplicini et al.[9]
Scenario #1	[redacted]	[redacted]	
Scenario #2	[redacted]	[redacted]	
Scenario #15	[redacted]	[redacted]	

Abbreviations: 6MWD: six-minute walk distance; CrI: credible interval; FVC: forced vital capacity; SE: standard error.

4.3.6.1 Year 1 treatment effect

For period 1 (baseline to year 1) the data used to inform relative treatment effects was dependent upon the comparator treatment being considered. In the alglucosidase alfa and cipaglucosidase alfa comparison, the PROPEL trial results at week 52 informed the change from baseline in FVC % predicted and 6MWD, while for the avalglucosidase alfa comparison the ML-NMR discussed in Section 3.4 was used to inform the relative effects. As previously described the ML-NMR includes evidence from the randomised trials PROPEL, LOTS and COMET, as well as non-randomised evidence from NEO1/NEO-EXT and ATB200-02.

EAG comments

The EAG is satisfied that PROPEL is the most appropriate source of evidence to inform the alglucosidase alfa and cipaglucosidase alfa comparison. However, as previously raised in Section 4.3.3.2, the EAG considers it inappropriate to pool data from ERT-naive and ERT-experienced patients, and considers it more appropriate to split the populations to reflect differences in the characteristics and relative effectiveness of alternative treatments. Subgroup analysis of PROPEL shows there are differences in baseline characteristics between these groups (see Section3.3) and indicates that [redacted] 3.4 [redacted] Moreover, the pooling of ERT-naïve and ERT-experienced patients has important consequences when considering the indirect comparisons with avalglucosidase alfa. These issues are more transparently explored when the populations are considered separately.

Regarding the comparison between avalglucosidase alfa and cipaglucosidase alfa, the EAG considers the company approach of using an ML-NMR ITC to be broadly appropriate. However, as discussed in detail in Section 3.4, the EAG considers that it is inappropriate to include the non-randomised trials in the ITC. Further, as previously outlined, the EAG considers the results of this analysis including the non-randomised trial evidence to be inconsistent with the available evidence and to lack face validity. The EAG considers the ML-NMR sensitivity analysis presented excluding the non-randomised studies to be to be the most methodologically appropriate approach, though the EAG does have specific concerns regarding the specification of the ML-NMR and how results have been generated for the ERT-naive and ERT-experienced populations. As previously discussed in Section 3.4, the

EAG considers that the covariate model used in the ML-NMR is mis-specified and considers it more appropriate to include duration of previous ERT as a dummy variable indicating whether patients are ERT-naive or ERT-experienced. Moreover, in generating the results for the ERT-naive and ERT-experienced populations, the covariate adjustment should reflect all differences in patient characteristics between these two groups and not just the partial effect of duration of treatment. In Section 6 the EAG explores the impact of using estimates from the presented sensitivity analysis excluding non-randomised studies. However, as indicated in Section 3.4, further analysis is required to address the EAG concerns regarding the specification of the covariate model and the estimation of treatment effects in ERT-naïve and ERT-experienced populations.

4.3.6.2 Subsequent changes in 6MWD and FVC % predicted: alglucosidase alfa comparison

Subsequent changes in 6MWD and FVC % predicted were modelled in two parts, period two and period three. Period two considered year 1 to 2 and year 2 to 3, while period three considered year 3 onwards.

In period two, data from ATB200-02 and Semplicini et al.[9] respectively informed outcome changes for cipaglucosidase alfa in combination with miglustat and alglucosidase alfa. In the cipaglucosidase alfa arm, data from ATB200-02 was adjusted to improve internal consistency. This was done to account for differences in the proportion of ERT-naive and ERT-experienced patients in PROPEL and ATB200-02. Other differences between the studies were not adjusted for. Semplicini et al.,[9] used to inform changes in the alglucosidase alfa arm, presents a linear mixed effects models and explores single phase and two-phase models. The former assumes a constant slope while the latter splits follow up into two time periods and allows for different rates of changes in these two periods. Results of the analysis presented in Semplicini et al.[9] suggested that a single-phase model was most appropriate for FVC % predicted, while a two phase model was most appropriate for 6MWD with a knot-point at 2.2 years. To align with this analysis, changes in 6MWD in period two (years 1 to 3) used the reported co-efficient for the first phase (baseline to 2.2 years). Values sourced from Semplicini et al[9] were used as observed, the modelled treatment effect in this period is therefore based on a naïve non-randomised comparison.

In the modelled period three (year 3 onwards) data from Semplicini et al.[9] is again used to inform changes in outcomes (6MWD and FVC % predicted) for the alglucosidase alfa arm. Similar to the first period, the results from the linear mixed effects regression model described above were used. To account for the two-phase model used for 6MWD, changes reflected the reported co-efficient from the second phase (2.2 years onwards). Because a single-phase model (with a constant slope) was used for FVC % predicted, modelled changes for this outcome in both period two and three of the economic model are the same. Long term decline in outcomes for cipaglucosidase alfa in combination with miglustat were also informed using the linear mixed effects regression model reported in Semplicini

et al.[9] However, a hazard ratio was applied assuming a [redacted] rate of decline. This hazard ratio was not informed by any data and appears to have been elicited at one of the clinical advisory boards conducted by the company. It is otherwise unclear why this specific value was selected. Scenario analysis also explored several alternative hazard ratios, a [redacted] rate and an [redacted] of progression.

EAG comments

The EAG has significant concerns regarding the use of non-randomised evidence to inform treatment effects between year 1 and 3 and considers this a key area of uncertainty. The applied changes in FVC % predicted and 6MWD imply an increasing treatment effect and divergence in the trajectory of these outcomes. The magnitude of relative treatment effects applied in this 2nd period (year 1 to 3) is an important driver of the overall cumulative treatment effect applied in the first 3 years of the model as can be seen from Table 22. The data informing this comparison is, however, limited by small sample size in ATB200-02 and concerns about the comparability of the recruited populations. As highlighted in Section 3.3, this comparison relies on comparing a trial population with observational data and there are clear differences in the characteristics of respective populations. For example, Semplicini et al.[9] includes only ERT-naive patients while ATB200-02 is a mixed population. There are also important differences in how data from the two studies are analysed. The data from ATB200-02 is adjusted for the mix of ERT-naive and ERT-experienced patients but is otherwise used as observed, while data from Semplicini et al.[9] are based on the applied linear mixed effects regression models. The estimated treatment effects applied in this second period are therefore highly uncertain, with the magnitude and direction of bias resulting from any confounding bias unknown. Given these sizable uncertainties, the EAG questions the validity of informing treatment effects using this non-randomised comparison and notes that in TA821 no further treatment effect was assumed beyond year 1. A more conservative and consistent approach, therefore, would be to assume equivalence in outcomes beyond year 1. Exploratory analysis can then be used to assess the impact of this assumption.

Regarding the model treatment effects applied beyond year 3, the EAG considers the use of Semplicini et al.[9] both reasonable and appropriate given the lack of alternatives. However, the treatment effect applied to the cipaglucosidase alfa arm is a significant area of uncertainty. As already highlighted this is not directly informed by any data and is an arbitrary value which speculates that the short-term benefits observed in PROPEL will translate into continued benefits.

The EAG considers the existence of a durable long-term effect plausible given the evidence from PROPEL and to be indirectly supported by results from ATB200-02 which seem to suggest durable improvements in both 6MWD and FVC % predicted. However, ATB200-02 is a small study and the results are difficult to fully interpret due to the single arm design. It is therefore difficult to draw

strong inferences based on this data and it is unknown whether any treatment effect (should it exist) will persist long-term.

It is also notable, given the results from ATB200-02 (which indicate no decline in outcomes), that the company explores only a small range of hazard ratios all of which assume relatively modest treatment effects. The EAG therefore does not consider the presented scenario analysis to have fully explored the uncertainty in the long-term treatment effect. This is important as the relationship between this parameter and the cost-effectiveness of cipaglucosidase alfa combined with miglustat is not straightforward and improved effectiveness can result in the deterioration of cost-effectiveness metrics e.g. increased ICERs. The EAG therefore explores additional scenario and sensitivity analysis in Section 6.

4.3.6.3 Subsequent changes in 6MWD and FVC % predicted: avalglucosidase alfa comparison

The assumptions applied in the comparison between cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa were not clearly documented in the CS and were not provided following a clarification request. Information provided in the executable model however has allowed the EAG to deconstruct the company's approach. The approach taken to modelling subsequent changes in 6MWD and FVC % predicted differs from that used in the alglucosidase alfa comparison. Specifically, the model does not split the remaining time horizon and instead the same rate of decline is assumed across periods two (year 1 to 3) and three (year 3 onwards), i.e. the same values are used from year 1 onwards. The approach used is similar to that applied in year 3+ for the alglucosidase alfa comparison, such that changes in FVC % predicted and 6MWD for both treatment arms are informed by data from Semplicini et al.[9] Consistent with the assumptions made in the alglucosidase alfa comparison a hazard ratio of [redacted] is applied to the cipaglucosidase alfa arm of the model. The company considers three scenarios when modelling avalglucosidase alfa as a comparator, each using alternative hazard ratios applied to the Semplicini et al.[9] data. The three scenarios consider a hazard ratio of [redacted] and [redacted]. Note across all scenarios, the hazard ratio applied to cipaglucosidase alfa arm is [redacted] therefore the first two scenarios assume that the subsequent rate of decline will be [redacted] in the cipaglucosidase alfa arm than in the avalglucosidase alfa, while the last assumes an [redacted] of decline. As in the alglucosidase alfa comparison, the hazard ratios applied are not informed by any data.

EAG comments

The EAG is puzzled by the inconsistent approach to modelling subsequent changes in 6MWD and FVC % predicted of cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa, and notes that functionality to model these changes similar to the way it was modelled for cipaglucosidase alfa in combination with miglustat and alglucosidase alfa is included in the model (using data from NEO1 and NEO-EXT). Using this data would have been more consistent with the approach adopted

in the alglucosidase alfa comparison. However, as discussed in Section 3.3 there are important differences between ATB200-02 and NEO1/NEO EXT. Consequently, the estimation of a relative treatment effect using these single arm studies is likely to be subject to considerable uncertainty and to be at high risk of bias. The broad approach of using data from Semplicini et al.[9] is therefore reasonable. The EAG however notes that, unlike the alglucosidase alfa comparison, the model does not account for improvements in 6MWD observed up to year 2. Other than simplicity, it is unclear why a different approach is adopted and is notable that declines modelled are inconsistent with data from both ATB200-02 and NEO1/NEO EXT.

With regards to the models hazard ratios, the EAG reiterate the discussion above that the values applied are largely arbitrary and it is unclear if this reflects the long-term benefits of treatment with cipaglucosidase alfa in combination with miglustat. The EAG, does take issue with the range of hazard ratios applied in the avalglucosidase alfa arm, which either assume avalglucosidase alfa is [redacted] to, or [redacted] to cipaglucosidase alfa in combination with miglustat. There is no *priori* reason to believe this is the case, and this is not supported by the RCT evidence. [redacted] In line with the alglucosidase alfa comparison, the EAG explores a range of further scenario and sensitivity analysis to explore uncertainty in the long-term trajectory of patients.

4.3.6.4 Mortality

Mortality rates applied in each health state are informed by general population rates adjusted for age and sex. To account for disease related excess mortality, standardised mortality ratios (SMRs) are applied to several health states. These reflect increasing mortality risks in patients with more severe disease. The applied SMRs applied in the base case economic analysis are presented in Table 23 and are informed by data from Gungor et al.[35] which is an international observational study of 268 LOPD patients.

Table 23: Hazard ratios (mortality compared to general population mortality; adapted from Table 49 of CS)

Health state	Hazard ratio
No wheelchair use or respiratory support	1.00
Intermittent mobility support	2.87
Wheelchair dependent	2.87
Intermittent, non-invasive respiratory support	2.05
Intermittent mobility and intermittent, non-invasive respiratory support	5.32
Wheelchair dependent and intermittent, non-invasive respiratory support	5.32

Wheelchair and invasive respiratory support dependent	5.32

The company's approach to modelling mortality does not directly attribute a specific survival advantage to any of the modelled treatments. However, mortality benefits are generated indirectly due to the modelled relative advantage of cipaglucosidase alfa in terms of both the short and long-term rates of disease progression. Consequently, the modelled long-term survival benefits are inferred from the short-term evidence on FVC % predicted and 6MWD. In the company base case analysis, the application of the increasing SMRs with increased disease severity leads to a positive life year gain of [redacted] years compared with alglucosidase alfa and a [redacted] compared with avalglucosidase alfa.

EAG comments

As described in Section 3.2, long-term data on the relative effectiveness of alternative ERTs is limited, and it is not possible to draw inferences about survival benefits. Evidence from Gungor et al., used to inform the modelled SMRs, however, shows a clear relationship between disease severity and mortality such that we would expect a positive correlation between any improvements in FVC % predicted/6MWD and long-term survival. The EAG therefore considers the application of differential mortality rates across health states to be reasonable and reflective of clinical experience. The EAG, however, highlights two points.

Firstly, mortality rates have a significant impact on total costs as they determine the duration of treatment and therefore total drug acquisition costs. They also impact the length of time spent in the *wheelchair and respiratory support-dependent* health state, where very high health state costs are applied. Uncertainty in SMR values applied therefore can have a disproportionate impact on cost-effectiveness estimates. The model is particularly sensitive to the SMR applied in the *wheelchair and respiratory support-dependent* health state. In this regard, the EAG notes that the Gungor et al. study does not differentiate between levels of respiratory support. The base case model, therefore, applies the same SMR regardless of the level of respiratory support required. To explore uncertainty in the SMR value applied to the *wheelchair and respiratory support-dependent* health state, the EAG presents an additional sensitivity analysis in Section 6.

Secondly, it is important to emphasise that there is significant uncertainty associated with modelled mortality benefits and that the existence of these benefits is contingent upon several assumptions. One, it requires there to be a meaningful difference in the relative effectiveness of the alternative ERTs. Two, it requires that these benefits are durable i.e. it results in a sustained difference in the long-term trajectory of patients. Three, that there is a positive relationship between the rate of disease progression and survival. On all three counts, there is significant uncertainty. As discussed in Section 3.2 the short-term relative benefits of alternative ERTs are difficult to establish given the current

evidence and in particular, the relative effectiveness of cipaglucosidase alfa and avalglucosidase alfa is highly uncertain. Further, there is little evidence to inform whether these benefits are sustained over the longer term and it is plausible that these early benefits will diminish over time. While a positive correlation between disease progression and mortality is highly plausible and supported by the Gungor et al. study, this is not a validated surrogate relationship and it is unclear whether the SMRs applied truly reflect the survival benefits associated with delaying disease progression.

4.3.6.5 Adverse events

The company did not model adverse events. The company justify this assumption because the AE profile across alternative ERT is likely to be similar and any differences are unlikely to materially impact cost-effectiveness estimates. This aligns with assumptions made in TA821 in where AEs were not modelled.

EAG comments

The EAG considers the exclusion of AEs from the model reasonable given the similarities between treatments and agrees that their inclusion would not materially impact model outcomes. Clinician input suggests that inclusion of miglustat is not expected to lead to increased adverse reactions as the dose used is significantly less than what is prescribed for Gaucher disease and Niemann-Pick type C disease.

4.3.7 Health related quality of life

4.3.7.1 Health state utilities

As described in Section 4.1, the company conducted an SLR to identify HRQoL studies for adult patients with Pompe disease. In the SLR, they identified 22 studies that met the eligibility criteria from which five reported EQ-5D utility values. None of the five studies reported utilities for the full range of health states in the progression of LOPD [28, 36-40] therefore the company did not use the utility values reported in the company base case analysis.

The company collected EQ-5D-5L data from PROPEL at repeated intervals (Screening and Weeks 12, 26, 38, and 52).[8, 41] These EQ-5D-5L values were mapped to EQ-5D-3L values using the Van Hout algorithm. However, these data are not used to inform the utility values in the company's base case model. The company argues that the data could not be used because most study participants had not reached the severe health states requiring invasive respiratory support or a combination of mobility and respiratory support at the 52-week trial follow-up period.

Health state utilities in the economic analysis were instead estimated from HRQoL data collected in a vignette study conducted by the company. Health state vignettes describing the quality of life of adults with LOPD were developed using PROPEL study participants and a targeted literature review

of the clinical, economic, resource and utility evidence in Pompe disease. The resultant vignette descriptions were refined and validated using interviews conducted with 12 adult LOPD patients and 2 clinicians specialised in treating people with LOPD. Seven vignettes were developed and validated to align with those in the economic model. The seven vignettes were evaluated through one-hour interviews with 100 members of the UK general public. The 100 participants were selected through convenience and snowball sampling. The 100 participants were recruited to be representative of UK demography based on the most recent UK census data.[42] This sample had a mean age of 42.9 (SD: 17.7) years and was 51% male.

During the interview, the participants evaluate the vignettes, with data collected using the EQ-5D-5L questionnaire, and mapped to the EQ-5D-3L using the Hernández-Alava et al. algorithm as recommended by NICE guidelines.[43, 44] The company also implemented a time trade-off (TTO) assessment with the 100 participants, to estimate utilities for the health state vignettes. In the submitted company model, the company base case analysis was based on the vignette data collected using the EQ-5D-5L questionnaire with an additional scenario implemented based on published utility values from Kanters et al. and Landfeldt et al. studies.[38, 45] The health state utilities are shown below in Table 24.

Table 24: Health state utility values (adapted from clarification response Table 40, Page 49)

Health state	Amicus Vignette Study (Base Case)	Published values	PROPEL	TA821 submission[d]
No wheelchair use or respiratory support (0–5 years alive from treatment initiation)	0.61 (0.12)	0.74 (0.15)[38]	[redacted]	0.652
No wheelchair use or respiratory support (6–15 years alive from treatment initiation)		0.70 (0.16)[38]		
No wheelchair use or respiratory support (>15 years alive from treatment initiation)		0.69 (0.23)[38]		
Intermittent mobility support	0.43 (0.19)	0.67 (0.21)[38]	[redacted]	-
Intermittent, non-invasive respiratory support	0.36 (0.19)	0.61 (0.26)[38]	-	0.614
Intermittent mobility support and intermittent, non-invasive respiratory support	0.29 (0.24)	[redacted]	-	0.545
Wheelchair dependent	0.11 (0.23)	0.146 (0.010)[45,b]	[redacted]	0.504
Wheelchair dependent and intermittent, non-invasive respiratory support	0.08 (0.22)	[redacted]	-	0.397
Wheelchair and invasive respiratory support dependent	-0.08 (0.22)	[redacted]	-	-

a Assumed values were used as no utilities for individuals that required both mobility and respiratory support were identified. These assumptions were generally viewed as appropriate for the scenario analysis by clinicians. Values were ordered to ensure logical values were produced for each iteration (i.e., the utility value of a particular health state could not be higher than an 'earlier' state). b Based on utilities in Duchenne muscular dystrophy. c Utility predictions extrapolated for severe health states (i.e. mobility dependent) from PROPEL data would be outside of sample estimates and consequently should be treated with caution. d EAG preferred health state values. Abbreviations: EQ-5D-5L: EuroQol 5 Dimension.

At points for clarification, the EAG asked for the EQ-5D data from PROPEL study. While these utility values are not used in the company's base case model, a scenario based on these data was provided. Details of values generated from the PROPEL data are shown in Table 24: Health state utility values (adapted from clarification response Table 40, Page 49), note values for all health states are not available and therefore the scenario analysis presented at the clarification stage supplemented trial sourced values with values from the vignette study.

EAG comments

Use of Non-reference case methods

The EAG has concerns regarding using the utility values generated from the vignette study given the availability of published utility values and EQ-5D data collected in PROPEL. The EAG considers that

the utilities applied in the base case model are unfit for decision making purposes, and are inconsistent with the NICE reference case. The value set captures only public preferences and includes no explicit consideration of the quality of life of patients themselves. In adopting this method, the company have failed to acknowledge the lived experience of patients and caregivers.

The NICE reference case guidance recommends using EQ-5D reported by patients, and when this is not possible, it should be obtained via a proxy with experience of the condition, e.g. from caregivers in preference to healthcare professionals. Where such values are unavailable the NICE reference case states utilities should be sourced from the published literature.[44] NICE TSD 11 states that vignettes and patient own health state valuations do not meet the NICE Methods Guidance for alternatives to EQ-5D. These only have a role where there are no data from validated HRQoL measures.

The intention of NICE cost-utility analyses is not to directly model public preferences, but rather to represent the patient's own perceived quality of life through the lens of public preferences via a validated tool such as EQ-5D. This also reflects the desire of decision-makers to measure health effects across appraisals on the same scale. Notwithstanding the small sample size and conduct of the company's utility elicitation exercise, in bypassing patients and caregivers entirely the cost-effectiveness analysis as currently presented cannot therefore claim to represent their perspective.

Methods and results of the utility study

Only limited details on the methods used to elicit the utilities are presented in the CS. For example, while the company provides some details of how the vignettes were generated the content of the vignettes was not supplied to the EAG. Nor has the company provided a detailed report of the results to allow inspection of the consistency of responses. However, based on what is reported the EAG has several concerns.

The first issue relates to the population recruited to evaluate the vignettes which is described as both a convenience sample and one designed to be representative of the UK population. The EAG considers that the use of a convenience sample is inconsistent with the latter and is unclear whether the representativeness of the recruited sample was evaluated.

The second issue relates to the sample size used in the pilot study to refine the vignettes. While the NICE reference guidance has not provided any sample size estimates for pilot studies for vignettes, standard practice recommends that a sample of at least 20 respondents would be sufficient unless saturation is reached.[46] The pilot study in the company's vignette study had 12 respondents recruited via patient advocacy organisations. No matter how good the qualitative work, the vignettes will not be able to fully reflect outcomes experienced by patients in each vignette state,[46] therefore a larger

respondent sample reduces the bias to inadvertently omit details that are important to some patients in the final vignette descriptions.

Validity of generated values and consistency with other sources

The EAG has substantive concerns regarding the validity of the utilities as currently implemented in the company's model, which imply a low quality of life across the majority of the modelled health states. Indeed, the lives of patients on alglucosidase alfa in the company's base case model generate just [redacted] discounted QALYs over [redacted] discounted life years, implying that the average utility is just [redacted]. If Pompe disease patients indeed experienced such poor quality of life as depicted by the health state values, this would be expected to be better reflected in the testimony of clinicians and patients.

The EAG notes that the utility derived from the vignette study are substantially lower than those obtained from any of the other source. Using the published values as an exemplar, the average difference is [redacted] with differences for individual health states ranging from between [redacted] and [redacted]. It is of great concern that the values generated from the vignettes are not consistent with those obtained from the clinical trial, suggesting a systematic bias in the results of the vignette study. Moreover, the EAG questions the face validity of values generated by the vignette study. While the EAG recognises the difficulties of living with Pompe disease, it is rare to apply utility values that are significantly below 0.50 and rarer still to assign health states with negative utility (implying a quality of life worse than death). Application of very low health state utility is likely to overstate the quality of life impact of more effective treatments and given the assumptions in the company's base case is likely to overstate the benefits of cipaglucosidase alfa in combination with miglustat. Given the outlined issues with the utility value from the vignette study, the EAG favours the utility values derived from the literature from the PROPEL study and notes that precedent from the only other previous appraisal in this disease area (TA821) supports this position.[5] The uncertainty around this parameter is explored further in Section 6.

4.3.7.2 Age adjustment

The model applies an age adjustment to all utility values used in the model which accounts for the impact of ageing on HRQoL. The adjustment is applied using a multiplicative approach in which a utility decrement is estimated relative to the utility of a 42.9-year-old (mean age in the Amicus Vignette study) in the general population using data from Ara and Brazier.[47] This decrement is then subtracted from each health state utility value to generate an age-specific value. An alternative scenario was conducted where a utility decrement is estimated relative to a 51-year-old (mean age in the Kanters et al. study[38]) in the general population using data from Ara and Brazier.[47]

EAG comments

The EAG considers the application of an age-related decrement appropriate, given the long time horizon considered in the economic analysis and the lifetime benefits predicted by the base case analysis compared to alglucosidase alfa and avalglucosidase alfa.

4.3.8 Resources and costs

The CS provided a description of resource use and costs applied in the model. This included drug acquisition and administration costs, some patient management costs, and costs associated with respiratory support and wheelchair use. In the original submission, the company did not include costs associated with management of adverse events, and some patient management costs such as physiotherapy. In response to points for clarification, the company confirmed that the original analysis also included additional health-state dependent patient management costs in the form of non-invasive ventilation support assessments and respiratory physiology consultant appointments.

The company used NHS reference costs 2020/2021, the British National Formulary (BNF) and Personal Social Services Research Unit (PSSRU) 2021 [48-50] to derive the cost values implemented in the model.

4.3.8.1 Confidential pricing arrangements

The EAG notes that there is a confidential commercial arrangement in place for avalglucosidase alfa, one of the comparator regimens. The treatment acquisition costs used in the analyses presented in the CS (reproduced in Section 5.1 and Section 6), include only the confidential pricing agreement for cipaglucosidase alfa in combination with miglustat. Cipaglucosidase alfa currently has a [redacted].

Table 25 presents details of which comparator and subsequent treatments have confidential prices which differ from the publicly available list prices used to generate the results in this report. These prices were made available to the EAG and were used to replicate **all** analyses presented in the EA Report for consideration by the Appraisal Committee. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices were correct as of 5th December 2022. Note alglucosidase alfa does not have a PAS discount.

Table 25: Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of confidential arrangement
Cipaglucosidase alfa	Simple PAS
Avalglucosidase alfa	Simple PAS

4.3.8.2 Drug acquisition costs

Acquisition costs for cipaglucosidase alfa in combination with miglustat was based on 105 mg vial cipaglucosidase alfa at a dose of 20mg/kg of body weight administered once every two weeks, per its draft SmPCs. Miglustat was administered at a dose of 195 mg (3*65 mg hard capsules) for subject weighing ≥40 kg to <50 kg or 260 mg (4*65 mg hard capsules) for subject weighing ≥50 kg, per its draft SmPCs. The specific dosages and administration procedures for the intervention and comparators are described in Section 4.3.4.

The unit cost per 105 mg vial associated with cipaglucosidase alfa is [redacted] a [redacted] discount on the list price of [redacted]. The miglustat acquisition cost is [redacted] for a pack of 4 hard capsules of 65 mg. In line with the individual patient simulation modelling approach, costs applied vary according to patient characteristics, average annual treatment cost for cipaglucosidase alfa modelled are [redacted] and [redacted] for miglustat.

The acquisition cost associated with alglucosidase alfa is £356.06 per 50 mg vial. The list price of avalglucosidase alfa is currently confidential, the company base case therefore assumes the per mg costs of avalglucosidase alfa align with alglucosidase alfa such that a cost of £712.12 per 100mg vial is applied in the model. The average annual treatment cost for both alglucosidase alfa and avalglucosidase alfa are [redacted]

EAG comments

Provision of miglustat

The EAG notes that the 65 mg capsules are not currently available in the UK NHS. Current provision in the NHS is in the form of 100 mg hard capsules with pack sizes 21, 84 or 126 hard capsules. The 65 mg miglustat capsules necessary for the intervention are provided by the company. Therefore, the reimbursement decision and Patient Access Scheme (PAS) arrangements should reflect the fact that both drugs are provided by the company at the stated price and not just cipaglucosidase alfa. From the BNF, the 84-pack size is available from £3,392 to £3,934.17 for a cost per mg of between £0.40 and £0.47, this compares to a cost of [redacted] at the proposed list-price used in the company base case model.

4.3.8.3 Treatment administration costs

For all three alternative ERTs, it was assumed that the first 3 treatments would be administered in a hospital and subsequent treatments administered at home with a nurse. The unit cost per hospital administration was £281.11 based on NHS Reference Costs 2020/21 (Outpatient Deliver Simple Parenteral Chemotherapy at First Attendance, Outpatient). For the home administrations, 90% of the patients are assumed to require nurse support while 10% are assumed to be able to self-infuse with minimal nurse support. The unit cost per hour for the nurse is estimated to be £55.00 informed by the

PSSRU and was based on a Band 6 nurse. For the 90% of the patients requiring nurse support, nurse time to reconstitute the infusion was assumed to be 5.2 hours for alglucosidase alfa and 4.7 hours for cipaglucosidase alfa and avalglucosidase alfa. Costs applied were therefore £286.00 for alglucosidase alfa and £258.50 for cipaglucosidase alfa and avalglucosidase alfa. For the 10% of the patients self-infusing and requiring minimal nurse support, 1.38 hours nurse time and 0.88 hours nurse time are assumed for reconstitution and infusion respectively leading to an estimated total cost of £75.63 for alglucosidase alfa and a cost of £48.13 for cipaglucosidase alfa and avalglucosidase alfa. These nurse times were informed by TA821 assuming that cipaglucosidase alfa with miglustat treatment administration costs are equal to those for avalglucosidase alfa.

EAG comments

The EAG is satisfied with the administration costs applied in the model.

4.3.8.4 Health state unit costs

The model included costs associated with equipment for respiratory support and wheelchair use. The annual estimated cost for non-invasive ventilation was £1,908 informed by Dretzke et al. and in line with TA821. Invasive ventilation was assumed to have an upfront cost of £133,277 and annual cost of £142,790 informed by Noyes et al. 2006.[51]

Intermittent mobility support through the use of a manual wheelchair was estimated to have an upfront cost of £703.64 and an annual cost of £49.08 informed by NHS reference costs 2020/21 (Repair and Maintenance, All Needs, Manual, WC07 and WC09). Wheelchair dependent costs were assumed to include the upfront costs for a powered wheelchair of £1,374.74 informed by NHS reference costs 2020/21 (Wheelchair services adults, Equipment, High need, Powered, WC09), home adjustment of £30,000 and hoist of £826.48 informed by TA821. In addition, wheelchair dependent costs are assumed to have an annual cost of £207.28 informed by NHS reference costs 2020/21 (Wheelchair services adults, Repair and Maintenance, All Needs, Powered, WC10).

EAG comments

The EAG acknowledges that the costs for invasive respiratory support used in the model are consistent with the previous appraisal (TA821). However, the EAG also notes that ventilation costs are an important driver of total costs, particularly in the alglucosidase alfa comparison. The estimated home invasive ventilation costs are informed by data on paediatric populations, published in 2006.[51] This source data is therefore old and does not match the population under consideration. The EAG has identified several studies evaluating the costs of invasive home mechanical ventilation though none are UK estimates. A Canadian study of 45 adult patients (various conditions, none indicated as POMPE disease) receiving invasive ventilation estimated median annual care costs of CAD 62,952 (£37,838) while a Czech study using healthcare insurance data estimated an average annual cost of

CZK 1,588,371 (£57,091).[52, 53] Differences across health systems and uncertainties in costing methodology mean that these costs are not transposable to a UK setting, however, they strongly suggest that modelled costs are a significant overestimate. The EAG considers there to be substantive uncertainty in the costs applied and explores the impact of using alternative costs in Section 6.

4.3.8.5 Patient management costs

All patients were assumed to attend regular six-month follow-up outpatient appointments. The unit cost per visit for this consultant neurologist led appointment as informed by NHS reference costs 2020/21 was £215.72, leading to a total annual cost of £431.44. This was the only patient management cost incurred by all patients.

In addition to the follow-up appointment visit, those with non-invasive ventilation support incurred one non-invasive ventilation support assessment a year at a cost of £194.68 while those with invasive ventilation support incurred one respiratory physiology consultant led appointment a year at a cost of £168.77. Both these costs were informed by NHS reference costs 2020/21. These were the only additional patient management costs incurred due to ventilatory or mobility support.

EAG comments

The patient management costs did not include hospital inpatient visits (elective and non-elective), outpatient appointments, attendances at accident and emergency departments, primary care appointments and sundry pharmaceuticals. At points for clarification the EAG noted the omission of these patient costs and requested that the company provide an additional scenario aligning health state costs with TA821. The company did not provide a scenario in their response, stating that there is lack of robust data to inform treatment-related difference in healthcare resource use beyond those already modelled. The company considered it unlikely that the inclusion of additional non-health state dependent management cost items would materially impact cost-effectiveness estimates. The EAG accepts that the addition of non-health state dependent management costs is unlikely to be decisive driver of cost-effectiveness estimates, but considers consistency with the assumptions accepted in TA821 to be a reasonable approach in the absence of more informed alternatives and provision of the requested scenario would have better illustrated the company's position (that the addition of these costs does not fundamentally alter cost-effectiveness estimates).

5 COMPANY'S COST EFFECTIVENESS RESULTS

This section summarises the results of the company's updated base case as presented in the clarification response. The results presented in the following sections include the proposed PAS discount for cipaglucosidase alfa. Results inclusive of available commercial arrangements for the comparator treatments are provided in a confidential appendix to the EAG report.

The proposed list price for cipaglucosidase alfa is [redacted] per 105 mg vial of cipaglucosidase alfa. [redacted], reducing the cost to [redacted] per vial. The applied cost per pack of 4 of 65mg capsules of miglustat is [redacted]The total annual cost for cipaglucosidase alfa in combination with miglustat based (assuming the average patient weight in PROPEL of [redacted] is [redacted].

5.1 Base Case Results

The company presents a series of ICERs for cipaglucosidase alfa in combination with miglustat for a pooled ERT-naïve and ERT-experienced patient population. The use of a pooled population in estimating costs and effects of treatment implies that the company does not view these populations as separate patient groups. As previously discussed in Sections 3.5 and 4.3.3, the EAG considers this characterisation as inappropriate. The EAG deems there to be two subgroups of relevance as listed in the NICE scope: i) people who have not received prior treatment with alglucosidase alfa (ERT-naive), and ii) people who have received prior treatment with alglucosidase alfa (ERT-experienced).

The EAG presents results in the following sections as pairwise comparisons, given that different assumptions are applied in the alglucosidase alfa and avalglucosidase alfa comparisons in the company base case, hence incremental results would not be possible. The results of the company's updated base case cost-effectiveness analysis are summarised in Table 26. Compared with alglucosidase alfa, the results suggest cipaglucosidase alfa in combination with miglustat is associated with lower costs (incremental cost of [redacted]) and greater benefits (QALY difference of [redacted]) yielding an ICER of [redacted] per QALY gained. This results in a net health benefit (NHB) for cipaglucosidase alfa in combination with miglustat of [redacted] and [redacted] at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY, respectively.

The company did not include avalglucosidase alfa in the base case and only included this as a secondary comparator in scenario analyses based on commercial unavailability. As highlighted in Sections 2.3, 4.3.4 and 4.3.6, the EAG does not agree with the inclusion of avalglucosidase alfa as a secondary comparator as this is inconsistent with the NICE scope and given it already has positive NICE guidance. The EAG considers avalglucosidase alfa as the primary comparator as it is expected

to become widely commercially available from early 2023 and will therefore be widely available as a treatment option and likely prioritised over alglucosidase alfa in treatment of adults with LOPD.

The overall results suggest that the cost-effective treatment option is cipaglucosidase alfa in combination with miglustat assuming a WTP threshold of £20,000 per QALY.

Table 26: Company updated base case: cipaglucosidase alfa in combination with miglustat vs alglucosidase alfa

Technologies	Total costs (£)	Total LYG (diss)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/ QALY)
Cipaglucosidase alfa + miglustat	[redacted]	[redacted]	[redacted]					
Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit.								

5.2 Company's sensitivity analyses

5.2.1 Probabilistic Sensitivity Analysis

The EAG requested several updates to the company's economic model at the clarification stage. The EAG asked that the company update the model so that baseline characteristics are determined using a joint distribution, rather than independent distribution, to account for correlation in measures such as the baseline 6MWT and FVC % predicted. The company was also requested by the EAG to use a single random draw across all treatments per parameter to reduce stochastic error and speed up the model runtime. The company updated the model to apply two random seed values for the normal distribution of relevant baseline characteristics that are likely to be correlated. The company combined these baseline characteristics into two groups: i) patient population age, height, and weight, and ii) 6MWT and FVC % predicted at Baseline. However, the individual baseline characteristics remain sampled based on their respective individual normal distributions informed by PROPEL trial data.

The company truncated distributions so that baseline characteristics remain [redacted], as requested by the EAG. The company also amended the model so that only baseline characteristics varied as part of the first-order iterations and variability determined using the standard error as per the EAG request. Uncertainty around parameters inputs were explored as part of the PSA rather than the first-order iterations in the

updated model. Results from the company's updated model are presented in the following sub-sections.

The EAG performed probabilistic analyses on the company's updated base case model, running 30,000 iterations for each comparison. These results are presented in Table 27. The mean probabilistic ICER for cipaglucosidase alfa in combination with miglustat compared to alglucosidase alfa was [redacted] than the deterministic ICER. Compared to alglucosidase alfa, the probability of the cipaglucosidase alfa in combination with miglustat being cost effective was [redacted] and [redacted] at WTP thresholds of £20,000 and £30,000 per QALY, respectively. Figure 2 and Figure 3 present the cost-effectiveness scatter plot and cost-effectiveness acceptability curve from the probabilistic sensitivity analysis.

Table 27: Company updated base case results: average probabilistic results

					Probability of being cost effective	
	Incremental costs	**Incremental QALYs**	**ICER**	**NHB (£20,000/QALY)**	**£20,000/QALY**	**£30,000/QALY**
Cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]

Figure 2: Cost-effectiveness scatter plot from PSA (WTP threshold: £20,000 per QALY (from company model)

Figure 3: Cost-effectiveness acceptability curve from PSA (from company model)

5.2.2 Comparisons with avalglucosidase alfa

The EAG requested clarification on the company's consideration of avalglucosidase alfa as a secondary comparator given the likelihood that it will be available and prioritised over alglucosidase alfa as a treatment for adults with LOPD. In their response, the company maintained that avalglucosidase alfa should only be considered as a secondary comparator and included only in

scenario analyses due to its current commercial unavailability. The company introduced an additional scenario analysis, Scenario #15, in their clarification response.

The EAG explored the following scenarios in the updated model:

- Scenario analysis #1: assumed [redacted] between avalglucosidase alfa and alglucosidase alfa i.e., both with [redacted] than with cipaglucosidase alfa in combination with miglustat,
- Scenario analysis #2: assumed [redacted] with avalglucosidase alfa compared to alglucosidase alfa i.e., [redacted] with avalglucosidase alfa than with cipaglucosidase alfa in combination with miglustat, and
- Scenario analysis #15: assumed [redacted] between avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat i.e., both [redacted] than with alglucosidase alfa.

The company's justification for these assumptions is based on clinical advice that avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat are relatively similar in short-term efficacy, hence long-term efficacy was also assumed to be likely similar [7].

The rates of long-term disease progression used in Scenario analyses #1, #2 and #15 are presented in Table 28. Results of Scenario analyses #1, #2 and #15 are presented in Table 29, Table 30 and

Table 31, respectively.

Table 28: Effectiveness inputs beyond Year 1 (Scenario analyses #1 and #15) (from company's clarification response)

Outcome	Mean annual predicted percentage change (SE) with alglucosidase alfa	Mean annual predicted percentage change (SE) with avalglucosidase alfa		
		Scenario #1	Scenario #2	Scenario #15
6MWD % predicted	-2.3% (0.003)	[redacted]	[redacted]	[redacted]
FVC % predicted	-0.9% (0.001)	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWD: six-minute walk distance; FVC: forced vital capacity; SE: standard error.

Table 29: Updated model results: Scenario #1 ([redacted] between avalglucosidase alfa and alglucosidase alfa) (from updated company model)

Technologies	Total costs (£)	Total LYG (diss)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/ QALY)
Cipaglucosidase alfa + miglustat	[redacted]	[redacted]	[redacted]					

Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit.								

Table 30: Updated model results: Scenario #2 ([redacted] with avalglucosidase alfa compared with alglucosidase alfa) (from updated company model)

Technologies	Total costs (£)	Total LYG (diss)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/ QALY)
Cipaglucosidase alfa + miglustat	[redacted]	[redacted]	[redacted]					
Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit.								

Table 31: Updated model results: Scenario #15 ([redacted] between avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat) (from updated company model)

Technologies	Total costs (£)	Total LYG (diss)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/ QALY)
Cipaglucosidase alfa + miglustat	[redacted]	[redacted]	[redacted]					
Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit.								

5.2.3 Company's deterministic sensitivity analyses

The company performed a series of deterministic sensitivity analyses (DSA), setting the lower and upper bounds of each parameter using 95% CI where available. Where CI data was not available, the company assumed variation to be a set percentage of the mean i.e., ±20% for mortality hazard ratios, ±15% for drug unit costs, and ±10% for health state costs. The upper and lower values were calculated by either adding or subtracting the respective percentage for cost inputs or by using this to further derive appropriate variations for mortality hazard ratios.

Figure 4 presents the DSA results from the updated model with 1,000 iterations. The most influential input parameters on the ICER were the unit cost per vial of alglucosidase alfa, followed by change from Year 1 to Year 2 in 6MWT with alglucosidase alfa.

Figure 4: Tornado diagram showing absolute change in incremental NMB in the DSA (from updated company model)

Abbreviations: 6MWT: six-minute walk test; DSA: deterministic sensitivity analysis; FVC: forced vital capacity; NMB: net monetary benefit; RR: risk ratio.

5.3 Model validation and face validity check

The CS outlines several validation steps undertaken to validate the adopted modelling approach this includes a [redacted] and a series of engagement activities with UK expert clinical advisors. The CS does not describe any specific quality control exercises implemented to check the robustness of model calculations and/or functions.

5.3.1 Validation undertaken by EAG

As part of the EAG assessment of the economic analysis, the EAG checked the internal validity of the model and considered the face validity of the model's predictions. This included a series of model calculation checks, including pressure tests, formula auditing (cell-by-cell validation) and validation of the visual basic code.

Several errors were identified as part of this validation exercise. This included a significant error in the calculation of drug acquisition and administration costs which were not half-cycle corrected. This error leads to total costs being overestimated for all treatments. Additionally, minor errors were also identified in the parametrisation of baseline characteristics which were not bounded correctly. These issues have rectified by the EAG. Results with the corrections applied are presented in Section 6.

In addition to these structural issues the EAG also notes several issues with the parameterisation of the model. The first of these issues has been discussed Section 4.3.2 and relates to the use of independent distributions for model parameters. This fails to recognise that some model parameters will be correlated and therefore drawn from a joint distribution. As previously discussed, the EAG does not consider the changes to the economic model implemented at the clarification stage to

properly rectify this issue, and recommends that the company updates the model at the technical engagement step (the EAG does not have access to the necessary data to implement a correction). Secondly, the EAG notes the probabilistic analysis is not fully parametrised. Specifically, the probabilistic analysis omits several model parameters including all baseline characteristics. Due to time constraints the EAG was unable to address this issue with the probabilistic analysis and recommends that it also be rectified by the company as part of Technical Engagement.

6 External assessment group's additional analyses

The EAG identified several limitations and areas of uncertainty in the cost-effectiveness analysis presented by the company, which are discussed in detail in Section 4.

The following section presents a number of alternative scenarios in which the EAG considers alternative approaches and assumptions. Given the high level of uncertainty associated with the relative effectiveness of cipaglucosidase alfa in combination with miglustat, particular consideration has been given to this issue. These scenarios explore a range of alternative assumptions including the use of an updated ITC conducted by the EAG.

Descriptions of the EAG's exploratory analyses are provided in Section 6.1, and the degree of change on the ICERs and net health benefit compared to the company's base case is explored in Section 6.2. Due to uncertainties in relative effectiveness estimates the EAG does not have a single base case analysis but explores a range of scenarios that include EAG preferences regarding other assumptions in Section 6.3. As previously noted, there are confidential commercial arrangements available for avalglucosidase alfa that impact significantly on the cost-effectiveness estimates. The analysis below is presented exclusive of this discount and employs the assumed list price of avalglucosidase alfa used in the company's base case analysis. All results presented in Section 6.2 are replicated in the confidential appendix, inclusive of all confidential commercial arrangements available to NHS England.

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted the following exploratory analyses after applying the corrections to the calculation of drug acquisition and administration costs. The EAG also reverts to using independent parameter distributions for baseline characteristics as per the original company base case. The EAG considers that this is the least worst option given the data available to the EAG and preferable to assuming that these characteristic are perfectly correlated as per the company revised base case analysis. Each of the following analyses are based upon this 'corrected' version of the company's model.

The EAG also runs all scenario analysis considering both alglucosidase alfa and avalglucosidase alfa as relevant comparisons. This aligns with EAG preferences as outlined in Section 2.3 and Section 4.3.4. The company did not present a single preferred analysis for the comparisons with avalglucosidase alfa considering a range of hazard ratios applied to model long-term progression. For consistency the EAG has taken the scenario with a hazard ratio of [redacted] applied to the avalglucosidase alfa as base case analysis. This assumes avalglucosidase alfa progress [redacted] alglucosidase alfa and [redacted] patients receiving cipaglucosidase alfa. The EAG consider this a

reasonable if arbitrary starting point given the assumptions accepted in TA821 and the similarities between cipaglucosidase alfa and avalglucosidase alfa. Scenario's 1 to 5 are presented as pairwise analysis only as different assumptions are applied in the cipaglucosidase alfa arm for each comparator. Consequently, these analyses cannot be used to generate a fully incremental analysis. Scenario 6 presents results using a preferred fully incremental analysis as a consistent approach to modelling the cipaglucosidase alfa arm is adopted in these scenarios.

Scenario 1: Rate of long-term disease progression

As described in Section 4.3.6.4, the EAG considers there to be considerable uncertainty regarding the long-term relative effectiveness of both cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa. There is very little data to inform how disease progression may evolve over the long-term and the EAG considers the limited scenario analysis presented by the company to be insufficient to explore the scope of uncertainty in this parameter. The EAG therefore presents a range of scenario analyses to explore this uncertainty considering a broad range of hazard ratios applied to the Semplicini et al.[9] data used to model progression in the alglucosidase alfa arm of the model. These analyses are summarised in Table 32.

Table 32: Summary of Hazard ratios applied

Scenario #	HR applied to cipaglucosidase alfa	HR applied to avalglucosidase alfa
Scenario 1a)	0.7	0.85
Scenario 1b)	0.5	0.85
Scenario 1c)	0.3	0.85
Scenario 1d)	0.85	0.7
Scenario 1e)	0.85	0.5
Scenario 1f)	0.85	0.3

Scenario 2: Higher mortality in State 7

As discussed in Section 4.3.6.4, mortality rates have a notable impact on total costs and time spent in the final 'alive' state, which has much higher health state costs. The EAG considers it appropriate to differentiate between levels of respiratory support, particularly the *wheelchair and respiratory support-dependent* health state. This scenario explores uncertainty in the mortality rate applied to the *wheelchair and respiratory support-dependent* health state by applying a mortality rate based on data characterising the long-term mortality effects of traumatic brain injury. While this is a very different population to the modelled population, it represents the mortality risks observed in patients who are in fixed ambulatory position with very limited mobility. The value applied of 9.92 is sourced from Cameron et al. 2008 a study of 1290 patients with a traumatic brain injury.[54]

Scenario 3: HRQoL value set

As discussed in Section 4.3.7.1, the EAG questions the use of values from the vignette study and notes that the utility values are considerably lower compared to values from published sources. The vignette values are also inconsistent with those obtained from the clinical trial, bringing to question its face validity. Scenario 3 explores uncertainty around this parameter and uses explores two alternative value sets. Scenario 3a) uses a value set based on published values, while scenario 3b) uses a value set based on the trial data.

Scenario 4: Include patient management costs

As explained in Section 4.3.8.5, the EAG requested that the company provide an additional scenario that includes a number of patient management costs, including hospital inpatient visits (elective and non-elective), outpatient appointments, attendances at accident and emergency departments, primary care appointments and sundry pharmaceuticals. The company did not provide this in their response on the reasoning of lack of robust data to inform treatment-related difference in healthcare resource use beyond those already modelled. This scenario presents that analysis aligning health state costs with TA821.

Scenario 5: Alternative invasive mechanical ventilation cost

As described in Section 4.3.8.4, the EAG notes the importance of ventilation costs in driving overall costs, particularly in the alglucosidase alfa comparison. The EAG notes that while consistent with TA821, the value applied in the company base case is based on data from a very different population and is an old study. The EAG two alternative costs values for this input based on international data both of which suggest the costs of invasive mechanical ventilation cost is much lower than modelled by the company. Scenario 5a) therefore uses data from a Canadian study, Nonoyama et al, suggesting an annual cost of £37,838, while scenario 5b) uses data from a Czech study Gajdoš et al, which suggests an annual cost of £57,091. In both scenarios one-off costs of requiring invasive ventilation are set to zero.

Scenario 6: Population and indirect treatment comparison methods

This scenario explores the related issues of whether it is appropriate to pool the modelled population and what is the most appropriate source of relative effectiveness estimates. As discussed in Sections 4.3.3.2 and 4.3.6 the EAG considers it more appropriate to consider the ERT-naïve and ERT-experienced patients separately. The EAG also considers the ML-NMR analysis inclusive of single arm studies to be flawed and prefers an analysis that uses only data from RCTs. The analyses presented are summarised in the Table 33: Summary of populations and ITC's modelled and are presented as fully incremental analysis as both comparators use the relevant ITC to inform treatment effects. In scenarios considering sub-populations, baseline characteristics are adjusted to reflect the

baseline characteristics of that population using data from PROPEL. Treatment effects for sub-populations are informed using the relevant sensitivity analysis for that population. Scenario 6h) uses a model averaging approach to estimate cost-effectiveness in the whole population. This is done using a weighted average of Scenarios 6b) and 6e). The analyses are weighted by the proportion of ERT-naïve and ERT-experienced patients in PROPEL.

Table 33: Summary of populations and ITC's modelled

Scenario	Population modelled	Source of relative treatment effect
Scenario 6a)	ERT-Naïve	ML-NMR (all studies)
Scenario 6b)	ERT-Naïve	ML-NMR (RCTs Only)
Scenario 6c)	ERT-Naïve	Bucher ITC
Scenario 6d)	ERT-Experienced	ML-NMR (all studies)
Scenario 6e)	ERT-Experienced	ML-NMR (RCTs only)
Scenario 6f)	Whole population	ML-NMR (all studies)
Scenario 6g)	Whole population	ML-NMR (RCTs Only)
Scenario 6h)	Whole population	ML-NMR (RCTs Only), model average of scenario 6b) and 6e).

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The results of the scenario analyses are presented in Table 34, Table 35, and Table 36. The results include the cipaglucosidase alfa PAS only.

Table 34: Scenarios with alglucosidase alfa as the comparator

Scenario	Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/QALY)
Updated company base case with EAG corrections	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
1. Rate of long-term disease progression **a) HR of 0.7 applied to cipaglucosidase alfa**	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
b) HR of 0.5 applied to cipaglucosidase alfa	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
c) HR of 0.3 applied to cipaglucosidase alfa	Cipaglucosidase alfa + miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Higher mortality in State 7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	Dominated	[redacted]
3. HRQoL value set **a) Based on published values**	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-[redacted]	Dominated	[redacted]
b) Based on trial data	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
4. Include patient management costs	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
5. Alternative invasive mechanical ventilation cost	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					

a) Annual cost of £37,838 from Nonoyama et al.	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
b) Annual cost of £57,091 from Gajdoš et al.	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

Table 35: Scenarios with avalglucosidase alfa as the comparator

Scenario	Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/QALY)
Updated company base case with EAG corrections	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
1. Rate of long-term disease progression **a) HR of 0.7 applied to cipaglucosidase alfa**	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
b) HR of 0.5 applied to cipaglucosidase alfa	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
c) HR of 0.3 applied to cipaglucosidase alfa	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]					
	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d) HR of 0.7 applied to avalglucosidase alfa	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
e) HR of 0.5 applied to avalglucosidase alfa	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-[redacted]
f) HR of 0.3 applied to avalglucosidase alfa	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2. Higher mortality in State 7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
3. HRQoL value set **a) Based on published values**	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
b) Based on trial data	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
4. Include patient management costs	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	Dominated	[redacted]
5. Alternative invasive mechanical ventilation cost **a) Annual cost of £37,838 from Nonoyama et al.**	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
b) Annual cost of £57,091 from Gajdoš et al.	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-[redacted]

Table 36: ITC modelled scenarios

Scenario	Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/QALY)
1. ERT-Naïve **a) ML-NMR (all studies)**	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
b) ML-NMR (RCTs only)	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c) Bucher ITC	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d) ERT-experienced ML-NMR (all studies)	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
e) ML-NMR (RCTs only)	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
f) Whole population ML-NMR (all studies)	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
g) ML-NMR (RCTs only)	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
h) Model average of scenario 6b) and 6e)	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3 EAG's preferred assumptions

The EAG presents does not have a single preferred analysis due the high level of uncertainty associated with the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa. A series of analysis are therefore presented which combine several assumptions explored in Section 6.2 with different assumption about the long-term rates or progression. To account for differences between ERT-naïve and ERT-experienced patients results are presented separately for each sub group as well for the whole population. Table 37 presents results for the ERT-naïve population, Table 38 results for the ERT-experienced population and Table 39 results for the whole population

The EAG base-case adopts the following scenarios described in Section 6.1:

- Scenario 3b: PROPEL trial utility value set
- Scenario 4: Patient management costs included as per TA821
- Scenario 5b: Invasive mechanical ventilation costs based on Gajdoš et al.
- Scenario 6: Treatment effects informed using data from the ML-NMR including RCTs only.

Table 37: EAG Exploratory Scenario Analyses on the EAG base case (ERT-Naïve)

Assumptions	Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/QALY)
1. HR applied to Cipaglucosidase alfa w. miglustat and avalglucosidase alfa	Alglucosidase alfa	[redacted]	[redacted]	[redacted]					
a) HR of 0.3	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c) HR of 0.85	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. HR applied to Cipaglucosidase alfa w. miglustat	Alglucosidase alfa	[redacted]	[redacted]	[redacted]					
a) HR of 0.3	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
3. HR applied to avalglucosidase alfa	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
a) HR of 0.3	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 38: EAG Exploratory Scenario Analyses on the EAG base case (ERT-Experienced)

Assumptions	Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/QALY)
1. HR applied to Cipaglucosidase alfa w. miglustat and avalglucosidase alfa	Alglucosidase alfa	[redacted]	[redacted]	[redacted]					
a) HR of 0.3	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c) HR of 0.85	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. HR applied to Cipaglucosidase alfa w. miglustat	Alglucosidase alfa	[redacted]	[redacted]	[redacted]					
a) HR of 0.3	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
3. HR applied to avalglucosidase alfa	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
a) HR of 0.3	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					

	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 39: EAG Exploratory Scenario Analyses on the EAG base case (whole population)

Assumptions	Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/QALY)
1. HR applied to Cipaglucosidase alfa w. miglustat and avalglucosidase alfa	Alglucosidase alfa	[redacted]	[redacted]	[redacted]					
a) HR of 0.3	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c) HR of 0.85	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. HR applied to Cipaglucosidase alfa w. miglustat	Alglucosidase alfa	[redacted]	[redacted]	[redacted]					
a) HR of 0.3	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
3. HR applied to avalglucosidase alfa	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
a) HR of 0.3	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]					
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.4 Conclusions of the cost effectiveness section

The company submitted a de novo economic analysis to assess the cost-effectiveness of cipaglucosidase alfa in combination with miglustat compared to alglucosidase alfa only. The company's model used a state transition individual patient simulation approach and was comprised of 7 alive health states plus death. Health states described progression of mobility and respiratory symptoms associated with LOPD and was broadly based on the model considered as part of TA821. The company's base-case analysis inferred relative treatment effects applied in the first year from the PROPEL trial with subsequent treatment effects based on a non-randomised comparison of long-term data and assumptions. Scenario analysis was also presented considering avalglucosidase alfa, with initial (first year) treatment effects informed by a ML-NMR which included randomised and non-randomised evidence.

The company's base-case analysis suggested that cipaglucosidase alfa in combination with miglustat is both less costly and more effective than alglucosidase alfa with a predicted net health benefit of [redacted] QALYs at a willingness-to-pay threshold of £20,000 per QALY. Cost savings were driven by the avoidance of additional health care costs in more severe health states and drug acquisition and administration costs. In scenarios including avalglucosidase alfa the company's analysis similarly suggested that cipaglucosidase alfa in combination with miglustat is both less costly and more effective with a predicted net health benefits relative to alglucosidase of [redacted] QALYs (includes model corrections) assuming a willingness to pay threshold of £20,000.

6.4.1 Conclusions of the EAG's critique

The EAG is concerned that the scope of the current appraisal is likely to lead to misleading estimates of cost-effectiveness. Alglucosidase alfa was never subject to a NICE assessment and consequently alfa underwent no formal public assessment of cost-effectiveness. The EAG considers it highly likely that alglucosidase alfa is not cost-effective compared to best supportive care and therefore any comparison to alglucosidase alfa or other comparators whose cost-effectiveness has been estimated relative to alglucosidase alfa is likely to generate misleading estimates of cost-effectiveness. The economic evaluation presented by the company, therefore, while consistent with the NICE scope and the previous TA821, is flawed and does not represent the additional value of cipaglucosidase alfa in combination with miglustat to the NHS.

The EAG's review of the company's evidence submission and executable model identified several areas of uncertainty, which the EAG has sought to highlight, and address where possible in the presented scenario analyses and revised base-case analyses.

The EAG's primary concern relates to the exclusion of avalglucosidase alfa as a relevant comparator. The EAG consider that avalglucosidase alfa should be considered as a comparator in all analyses and that it is likely to be the most relevant for decision making given that clinical advice suggests that avalglucosidase alfa will replace alglucosidase alfa as the preferred first-line treatment option in patients with LOPD.

The EAG also has significant concerns regarding the company's approach to modelling first year treatment effects which are informed by ML-NMR that includes evidence from both randomised trials and single arm studies. The results of this analysis lead to estimated relative treatment effects that are inconsistent with the available evidence and does not represent best practice for this type of analysis; non-randomised studies should not be used when randomised evidence is available. Related to this issue the EAG also considers that it would be more appropriate to consider ERT-naïve and ERT-experienced patients as separate populations. There are several important differences in the characteristics of ERT-naive and ERT-experienced and it is expected that these patients will respond differently to treatment; this is illustrated by the differential treatment effects observed in PROPEL. Moreover, the available trial evidence is better able to inform the relative effectiveness of avalglucosidase alfa and cipaglucosidase alfa in an ERT-naïve population than it is in an ERT-experienced population due to the absence of ERT-experienced patients in the COMET trial.

Long-term treatment effects are a further source of uncertainty. Long term data on the effectiveness of cipaglucosidase alfa in combination with miglustat are limited. Available evidence indicates the durability of initial treatment effects. However, the lack of long-term comparative evidence means it is difficult to make strong inferences on the basis of this evidence and as such assumptions made regarding the relative long-term effectiveness of cipaglucosidase alfa are subject to very high levels of uncertainty. The company's base case analysis assumes a modest long-term treatment effect in favour of cipaglucosidase alfa relative to alglucosidase alfa, which is consistent with assumptions previously accepted by the committee in TA821. However, the model is sensitive to this parameter and it is plausible that the relatively modest treatment effect applied in the company analysis under or overestimates the true treatment effect. Lack of strong, long-term, data for avalglucosidase alfa means that long-term effectiveness relative to avalglucosidase alfa is also highly uncertain.

In addition to these issues the EAG also explores uncertainties in several other model parameters including the utility value set, applied health state costs and the applied cost of invasive mechanical ventilation which is major model driver in the alglucosidase alfa comparison.

The impact of these uncertainties was considered in a series of exploratory analyses. The assumptions with the largest impact upon the cost-effectiveness of cipaglucosidase alfa included use of ML-MMR ITC, the costs of invasive mechanical intervention and the long-term effectiveness of treatments. The EAG did not produce a base case but has several preferred analyses in which long-term treatment effects are explored. In these analyses net health benefits relative to alglucosidase ranged between [redacted] and [redacted] QALYs. Analysis inclusive of commercial arrangements for the other drugs used in the model has a substantial effect on estimates of the cost-effectiveness of cipaglucosidase alfa.

7 SEVERITY MODIFIER

The company undertook a QALY shortfall analysis by calculating the expected quality-adjusted life expectancy (QALE) for the general population. Life expectancy for the modelled population was calculated using ONS population mortality data from 2018-2020 and did not account for specific patient characteristics associated with this population other than age and sex mix. Life expectancy was quality-adjusted using UK population norm values as reported in Health Survey from England (HSE) 2014, as recommended by the NICE DSU.[55]

The company assumed that the total QALYs for the patients with LOPD was equal to the total QALYs associated with the alglucosidase alfa arm in the base-case analysis. The results of the company's QALY shortfall analysis are presented in Table 40, along with the values generated in the EAG base-case (mot pessimistic values for SoC). The absolute and proportional QALY shortfall associated with the condition fell below the threshold of 12 and 0.85 respectively, for the use of a severity modifier of 1.2. Therefore, the company and EAG applied a severity modifier of 1 in the base-case results.

Table 40: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs achieved on SoC in population with LOPD	Absolute QALY shortfall	Proportional QALY Shortfall
Company base-case			
[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case			
[redacted]	Alglucosidase alfa: [redacted] Avalglucosidase alfa: [redacted]	Alglucosidase alfa: [redacted] Avalglucosidase alfa: [redacted]	Alglucosidase alfa: [redacted] Avalglucosidase alfa: [redacted]

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9 APPENDIX 1: APPRAISAL OF ECONOMIC EVIDENCE IDENTIFICATION

9.1 Cost-effectiveness studies

The original company submission included searches to identify cost-effectiveness studies for adult patients with Pompe disease. A description of the searches and the search strategies were included in CS Appendix G (pp. 140-155).

Table 41: EAG appraisal of cost-effectiveness evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	Extremely comprehensive. As Centre for Review and Dissemination (CRD) Databases are no longer updated, the report of NHS Economic Evaluation Database (EED) being searched up until 8th June 2022 (Appendix G, p. 140) is inaccurate as this database not been updated since March 2015.
Were appropriate sources searched?	YES	An excellent range of relevant databases, conference proceedings, grey literature sources and trials registry databases were used.
Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy. The only use of date limits was to remove conference abstracts published before 2020 which was justified and explained by the company.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study types.
Were appropriate search terms used?	YES	Search terms are extremely comprehensive and designed very carefully. Although there are no search terms for the intervention this is because all studies using terms for the intervention will be on Pompe disease, so will not miss relevant studies.
Were any search restrictions applied appropriate?	YES	Yes, animal studies and irrelevant paper types are removed appropriately.
Were any search filters used validated and referenced?	YES	Various search filters were used and referenced, although there was no mention of whether filters were validated.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

9.2 Health–related quality of life studies

The original company submission included searches to identify health-related quality of life studies for adult patients with Pompe disease. A description of the searches and the search strategies were included in Appendix G (pp. 140-155) with further details including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram included in Appendix H (pp. 165-167).

Table 42: EAG appraisal of health-related quality of life evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	Extremely comprehensive. As Centre for Review and Dissemination (CRD) Databases are no longer updated, the report of NHS Economic Evaluation Database (EED) being searched up until 8th June 2022 (Appendix G, p. 140) is inaccurate as this database not been updated since March 2015.
Were appropriate sources searched?	YES	An excellent range of relevant databases, conference proceedings, grey literature sources and trials registry databases were used.
Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy. The only use of date limits was to remove conference abstracts published before 2020 which was justified and explained by the company.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study types.
Were appropriate search terms used?	YES	Search terms are extremely comprehensive and designed very carefully. Although there are no search terms for the intervention this is because all studies using terms for the intervention will be on Pompe disease, so will not miss relevant studies.
Were any search restrictions applied appropriate?	YES	Yes, animal studies and irrelevant paper types are removed appropriately.
Were any search filters used validated and referenced?	YES	Various search filters were used and referenced, although there was no mention of whether filters were validated.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

9.3 Cost and Healthcare Resource Identification, Measurement and Valuation studies

The original company submission included searches to identify cost and healthcare resource identification, measurement and valuation studies for adult patients with Pompe disease. A description of the searches and the search strategies were included in Appendix G (pp. 140-155) with further details including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram included in Appendix I (pp. 211-213).

Table 43: EAG appraisal of cost and healthcare resource evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	Extremely comprehensive. As Centre for Review and Dissemination (CRD) Databases are no longer updated, the report of NHS Economic Evaluation Database (EED) being searched up until 8th June 2022 (Appendix G, p. 140) is inaccurate as this database not been updated since March 2015.
Were appropriate sources searched?	YES	An excellent range of relevant databases, conference proceedings, grey literature sources and trials registry databases were used.
Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy. The only use of date limits was to remove conference abstracts published before 2020 which was justified and explained by the company.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study types.
Were appropriate search terms used?	YES	Search terms are extremely comprehensive and designed very carefully.
Were any search restrictions applied appropriate?	YES	Yes, animal studies and irrelevant paper types are removed appropriately.
Were any search filters used validated and referenced?	YES	Various search filters were used and referenced, although there was no mention of whether filters were validated.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Single Technology Appraisal (STA)

Cipaglucosidase alfa in combination with miglustat for the treatment of adults with LOPD [ID3771]

EAG report document addendum

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

Date 7th February 2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number ID3771.

Declared competing interests of the authors

None

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted], all academic-in-confidence (AIC) data are highlighted in [redacted].

1 Cost-effectiveness results corrections including of the cipaglucosidase alfa PAS only

This addendum to the Evidence Assessment Group (EAG) report presents corrections to the cost-effectiveness results in the EAG critique of the company's submission. The results in Table 1 have been updated to align with the text referring to Table 26 of the EAG report. The results in Table 2 and Table 3 are identical to those presented in Tables 29 and 30 of the EAG report with only the labelling updated. The results in Table 4 reflect the outcomes of the company updated model Scenario #15 with the available patient access scheme (PAS) discount for cipaglucosidase alfa applied but excludes available discounts for other treatments. This is a correction to the results presented in Table 31 of the main EAG report.

Table 1 Company updated base case: cipaglucosidase alfa in combination with miglustat vs alglucosidase alfa

Technologies	Total costs (£)	Total LYG (diss)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/ QALY)
Cipaglucosidase alfa + miglustat	[redacted]	[redacted]	[redacted]					
Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit.								

Table 2: Updated model results: Scenario #1 [redacted] between avalglucosidase alfa and alglucosidase alfa) (from updated company model)

Technologies	Total costs (£)	Total LYG (diss)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/ QALY)
Cipaglucosidase alfa + miglustat	[redacted]	[redacted]	[redacted]					
Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit.								

Table 3: Updated model results: Scenario #2 ([redacted] with avalglucosidase alfa compared with alglucosidase alfa) (from updated company model)

Technologies	Total costs (£)	Total LYG (diss)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/ QALY)
Cipaglucosidase alfa + miglustat	[redacted]	[redacted]	[redacted]					

Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit.								

Table 4: Updated model results: Scenario #15 ([redacted]between avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat) (from updated company model)

Technologies	**Total costs (£)**	**Total LYG (diss)**	**Total QALYs**	**Incr. costs (£)**	**Incr. LYG**	**Incr. QALYs**	**ICER vs baseline (£/QALY)**	**NHB (£20,000/ QALY)**
Cipaglucosidase alfa + miglustat	[redacted]	[redacted]	[redacted]					
Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit.								

Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease [ID3771]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 24 January 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Executive summary – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 1, row 2, page 11 *"The anticipated license does not reflect the intervention as described in the decision problem"*	Please remove Issue 1.	Amicus believes this statement to be inaccurate. The CHMP opinion for cipaglucosidase alfa states "Pombiliti (cipaglucosidase alfa) is a long-term enzyme replacement therapy used **in combination with the enzyme stabiliser miglustat** for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency)." [redacted] Therefore, the anticipated licenses for the two treatments are expected to indicate that they are used only in combination, and therefore reflect the intervention as described in the decision problem. Although miglustat 100 mg (generic) is available in the UK, miglustat 65 mg (undergoing EMA review) will be required for treatment in combination with cipaglucosidase alfa. [redacted] Therefore, no change is expected to the licenses or how the medicines will be used; hence, the anticipated licenses still reflect the intervention as described in the decision problem.	This issue has been removed, as suggested. The clarification provided here has been added to section 2.3.

Issue 1, page 12	Please remove Issue 1.	As described in the row above, the anticipated licenses for cipaglucosidase alfa and miglustat reflect the intervention as described in the decision problem (cipaglucosidase alfa in combination with miglustat).	This issue has been removed, as suggested.
Issue 2, row 2, page 13 *"The exclusion of avalglucosidase alfa from the base case analysis is inconsistent with the NICE scope and current NICE guidance."*	Please amend to "*The exclusion of avalglucosidase alfa from the base case analysis is inconsistent with the NICE scope* ***~~and current NICE guidance~~****."*	Current NICE guidance (PMG36) states that relevant comparators are those "that are established practice in the NHS". Given that avalglucosidase alfa does not represent established practice in the NHS, the exclusion of avalglucosidase alfa from the base case analysis is not inconsistent with current NICE guidance. Amicus anticipates that this will be a discussion point during technical engagement.	The NICE guidance referred to is guidance for avalglucosidase alfa (TA821), rather than NICE guidance on the process and methods for NICE health technology evaluations (PMG36). This has been clarified in the text.
Issue 3, row 2, page 14 *"There is also an expectation that response to treatment will differ between ERT-naïve and ERT-experienced patients."*	Please amend to "***~~There is also an expectation that~~*** **R**esponse to treatment ***~~will~~*** **may** differ between ERT-naïve and ERT-experienced patients."	This statement may not be definitively correct. Advice from multiple clinicians experienced in treating Pompe disease indicates that there is no biological reason to believe that the clinical effectiveness of cipaglucosidase alfa in combination with miglustat would differ between ERT-naïve and ERT-experienced adults with LOPD. This statement should therefore be amended, to account for the advice provided by the clinicians that Amicus has engaged with, and therefore the potential for differences in clinical opinion on this topic. For example, *"will differ"* could be considered too definitive in this scenario.	Amended as suggested.
Issue 4, row 4, page 15 *"In comparisons with alglucosidase alfa, reducing the rate of long-term disease progression for cipaglucosidase alfa with*	Please amend as follows: *"In* ***some*** *comparisons with alglucosidase alfa, reducing the rate of long-term disease progression for cipaglucosidase alfa with*	i) For clarity: The NHB estimates for cipaglucosidase alfa in combination with miglustat are not less than zero in all scenarios conducted by the EAG. ii) To align with labelling in Table 2, and to avoid any possible confusion with the HRs of	Amended as suggested.

miglustat to 30% of that modelled for alglucosidase alfa patients leads to NHB (£20,000 WTP) estimates less than zero"	*miglustat to 30% of that modelled for alglucosidase alfa patients **(HR of 0.3 applied to cipaglucosidase alfa in combination with miglustat)** leads to NHB (£20,000 WTP) estimates less than zero **for cipaglucosidase alfa in combination with miglustat**"*	0.7 (in which long-term disease progression for cipaglucosidase alfa with miglustat **by** 30% of that modelled for alglucosidase alfa patients) iii) For clarity, to avoid any confusion as to which treatment the NHB applies to, as in Table 2 the NHBs are presented for the costlier treatments in each scenario, rather than consistently for the intervention.	
Issue 7, row 2, page 17 *"Therefore, the company's economic evaluation, while consistent with the NICE scope and the previous TA of avalglucosidase alfa, is flawed and does not represent the additional value of cipaglucosidase alfa in combination with miglustat to the NHS."*	Please remove this statement.	Amicus believe this statement to be inaccurate. We acknowledge that alglucosidase alfa has not undergone evaluation by NICE, but clinician opinion indicates that almost all adults with LOPD in England have received this treatment (as the EAG recognise that it is standard of care). Therefore, a full cost-utility analysis comparing cipaglucosidase alfa in combination with miglustat to alglucosidase alfa does demonstrate the cost-effectiveness (and hence additional value) of the intervention compared with the current use of NHS resources (i.e., compared with standard of care in LOPD). Amicus anticipates that this will be a discussion point during technical engagement.	Not a factual inaccuracy. The EAG maintains its concern over the cost-effectiveness of alglucosidase alfa in its current use and its value to the NHS given it underwent no formal public assessment of cost-effectiveness.
Issue 8, row 2, page 17 *"The economic model has been parameterised such that the model uses independent distributions for each parameter, this is despite the*	Please amend to *"The economic model has been parameterised such that the model uses independent distributions for each parameter, this is despite the acknowledgement that model*	Typographical error.	Corrected.

acknowledgement that model parameters maybe correlated."	*parameters **may be** correlated."*		
Issue 9, row 2, page 18 *"This approach was justified on the basis that the PROPEL trial could not populate utility values applied in all health states."*	Please amend to *"This approach was justified on the basis that the PROPEL trial **and literature search were not able to comprehensively and reliably populate utility values for** all health states."*	The hierarchy of preferred HRQoL methods published by NICE (PMG36) indicates that if appropriate utilities are not available from the trial **or literature**, then vignettes can be used. It should be clarified that utilities from PROPEL and the literature could not comprehensively and reliably populate utility values for all health states. In Amicus' view, utilities generated in the vignette study formed the most comprehensive and appropriate set of utility data available for use in the cost-effectiveness model.	Not a factual inaccuracy. The EAG maintains its concern over the use of the vignette study utility values as the primary source of utility values especially since these utility values are lower than those from PROPEL trial, published literature or TA821 and have a significant effect on the total QALYS generated from the model. The EAG notes that only 3 out of nine health states do not have available utility values from PROPEL trial, published literature or TA821. Furthermore, the NICE manual 2022 lists the hierarchy of preferred HRQoL methods as; first from relevant trial, then from published literature, then an estimate from another measure using statistical mapping and finally from vignette studies and ultility values derived from 'proxy conditions'. The EAG therefore prefers using the utility values set generated from the PROPEL trial data supplemented by data from the published literature as a majority of the health states (6 out of 9)

			have available utility values. We have added the sections in bold "that basis that the PROPEL trial **and published literature** could not populate utility values applied in all health states" to show this.
Paragraph 1, page 19 *"Given the high level of uncertainty associated with the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat, the EAG has presented series of analysis to represent its base case. These consider a range of hazard ratios applied exploring to long-term disease progression rates relative to alglucosidase alfa. Results presented are inclusive of commercial arrangements for cipaglucosidase alfa but do include PAS discounts for, avalglucosidase alfa. Please refer to the confidential appendix to this report for results inclusive of all available commercial pricing arrangements. The results of the EAG's alternative base-case analyses are presented in Table 2."*	Please amend as follows: *"Given the high level of uncertainty associated with the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat, the EAG has presented series of analys**e**s to represent its base case. These consider a range of hazard ratios applied exploring ~~**to**~~ long-term disease progression rates relative to alglucosidase alfa. Results presented are inclusive of commercial arrangements for cipaglucosidase alfa but do **not** include PAS discounts for~~,~~ avalglucosidase alfa."*	Typographical errors.	Typographical errors have been corrected.

Table 2, page 20 Cost-effectiveness results for the individual presented scenarios are currently order by always listing the treatment with the lowest total costs first (n.b. this applies to all tables where results are presented).	Please amend all cost-effectiveness results tables to apply a consistent order of treatments across all presented scenarios (e.g. cipaglucosidase alfa with miglustat, alglucosidase alfa, avalglucosidase alfa).	Whilst not a factual error, Amicus would suggest that the consistent order of treatments might be helpful in facilitating the interpretation and comparison of the different scenario results. It is expected that this amendment would also be reflected in other parts of the report where similar results are presented (e.g. Section 6).	The EAG have not updated the cost-effectiveness results tables as suggested. The EAG carried out fully incremental analyses with the treatment options listed by ascending costs as recommended by the NICE methods 2022. This also illustrates the significance of the price of ERT in driving cost-effectiveness results.

Issue 2 Introduction and Background – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Paragraph 2, page 22 *"Cipaglucosidase alfa with miglustat consists of intravenous enzyme replacement therapy (ERT); cipaglucosidase alfa, with an orally administered enzyme stabiliser; miglustat."*	Please add the following citations to support this statement: Amicus Therapeutics Data on File. Cipaglucosidase alfa Draft SmPC, 2022. Amicus Therapeutics Data on File. Miglustat Draft SmPC, 2022.	This statement was not supported in the EAR and the included citations align with the company submission.	The source used was the company submission, not the draft SmPCs. A reference to the page in the CS has been added to the text.
Paragraph 2, page 22 *"Patients meeting certain criteria, such as being symptomatic (i.e. having*	Please add a citation to this claim or clarify that it is informed by the EAG's clinical advisor.	It is currently unclear if this information is supported by the Pompe Consortium 2017 guidelines or the input from the EAG's clinical advisor.	As indicated in the previous sentence, this information is supported by both the Pompe Consortium 2017 guidelines and

skeletal muscle weakness or respiratory muscle involvement observed using clinical assessments), having residual skeletal and respiratory muscle function (which is considered functionally relevant and clinically important for the patient to maintain or improve), and not having another life-threatening illness at an advanced stage (where treatment to sustain life is inappropriate), are eligible for ERT."			input from the EAG's clinical advisor. A reference for the guidelines has been added.
Paragraph 3, page 22 "*The current commercially available ERT for LOPD patients is alglucosidase alfa (Myozyme®), which has been available since 2006."*	Please add the following citations to support this statement: Sanofi Genzyme. Myozyme. 2021. Available at: https://www.medicines.org.uk/emc/product/263/smpc. [accessed: May 2022]. NHS England and NHS Improvement. Highly Specialised Services 2019. Available at: https://www.england.nhs.uk/wp-content/uploads/2021/03/Highly-Specialised-Services-	This statement was not supported in the EAR and the proposed citations align with the company submission.	The source used was the company submission, not Sanofi Genzyme and NHS England and NHS Improvement. A reference to the page in the CS has been added to the text.

	2019.pdf. [accessed: June 2022]		
Paragraph 4, page 22 *"The mechanism of action of alglucosidase alfa, avalglucosidase alfa and cipaglucosidase alfa is the same, the key difference between the therapies relates to pharmacokinetics, as described in Table 2 of the CS, particularly with the addition of miglustat to cipaglucosidase alfa."*	Please amend to *"The mechanism**s** of action of alglucosidase alfa, avalglucosidase alfa and cipaglucosidase alfa **~~is the same~~ are similar**, the key difference between the therapies relates to pharmacokinetics, as described in Table 2 of the CS, particularly with the addition of miglustat to cipaglucosidase alfa."*	Although the mechanisms of actions of the treatments are similar, there is no evidence to suggest that they are the same. The statement is also not completely representative of the differences between treatment, e.g. there are pharmacokinetic differences between cipaglucosidase alfa and alglucosidase alfa as explained in Table 2 of the company submission.	Amended as suggested.
Paragraph 4, page 23 *"The anticipated license does not reflect the intervention as described in the decision problem:* [redacted]"	Please amend as follows: *"**~~The anticipated license does not reflect the intervention as described in the decision problem:~~*** [redacted]"	i) As described above in Issue 1, the anticipated licenses for cipaglucosidase alfa and miglustat reflect the intervention as described in the decision problem (cipaglucosidase alfa in combination with miglustat). ii) The updated wording has been provided for clarity (to avoid any misinterpretation about the medicines being used separately).	Amended as suggested.
Paragraph 5, page 23	Please amend to "*The exclusion of avalglucosidase alfa from the base case*	As described in Issue 1, current NICE guidance (PMG36) states that relevant comparators are those "that are established practice in the NHS". Given that	The NICE guidance referred to is guidance for avalglucosidase alfa (TA821), rather than NICE

"The exclusion of avalglucosidase alfa from the base case analysis is inconsistent with the NICE scope and current NICE guidance."	*analysis is inconsistent with the NICE scope* ***~~and current NICE guidance~~****."*	avalglucosidase alfa does not represent established practice in the NHS, the exclusion of avalglucosidase alfa from the base case analysis is not inconsistent with current NICE guidance.	guidance on the process and methods for NICE health technology evaluations (PMG36). This has been clarified in the text.
Paragraph 5, page 23 *"In ERT-experienced patients, it is expected that patients will only switch treatments if they experience a decline in health outcomes on alglucosidase alfa; the primary alternative treatment in this scenario will be avalglucosidase alfa."*	Please amend to: *"In ERT-experienced patients, it is expected that patients will only switch treatments if they experience a decline in health outcomes on alglucosidase alfa; the primary alternative treatment* ***to cipaglucosidase alfa in combination with miglustat*** *in this scenario will be avalglucosidase alfa."*	This statement in its current form may be misleading to the reader, as it suggests that avalglucosidase alfa would be a preferred treatment option compared to cipaglucosidase alfa in combination with miglustat. There is no evidence to suggest that this is the case; furthermore, the positive opinion for cipaglucosidase alfa issued by the CHMP does not specify any line of therapy or prior treatment status.  Additionally, feedback from clinicians indicates that the decision between treatment with avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat is currently heavily influenced by patient preference and practical factors. The statement should therefore be amended to avoid suggesting that the primary alternative treatment to alglucosidase alfa will be avalglucosidase alfa, which does not align with clinical evidence nor advice from clinicians.	The text in the paragraph has been amended for clarification, although we have not used the wording suggested by the company.

Table 3, row 3, page 25 *"However, in the company's response to the EAG's points for clarification, they stated that* [redacted] *."*	Please amend to *"However, in the company's response to the EAG's points for clarification, they stated that* [redacted] *."*	The updated wording has been provided for clarity (to avoid any misinterpretation about the medicines being used separately).	Amended as suggested.

Issue 3 Clinical effectiveness – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 5, page 31	Please amend so all text is size 10.	Updated for consistent formatting.	Corrected.
Paragraph 1, page 31 *"cipaglucosiase"*	Please amend "cipaglucosiase" to "cipaglucosidase".	Typographical error.	Corrected.
Paragraph 1, page 32 *"cipaglucosiase"*	Please amend "cipaglucosiase" to "cipaglucosidase".	Typographical error.	Corrected.
Paragraph 4, page 34 *"The interventional arm received cipaglucosidase alfa 20 mg/kg every 2 weeks as a 4-hour IV infusion plus miglustat (195 mg for participants weighing ≥ 40 kg*	Please add the following citations to support this text: Amicus Therapeutics Data on File. Cipaglucosidase alfa Draft SmPC, 2022.	This statement is currently not supported by a reference.	The source used was the company submission, not the draft SmPCs. A reference to the page in the CS has been added to the text.

to < 50 kg or 260 mg daily for participants weighing ≥ 50 kg, administered as oral capsules). The control arm received alglucosidase alfa 20 mg/kg every 2 weeks as a 4-hour IV infusion plus placebo (195 mg for participants weighing ≥ 40 kg to < 50 kg or 260 mg daily for participants weighing ≥ 50 kg, administered as oral capsules).”	Amicus Therapeutics Data on File. Miglustat Draft SmPC, 2022.		
Bullets 1– 3, page 35 • *“Change in motor function (6MWD assessed using 6MWT)* • *Change in respiratory function (assessed using sitting FVC % predicted)* • *Change in muscular function (assessed using manual muscle testing (MMT) and the Gait, Stairs, Gowers’ manoeuvre, and Chair (GSGC) assessments)”*	Please amend as follows: • *“Change in motor function (6MWD assessed using 6MWT **and the Gait, Stairs, Gowers’ manoeuvre, and Chair (GSGC) assessments**)* • *Change in respiratory function (assessed using sitting FVC % predicted)* • *Change in muscular function (assessed using manual muscle testing (MMT))”*	The GSGC assessment primarily measures motor function rather than muscular function (as noted in paragraph 2, page 41).	Amended as suggested.

Paragraph 2, page 36 *"The analyses excluded one patient who had faked their test in order to be included in the trial."*	Please amend to *"The analyses excluded one patient who had **deliberately underperformed at baseline** in order to be included in the trial."*	Updated to formalise the language used.	Amended as suggested.
Paragraph 5, page 38 *"It should be noted that the number of participants in the ERT-naïve group was small (N=7)."*	Please amend to *"it should be noted that the number of participants in the ERT-naïve group **receiving alglucosidase alfa + placebo** was small (N=7)"*	The population given is that for the ERT-naïve population receiving alglucosidase alfa in combination with the placebo.	Amended as suggested.
Table 6, page 39 • *"-0.002 (39.34)"* • *"n=65"* • *"n=30"*	Please amend as follows: • *"**-0.02** (39.34)"* • *"n=**61**"* • *"n=**29**"*	Typographical errors (n=61 and n=29 align with responses submitted to EAG's points of clarification).	Amended as suggested.
Paragraph 1, page 40 *"From the results of the subgroup analyses presented in Table 6 and Table 7 above, ERT-naïve patients appear to respond slightly better to alglucosidase alfa + placebo compared with cipaglucosidase alfa + miglustat, whereas ERT-experienced patients who have been on alglucosidase alfa + placebo for an average of 7 years respond better to*	Please amend to "From the results of the subgroup analyses presented in Table 6 and Table 7 above, ERT-naïve patients appear to respond slightly better to alglucosidase alfa + placebo compared with cipaglucosidase alfa + miglustat, whereas ERT-experienced patients who have been on alglucosidase alfa **~~+ placebo~~** for an average of **7.10** years	Typographical error: participants had previously been treated with alglucosidase alfa (not in combination with placebo).	Corrected.

cipaglucosidase alfa + miglustat."	respond better to cipaglucosidase alfa + miglustat."		
Bullets 9–11, page 49 • *"Change in motor function (6MWD assessed using 6MWT)* • *Change in respiratory function '(assessed using sitting FVC % predicted)* • *Change in muscular function (assessed using MMT and GSGC assessments)"*	Please amend as follows: • *"Change in motor function (6MWD assessed using 6MWT **and GSGC**)* • *Change in respiratory function (assessed using sitting FVC % predicted)* • *Change in muscular function (assessed using MMT)"*	The GSGC assessment primarily measures motor function rather than muscular function (as noted in paragraph 2, page 41).	Amended as suggested.
Paragraph 2, page 49 *"upright FVC ≥ 30% to 80%"*	Please amend *to "upright FVC **between** 30% **and** 80%"*	Updated for clarity and alignment with 6MWD criterion.	Amended as suggested.
Paragraph 6, page 50 *"Protocol deviations were not reported in the CS but are presented in Table 9 of the CSR. All participants experienced at least one protocol deviation. The most common reasons for protocol deviations included errors in administration of the study drug [redacted], issues related to*	Please amend to *"Protocol deviations were not reported in the CS but are presented in Table **10** of the CSR. All participants experienced at least one protocol deviation. The most common reasons for protocol deviations included **issues related to laboratory/endpoint data** [redacted], **visit window***	To align with data presented in ATB200-02 CSR Table 10.	Amended as suggested.

informed consent [redacted], overdose or misuse [redacted] and issues related to study inclusion criteria [redacted].”	***[redacted], study drug [redacted] and assessment safety [redacted].”***		
Paragraph 2, page 51 *“Whilst 6MWD and FVC are objective assessments used in clinical practice, the patient reported outcomes are likely to capture outcomes important to patients”*	Please amend to *“Whilst 6MWD and FVC are objective assessments used in clinical practice, the patient reported outcomes are likely to capture outcomes important to patients**.**”*	Full stop is missing at end of sentence.	Corrected.
Paragraph 7, page 51 *“At month 48, the majority of participants form Cohorts 1 and 4 and all participants in cohort 2 had either no change or reported improvement from baseline in overall physical wellbeing.”*	Please amend to *“At month 48, the majority of participants **from** Cohorts 1 and 4 and all participants in **C**ohort 2 had either no change or reported improvement from baseline in overall physical wellbeing.”*	Typographical errors.	Corrected.
Paragraph 1, page 53 *“There is also an expectation that response to treatment will differ between ERT-naïve and ERT-experienced patients.”*	Please amend to *“**~~There is also an expectation that~~** **R**esponse to treatment **~~will~~** **may** differ between ERT-naïve and ERT-experienced patients.”*	This statement may not be definitively correct. Advice from multiple clinicians experienced in treating Pompe disease indicates that there is no biological reason to believe that the clinical effectiveness of cipaglucosidase alfa in combination with miglustat would differ between ERT-naïve and ERT-experienced adults with LOPD. This statement should therefore be amended, to account for the advice provided by the clinicians that Amicus has engaged with, and therefore the potential for differences in clinical opinion on this topic. For example, *“will differ”* could be considered too definitive in this scenario.	Amended as suggested.

Paragraphs 2 and 3, page 52 *"clinical studies register"*	Please amend to "*clinical study report*" in both instances.	Typographical error.	Corrected.
Paragraph 1, page 54 "*One further study[20] was not considered eligible for inclusion because it was exploratory and had short follow up*."	Please amend to *"One further study **(EMBASSY)**[20] was not considered eligible for inclusion because it was exploratory and had short follow up."*	For completeness and consistency, it is important to specify the name of the study here.	Amended as suggested.
Table 16 (NEO exclusion criteria), page 55 *"Previous treatment with ERT for Pomple disease"*	Please amend to *"Previous treatment with ERT for **Pompe** disease"*	Typographical error.	Corrected.
Paragraph 2, page 55 *"LOTS OLE[16] and NEO-1[19] were of serious risk of bias and moderate risk of bias respectively"*	Please amend to *"LOTS OLE[16] and NEO-1[19] were **both of low to moderate risk of bias**"*	The updated statement reflects the company submission and ITC report.	There is a discrepancy between the CS appendix and the ITC report, therefore no change has been made. Table 39 in appendix D of the CS states that LOTS-OLE is at an overall serious risk of bias. However, the ITC report states that both studies are at an overall moderate risk of bias.
Paragraph 2, page 55 *"However, no details were included to justify these assessments."*	Please remove this statement.	The reference provided to NICE, "Amicus Data on File 2022 Indirect Treatment Comparison Report", contains the risk of bias assessment for LOTS OLE and NEO-1.	No changes made. Answers to the signalling questions for ROBINS-I are provided in the Appendix to the ITC report, but there is no text to justify the

			responses. The critical appraisal should include quotes from trial documents or information from the person undertaking the critical appraisal to justify the answers.
Paragraph 2, page 56 *"This included both ERT-naïve and ERT experienced participants and adjusted for baseline characteristics such as age, gender, ethnicity, previous ERT duration, baseline 6MWD and baseline FVC % predicted using individual patient data from the PROPEL trial[13]"*	Please amend to "This included both ERT-naïve and ERT experienced participants and adjusted for **the following** baseline characteristics**:** ~~**such as**~~ age, gender, ethnicity, previous ERT duration, **visit time, and** baseline 6MWD and baseline FVC % predicted **(depending on the endpoint considered)** using individual patient data from the PROPEL trial[13]"	The statement contained all of the characteristics adjusted for, except visit time. Therefore, the statement has been updated for completeness.	Corrected.
Paragraph 3, page 56 *"The company's response to clarification question A16 was not sufficiently clear on how the matching was done, as the paper referenced[23] reported different models for matching: a pooled model where different data are not distinguished (i.e. the matched data are treated the same as RCTs) and a hierarchical model (down weighting the*	Please amend to *"A pooled model where different data are not distinguished (i.e. the matched data are treated the same as RCTs) was used."*	Amicus acknowledges that this information was not provided in the company submission, however, can confirm that the pooled model was used.	Amended as suggested.

matched data). It is unclear which of these was used."			
Footnote to Table 17, page 58	Please amend so that footnote text size is 9pt and line spacing is 0pt before and 12pt after.	Update for consistent formatting.	Amended as suggested.
Paragraph 4, page 58 *"However, caution should be applied when interpreting results from ML-NMR as estimates have been extrapolated from a regression model based on data from few participants"*	Please remove this statement.	This is subjective and hence should be removed: data from the whole PROPEL trial were used to build the regression model, which is considered large enough to reasonably predict treatment effect based on previous ERT duration.	This is not a factual inaccuracy, it is a statement of the EAG's opinion. PROPEL is not a large trial and there are few ERT-naïve participants.
Paragraph 1, page 59 *"The EAG do not agree with the company's reasoning regarding undertaking separate analyses on ERT-naïve and ERT-experienced participants as the subgroups were pre-specified in the NICE final scope and data are available"*	Please amend to "*The EAG do not agree with the company's reasoning regarding undertaking separate analyses on ERT-naïve and ERT-experienced participants as the subgroups were pre-specified in the NICE final scope and data are available* ***for ERT-naïve participants***"*	This statement is not wholly accurate: data for avalglucosidase alfa are only available from single-arm studies for ERT-experienced participants; the COMET population was comprised entirely of ERT-naïve patients.	Amended as suggested.
Paragraph 2, page 59 *"The study by Semplicini et al.[9] is mentioned in the CS in Section B.3.3.3 (p. 126) and results from the study are*	Please amend to *"The study by Semplicini et al.[9] is mentioned in the CS in Section B.3.3.3 (p.* ~~***126***~~ ***127****) and results from the study are used to estimate annual*	Typographical error.	Corrected.

used to estimate annual change in FVC and 6MWD % in the economic model."	*change in FVC and 6MWD % in the economic model."*		
Paragraph 2, page 60 *"The study outcome data were reported for up to 120 treated patients."*	Please remove this statement.	This statement is not wholly accurate: in the cited study, FVC over time was measured in 143 patients (as stated in paragraph 5, page 60). Therefore, this statement should be removed.	Statement has been removed.
Paragraph 4, page 62 *"However, caution should be applied when interpreting results from ML-NMR as estimates have been extrapolated from a regression model based on data from few participants."*	Please remove this statement.	This is subjective and hence should be removed: data from the whole PROPEL trial were used to build the regression model, which is considered large enough to reasonably predict treatment effect based on previous ERT duration.	This is not a factual inaccuracy, it is a statement of the EAG's opinion. PROPEL is not a large trial and there are few ERT-naïve participants.
Paragraph 4, page 62 *"Avalglucosidase alfa also shows a numerically favorable effect compared to cipaglucosidase alfa + miglustat for 6MWD."*	Please amend to *"Avalglucosidase alfa also shows a numerically favo**u**rable effect compared to cipaglucosidase alfa + miglustat for 6MWD."*	Typographical error.	Corrected.

Issue 4 Cost effectiveness – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 19, page 65	Please amend to *"The economic model had a lifetime horizon of **up to** 106*	Suggested amendment for greater accuracy, in line with equivalent wording in Section 4.3.5 of the report.	Amended as suggested.

"The economic model had a lifetime horizon of 106 years. No patients were expected to be alive beyond this period."	*years. No patients were expected to be alive beyond this period."*		
Paragraph 3, page 70 *"The company's justification for not considering the subgroups was that prior ERT status should not influence access to treatment to allow fair and equitable access."*	Please amend to "*The company's justification for not considering the subgroups was that prior ERT status should not influence access to treatment to allow fair and equitable access;* ***in addition, it was considered that, due to comparatively small patient numbers for the ERT-naïve subgroup in particular (n=28), the total cohort is the most reliable and meaningful source of data for the cost-effectiveness analysis****."*	For increased accuracy, Amicus would suggest including all relevant argumentation from the company submission. As detailed in Issues 1 and 3, advice from multiple clinicians experienced in treating Pompe disease indicates that there is no biological reason to believe that the clinical effectiveness of cipaglucosidase alfa in combination with miglustat would differ between ERT-naïve and ERT-experienced adults with LOPD. It is not expected that this amendment will have any wider impact on the report.	Amended to augment the company's justification by adding the phrase **"In addition, the company argued that the total cohort is the most reliable and meaningful source of data for the cost-effectiveness analysis due to comparatively small patient numbers for the ERT-naïve subgroup in the PROPEL trial (n=28)".** However, the EAG considers that the comparison of a combined ERT-naïve and ERT-experienced population is not appropriate and that these subgroups should be considered separately as explained in section 3.5.1 and 4.3.3.2 of the report.
Paragraph 4, page 72 [redacted]	Please replace this statement with: [redacted]	As described above, the anticipated licenses for cipaglucosidase alfa and miglustat reflect the intervention as described in the decision problem (cipaglucosidase alfa in combination with miglustat). They were always intended to have separate marketing authorisations, with the licenses stating that they must be used in combination.	Amended as suggested.

[redacted]	[redacted]”	The updated wording has been provided for clarity (to avoid any misinterpretation about the medicines being used separately).	
Paragraph 4, page 73 *“For example, it may be more cost-effective to use cipaglucosidase alfa as a 2nd line treatment following use of the likely more efficacious avalglucosidase alfa.”*	Please remove this statement.	Amicus believes that this statement is subjective, and as described above (Issue 2), not evidence-based. There is no evidence to indicate that avalglucosidase alfa is more efficacious than cipaglucosidase alfa in combination with miglustat; this statement is factually incorrect and should be removed. • Comparative data for avalglucosidase alfa derives only from COMET, which comprised ERT-naïve patients only, and showed no significant benefit versus alglucosidase alfa. • The ML-NMRs presented by Amicus, as well as the Bucher comparisons presented by the EAG, do not suggest that avalglucosidase alfa is more effective than cipaglucosidase alfa in combination with miglustat especially considering the large uncertainty in relative effectiveness estimates. • Clinical advice indicates that, given that the short-term effects for avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat are relatively similar, this could be extrapolated to suggest that long-term effects are also likely to be similar. In addition, feedback from clinicians indicates that the decision between treatment with avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat is currently heavily influenced by patient preference and practical factors. Additionally, advisors did not feel that there were clinical grounds	The EAG has removed the statement relating to the relative effectiveness of avalglucosidase alfa but has retained the sentence as it is important to recognise that the cost-effectiveness of cipaglucosidase alfa in combination with miglustat may depend on its position in the pathway. The sentence has been amended to: “For example, it may be more cost-effective to use cipaglucosidase alfa as a 2nd line treatment following use of ~~**the likely more efficacious**~~ avalglucosidase alfa.

		to develop criteria for switches between avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat. Therefore, it is extremely misleading to suggest that cipaglucosidase alfa in combination with miglustat may be used as a 2nd line treatment following use of avalglucosidase alfa, or that this may be the usual treatment sequence when evidence does not support this statement.	
Paragraph 1, page 74 *"While the EAG agrees there is limited clinical experience of sequencing ERT, this does not imply that this will not occur in the future and the EAG notes that the modelled population of ERT-experienced patients is predicated on the idea that patients will sequence ERT treatments."*	Please amend to *"While the EAG agrees there is limited clinical experience of sequencing ERT, this does not imply that this will not occur in the future and the EAG notes that the* ***~~modelled population of~~ the availability of data for*** *ERT-experienced patients is predicated on the idea that patients will sequence ERT treatments."*	Suggested amendment for greater accuracy, as ERT-experienced patients had not been modelled as a distinct population for the originally submitted analysis (as also noted elsewhere in the report). It is not expected that this amendment will have any wider impact on the report.	Amended to: "While the EAG agrees there is limited clinical experience of sequencing ERT, this does not imply that this will not occur in the future and the EAG notes that the modelled population **from the available data for** ERT-experienced patients is predicated on the idea that patients will sequence ERT treatments."
Paragraph 2, page 74 *"Clinical advice to the EAG also suggests that stopping rules are applied in practice where patients on ERT experience a continuous decline to the point they require ventilatory support, or where treatment does not add further to the patient's QoL. These stopping rules help to ensure treatment is used in*	Please remove this statement.	Amicus appreciates that clinical opinion may differ; however, from Amicus' understanding based on feedback from a number of clinicians, this statement is inaccurate. Feedback from clinicians Amicus has engaged with indicates that stopping rules are only applied in clinical practice in the UK for a very small number of patients, and only during end-of-life/palliative care rather than when a patient progresses to requiring ventilatory support.	Not a factual inaccuracy. Clinical advice to the EAG and The European Pompe Consortium guidelines suggest that stopping rules are applied in practice.

patients who experience meaningful benefits thus optimising cost-effectiveness of treatment."			
Paragraph 3, page 74 *"The model assumes that patients will continue to benefit from treatment throughout their lifetime, implying that patients survive far longer and incur more costs from treatment. This is inconsistent with the natural disease progression and previously observed ERT treatment effects; patients on alglucosidase alfa have been shown to experience an initial improvement or stabilisation in the first 2 to 3 years, followed by a steady decline or plateau in health benefit."*	Please amend to "*The model assumes that patients will continue to benefit from treatment throughout their lifetime, implying that patients survive far longer and incur more costs from treatment. This is* ***~~inconsistent~~ modelled consistently*** *with the natural disease progression and previously observed ERT treatment effects; patients on alglucosidase alfa have been shown to experience an initial improvement or stabilisation in the first 2 to 3 years, followed by a steady decline or plateau in health benefit."*	Amicus would like to clarify that the life-long treatment effect that patients treated with cipaglucosidase alfa with miglustat are modelled to benefit from is expressed in a **slowed disease progression** compared to alglucosidase alfa (i.e. following an initial improvement, patients treated with cipaglucosidase alfa with miglustat are still experiencing steadily declining 6MWD and %pred FVC over their lifetime, but the rate of decline is slower than that of alglucosidase alfa); as such, the statement on apparent inconsistencies should be considered inaccurate. It is not expected that this amendment will have any wider impact on the report.	The EAG has amended the text to remove this sentence entirely.
Paragraph 2, page 80 *"The EAG is puzzled by the inconsistent approach to modelling subsequent changes in 6MWD and FVC % predicted and notes that functionality is included in the model (using data from NEO1 and NEO-EXT)."*	Please amend to "*The EAG is puzzled by the inconsistent approach to modelling subsequent changes in 6MWD and FVC % predicted and notes that functionality* ***[to …]*** *is included in the model (using data from NEO1 and NEO-EXT)."*	Please could further information be provided (for clarity) about what functionality the EAG is referring to? It is not expected that this amendment will have any wider impact on the report.	The functionality description has been added.

Paragraph 1, page 80 *"The broad approach of using data from et al.[9] is therefore reasonable."*	Please amend to *"The broad approach of using data from **Semplicini** et al.[9] is therefore reasonable."*	Typographical error.	Corrected.
Paragraph 2, page 80 "*There is no priori reason to believe this is the case, and this is not supported by the trial evidence* [redacted]	Please remove this statement.	As stated above (Paragraph 4, page 73), there is no evidence to indicate that cipaglucosidase alfa in combination with miglustat is inferior to avalglucosidase alfa; this statement is factually incorrect and should be removed. • Comparative data for avalglucosidase alfa derives only from COMET, including ERT-naïve patients only, which showed no significant benefit versus alglucosidase alfa; • The ML-NMRs presented by Amicus, as well as the Bucher comparisons presented by the EAG, do not suggest that avalglucosidase alfa is more effective than cipaglucosidase alfa in combination with miglustat, especially considering the large uncertainty in relative effectiveness estimates. Therefore, it is inaccurate to suggest that cipaglucosidase alfa in combination with miglustat is inferior to avalglucosidase alfa. [redacted];	Not a factual accuracy. The EAG stands by this statement. The EAG has, however, edited the text for clarity.

		• Clinical advice indicates that, given that the short-term effects for avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat are relatively similar, this could be extrapolated to suggest that long-term effects are also likely to be similar.	
Paragraphs 1–3, page 85 *"The value set captures only public preferences and includes no explicit consideration of the quality of life of patients themselves. In adopting this method, the company have failed to acknowledge the lived experience of patients and caregivers."* *"Where such values are unavailable the NICE reference case states utilities should be sourced from the published literature. NICE TSD 11 states that vignettes and patient own health state valuations do not meet the NICE Methods Guidance for alternatives to EQ-5D. These only have a role where there are no data from validated HRQoL measures."* *"Notwithstanding the small sample size and conduct of the company's utility elicitation*	Please amend as follows: *"The value set captures only public preferences and includes no explicit consideration of the quality of life of patients themselves~~. In adopting this method, the company have failed to acknowledge the lived experience of patients and caregivers~~."* *"Where such values are unavailable the NICE reference case states utilities should be sourced from the published literature.* ***Otherwise, as per the hierarchy of preferred HRQoL methods presented as part of the updated NICE manual for health technology evaluations (from January 2022), vignette-based studies can also be considered as long as vignettes are developed in line with best practice***	Amicus would like to highlight that health-state vignettes applied for the elicitation of utilities used in the presented analysis have been developed and valuated using EQ-5D in line with the NICE hierarchy of preferred HRQoL methods and DSU best practice recommendations; this involved the use of patient-reported data from PROPEL for the drafting of vignettes and further validation of the draft vignettes by a sample of patients with LOPD. As such, Amicus consider the flagged statements, which state that the applied method does not meet NICE guidance and completely bypasses patients, to be inaccurate and request the suggested amendment/deletions. It is expected that this amendment would also need to be reflected in other related parts of the report (e.g. in the executive summary).	Not a factual accuracy. The EAG maintains its concern over the use of the vignette study utility values as the primary source of utility values, especially since these utility values are lower than those from the PROPEL trial, published literature or TA821 and have a significant effect on the total QALYs generated from the model. The EAG notes that only three out of nine health states do not have available utility values from the PROPEL trial, published literature or TA821. Furthermore, the NICE manual 2022 lists the hierarchy of preferred HRQoL methods as: first from a relevant trial (in this case the PROPEL trial), then from published literature, then an estimate from another measure using statistical mapping and finally from vignette studies and utility values derived from 'proxy conditions'. In line with the NICE manual 2022, TSD11 reinforces that hierarchy

exercise, in bypassing patients and caregivers entirely the cost-effectiveness analysis as currently presented cannot therefore claim to represent their perspective."	***recommendations and are valued by a sample of the general population using appropriate techniques. ~~NICE TSD 11 states that vignettes and patient own health state valuations do not meet the NICE Methods Guidance for alternatives to EQ-5D. These only have a role where there are no data from validated HRQoL measures~~."*** *"~~Notwithstanding the small sample size and conduct of the company's utility elicitation exercise, in bypassing patients and caregivers entirely the cost-effectiveness analysis as currently presented cannot therefore claim to represent their perspective~~."*		by stating that "vignettes may have a limited role where there are no data available using validated HRQL measures." The EAG therefore prefers using the utility value set generated from the PROPEL trial data supplemented by data from the published literature as a majority of the health states (6 out of 9) have available validated utility values.
Paragraph 5, page 85 *"The EAG considers that the use of a convenience sample is inconsistent with the latter and is unclear whether the representativeness of the recruited sample was evaluated."*	Please amend to *"The EAG considers that the use of a convenience sample is inconsistent with the latter* ***~~and is unclear whether the representativeness of the recruited sample was evaluated~~."***	The company submission states that *"The UK sample had demographics representative of the UK population, including a mean age of 42.9 (SD: 17.7) years and 51% male participants (based on the UK census 2011). The demographics in this sample were considered generalisable to the PROPEL clinical trial also (e.g. mean age in the sample was 42.9 years, compared with [redacted] years in PROPEL)."*	Not a factual accuracy. The assertion that the demographics are representative of the UK population does not include any reference to how this was evaluated. The EAG therefore stands by this comment.

Paragraph 2, page 86 *"The EAG has substantive concerns regarding the validity of the utilities as currently implemented in the company's model, which imply extremely low quality of life across the majority of the modelled health states."*	Please amend to "*The EAG has substantive concerns regarding the validity of the utilities as currently implemented in the company's model, which imply* ***~~extremely~~*** *low quality of life across the majority of the modelled health states."*	The use of "extremely" appears non-factual in this context and should be removed accordingly. It is not expected that this amendment will have any wider impact on the report.	Amended as suggested.
Paragraph 2, page 86 *"Indeed, the lives of patients on alglucosidase alfa in the company's base case model generate just [redacted] QALYs over [redacted] life years, implying that the average utility is just [redacted]."*	Please amend to *"Indeed, the lives of patients on alglucosidase alfa in the company's base case model generate just [redacted]* ***discounted*** *QALYs over [redacted]* ***discounted*** *life years, implying that the average utility is just [redacted]."*	Update to use discounted (rather than undiscounted) QALYs and LYs as these values are readily available from the model.	Amended as suggested.
Paragraph 2, page 86 *"If Pompe disease patients indeed experienced such poor quality of life as depicted by the health state values, this would be expected to be better reflected in the testimony of clinicians and patients."*	Please included specific examples and/or sources for the referred to clinician/patient testimony.	Amicus suggest that, for improved clarity, this statement should be supported by corresponding examples/references. It is not expected that this amendment will have any wider impact on the report.	Not a factual accuracy The EAG is referring to the totality of the evidence on the patient experience and not a specific document.
Paragraph 2, page 87 *"In the original submission, the company did not include costs associated with management*	Please amend to "*In the original submission, the company did not include costs associated with management of adverse*	Amicus suggest this amendment to more accurately reflect the corresponding response that had been provided for clarification question B17.	Amended as suggested.

of adverse events, and some patient management costs such as physiotherapy and respiratory consultant costs . In response to points for clarification, the company included additional health-state dependent patient management costs in the form of non-invasive ventilation support assessments and respiratory physiology consultant appointments..”	*events, and some patient management costs such as physiotherapy* ***~~and respiratory consultant costs~~*** *. In response to points for clarification, the company* ***~~included~~ confirmed that the original analysis also included*** *additional health-state dependent patient management costs in the form of non-invasive ventilation support assessments and respiratory physiology consultant appointments..”*	It is not expected that this amendment will have any wider impact on the report.	
Paragraph 3, page 89 *“The annual estimated cost for non-invasive ventilation was £1,908 informed by TA821”*	Please amend to *“The annual estimated cost for non-invasive ventilation was £1,908 informed by* ***Dretzke et al. in line with*** *TA821”*	It is important to note the source used, which Amicus deemed appropriate (and was also in line with TA821).	Amended as suggested.
Paragraph 4, page 89 *“Wheelchair dependent costs were assumed to include the upfront costs for a powered wheelchair of £1,374.74 informed by NHS reference costs 2020/21 (Wheelchair services adults, Equipment, High need, Powered, WC09), home adjustment of £30,000*	Please amend to *“Wheelchair dependent costs were assumed to include the upfront costs for a powered wheelchair of £1,374.74 informed by NHS reference costs 2020/21 (Wheelchair services adults, Equipment, High need, Powered, WC09), home adjustment of £30,000 and hoist of* ***£826.48*** *informed by TA821.”*	Typographical error.	Corrected.

and hoist of £826 informed by TA821."			
Paragraph 4, page 90 *"The patient management costs included hospital inpatient visits (elective and non-elective), outpatient appointments, attendances at accident and emergency departments, primary care appointments and sundry pharmaceuticals."*	Please amend to *"The patient management costs* ***~~included~~*** ***did not include*** *hospital inpatient visits (elective and non-elective), outpatient appointments, attendances at accident and emergency departments, primary care appointments and sundry pharmaceuticals."*	Inaccurate description of the originally submitted economic analysis. It is not expected that this amendment will have any wider impact on the report.	Amended as suggested.

Issue 5 Company's cost effectiveness results – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Paragraph 4, page 91 *"Compared with alglucosidase alfa, the results suggest cipaglucosidase alfa in combination with miglustat is associated with lower costs (incremental cost of [redacted]) and greater benefits (QALY difference of [redacted]) yielding an ICER of [redacted] per QALY gained. This results in a net health benefit (NHB) for cipaglucosidase alfa in combination with miglustat of*	Please amend to *"Compared with alglucosidase alfa, the results suggest cipaglucosidase alfa in combination with miglustat is associated with lower costs (incremental cost of [redacted]) and greater benefits (QALY difference of [redacted]) yielding an ICER of [redacted] per QALY gained. This results in a net health benefit (NHB) for cipaglucosidase alfa in combination with miglustat of [redacted] and [redacted] at willingness-to-*	Values provided in proposed amendment align with those presented in Appendix 1 of the response to the EAG's points of clarification (Updated model base case).	Amended as suggested.

[redacted] *and* [redacted] *at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY, respectively."*	*pay (WTP) thresholds of £20,000 and £30,000 per QALY, respectively."*		

Issue 6 External assessment group's additional analyses – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Paragraph 4, page 101 *"Scenario 5a) therefore uses data from a Canadian study, Nonoyama et al, suggesting an annual cost of £37,87, while scenario 5b) uses data from a Czech study Gajdoš et al, which suggests an annual cost of £57,091"*	Please amend to "*Scenario 5a) therefore uses data from a Canadian study, Nonoyama et al, suggesting an annual cost of* ***£37,838****, while scenario 5b) uses data from a Czech study Gajdoš et al, which suggests an annual cost of £57,091"*	Typographical error.	Corrected.
Section 6.2, page 103 onward Cost-effectiveness results for the individual presented scenarios are currently order by always listing the treatment with the lowest total costs first (n.b. this applies to all tables where results are presented).	Please amend all cost-effectiveness results tables to apply a consistent order of treatments across all presented scenarios (e.g. cipaglucosidase alfa with miglustat, alglucosidase alfa, avalglucosidase alfa).	Whilst not a factual error, Amicus would suggest that the consistent order of treatments might be helpful in facilitating the interpretation and comparison of the different scenario results. It is expected that this amendment would also be reflected in other parts of the report where similar results are presented (e.g. as part of the executive summary).	Not a factual accuracy. The EAG have not updated the cost-effectiveness results tables as suggested. The EAG carried out fully incremental analyses with the treatment options listed by ascending costs as recommend by the NICE manual 2022. This also illustrates the significance of the price of ERT in driving cost-effectiveness results.

Table 37, row 3, page 107 *ICER (avalglucosidase alfa vs alglucosidase alfa):* [redacted] *NHB (avalglucosidase alfa vs alglucosidase alfa):* [redacted]	Based on the provided total/incremental costs and QALYs, please amend to: *ICER (avalglucosidase alfa vs alglucosidase alfa):* [redacted] *NHB (avalglucosidase alfa vs alglucosidase alfa):* [redacted]	Possible calculation error.	Corrected. This was a copy-and-paste error and does not impact any other results or those presented in the confidential appendix.
Paragraph 1, page 114 *"In these analyses net health benefits relatives to alglucosidase ranged between [redacted] and [redacted] QALYs."*	Please could clarification/further detail be provided about where the numbers [redacted] and [redacted] come from and whether they are calculated using a WTP threshold of £20,000/QALY or £30,000 per QALY?	Amicus were unable to find these values in the tables of scenario results presented by the EAG.	Corrected.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease [ID3771]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Thursday 2nd March 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Amicus Therapeutics
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Amicus thanks the external assessment group (EAG) for their assessment of the original submission. In response to the EAG's key issues, the cost-effectiveness analysis has been revised (Table 6). The model structure and inputs not discussed within this response document are otherwise aligned with the company submission and the response to the clarification questions from the EAG. The results from the updated base case and new scenario analyses can be found in Table 11. Within each of these scenario analyses, one aspect of the model is varied at a time (e.g. hazard ratios [HRs] for long-term disease progression) for each comparator to ensure that any effects of varying each aspect on the model results are clear. All results use the [redacted].

In response to Key Issue 7, the model has been updated to sample the correlated baseline parameters from PROPEL via Cholesky decomposition. As part of this process, all mean estimates and standard deviations for the baseline characteristics were updated to be based directly on the PROPEL individual patient data (IPD); this resulted in an update to the average participant weight used in the model. The model included in the original company submission used the mean weight in the cipaglucosidase alfa in combination with miglustat arm of PROPEL, [redacted] kg, whereas the updated base case uses the mean weight of [redacted] kg across both treatment arms. The updated base case and sensitivity analyses presented in this response document have been run with the updated participant weight of [redacted] kg. The probabilistic sampling of weight is based on a standard deviation of [redacted] kg from the PROPEL trial. Therefore, the effect of the difference of [redacted] kg between the two average values on the cost-effectiveness estimates is minimal: the original base case, submitted with the response to the EAG's request for clarification, was run using average weights of [redacted] kg and [redacted] kg, with resultant net health benefits (NHB) of [redacted] and [redacted], respectively. Figure 1 in the Appendix further shows that the distributions of sampled weights demonstrate near-complete overlap for the mean weights of [redacted] kg and [redacted] kg. The model has undergone an independent, full input QC to ensure that no further changes to the data inputs are required.

Table 2: Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: The inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion from the base case analysis	Yes	**Amicus understands that avalglucosidase alfa has recently been made commercially available on the National Health Service (NHS) in England, since the time of the original company submission. The base case analysis has therefore been updated to include avalglucosidase alfa as a comparator as requested by the EAG. However, given avalglucosidase alfa was only recently made commercially available in February 2023,[1] and the fact that alglucosidase alfa is widely used in the United Kingdom (UK), Amicus maintains that alglucosidase alfa remains the standard of care treatment, rather than avalglucosidase alfa, in line with UK expert opinion. Therefore, whilst a fully incremental analysis is presented featuring both comparators, Amicus maintains that alglucosidase alfa remains established care at present.** Avalglucosidase alfa was not commercially available in the UK for the treatment of adults with late-onset Pompe disease (LOPD) at the time of the original company submission in October 2022,[2, 3] and as a result was not included as a primary comparator. Since avalglucosidase alfa was made available on the NHS in February 2023,[1] it has been included as a comparator in the updated base case. However, since its approval for use in Pompe disease in 2006, alglucosidase alfa remains the established standard of care for the treatment of adults with Pompe disease in England, making it the most relevant comparator for the decision problem. Please see Section B.1.3.3 of the main company submission for further information regarding the widespread use of alglucosidase alfa in adults with LOPD.

		In line with the EAG's base case, Amicus presents in this response a fully incremental analysis to assess the cost-effectiveness of cipaglucosidase alfa in combination with miglustat vs both alglucosidase alfa and avalglucosidase alfa. In the updated base case, treatment effectiveness is informed by results from the randomised control trial (RCT)s-only multilevel network meta-regression (ML-NMR; see response to Key Issue #4), so that consistent assumptions are applied to each treatment (as described below), allowing a fully incremental analysis to be conducted in line with NICE preferences. Treatment effectiveness is modelled as follows for all three treatments (with effectiveness data presented in Table 8, Table 9 and Table 10 for the total, enzyme replacement therapy (ERT)-naïve and ERT-experienced population respectively [see response to Key Issues #2 and #5]): • **Baseline characteristics** continue to be informed by the PROPEL trial (see the response to Key Issue #7); • **Change from Baseline to Year 1** in six-minute walk distance (6MWD) and forced vital capacity (FVC) % predicted are informed by the ML-NMR results using RCT data only, i.e. excluding single arm trials (see the response to Key Issue #4); • **Subsequent annual change from Year 2 onwards** in 6MWD and FVC % predicted is informed by long-term data from Semplicini *et al*. (reporting on treatment with alglucosidase alfa), with HRs for the rate of disease progression applied to each treatment individually (see the response to Key Issue #3). Additionally, the cost per vial of avalglucosidase alfa has been updated from an estimated £712.12 (in the original submission) to £783.33 in the updated base case, in line with the recently published UK list price.[4] All further inputs relating to

		avalglucosidase alfa are detailed in the response to the EAG's points for clarification (Question B8).
Issue 2: Differences between the ERT-naïve and ERT-experienced populations	Yes	**Clinical opinion from UK consultants indicates that there is no biological plausibility for a difference in expected benefit between ERT-naïve and ERT-experienced adults with Pompe disease. Additionally, to Amicus' knowledge, NICE evaluated avalglucosidase alfa (TA821) in the total population of LOPD, without considering prior ERT-defined subpopulations in detail, despite COMET exclusively including ERT-naïve participants. However, Amicus accepts the EAG's base case approach of presenting results separately for the total population and each subpopulation to explore the assumption that there are minimal expected differences in cost-effectiveness between ERT-naïve and ERT-experienced adults with LOPD. In these analyses, cipaglucosidase alfa in combination with miglustat remains cost-effective across the total population and within each subpopulation. However, Amicus maintains that the value of cipaglucosidase alfa in combination with miglustat should be assessed in the overall population of adults with LOPD.** Clinical advice provided to the EAG suggested a hypothesis that a larger, but delayed, treatment effect is expected for ERT-naïve adults treated with cipaglucosidase alfa in combination with miglustat compared to ERT-experienced adults, who would already have an improved clinical status from previous treatment. However, Amicus do not believe that this statement is reflective of PROPEL or what is observed in clinical practice: • ERT-naïve adults often present with improved clinical status in comparison to ERT-experienced adults, given they are often in the earlier stages of disease progression. Contrary to the clinical advice provided to EAG, it cannot be generally assumed that ERT-naïve adults will experience a larger improvement in the response to treatment compared with ERT-experienced

		adults. Both ERT-naïve and ERT-experienced individuals would be expected to benefit from the treatment. • Additionally, the importance of the benefits of cipaglucosidase alfa in combination with miglustat in ERT-experienced individuals should not be diminished: benefits with alglucosidase alfa are not typically sustained, and decline in motor and respiratory function is typically observed within 2–3 years of ERT treatment.[5-9] Therefore, clinical improvements in the ERT-experienced group are also considered highly relevant and meaningful to adults with LOPD. • The substantial unmet need for effective treatments in the ERT-experienced LOPD population as explained above is supported by demand seen for the early access to medicines scheme (EAMS) for cipaglucosidase alfa in combination with miglustat, for which ERT-experienced were eligible.[10] ERT-experienced adults have been treated under the EAMS since November 2021, and have noted being able to perform daily activities, having "more energy", "in general feeling much better and stronger every day" and feeling an "enormous" decrease in pain levels.[11] • Results from PROPEL indicated significant reductions in biomarkers of disease activity, creatine kinase and hexose tetrasaccharide, with cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa in both the ERT-naïve and ERT-experienced subpopulations. This indicates response to treatment in both subpopulations. Therefore, given the evidence described above, Amicus does not believe that it is appropriate to conclude that the benefits of cipaglucosidase alfa in combination with

		miglustat would be of different magnitude or value to individuals in either subpopulation. Furthermore, Amicus has concerns with decision-making based on assessment of the cost-effectiveness of cipaglucosidase alfa in combination with miglustat separately in the ERT-naïve and ERT-experienced participants, for the reasons listed below. • Clinicians in the UK do not anticipate treating ERT-naïve and ERT-experienced adults any differently, and as explained above from a biological perspective, there is no reason to expect different efficacy results between ERT-experienced and ERT-naïve adults with LOPD.[9] • This precedent was also set in the NICE appraisal for avalglucosidase alfa which, to Amicus' knowledge, appraised and accepted the clinical and cost-effectiveness of avalglucosidase alfa within its marketing authorisation for treating Pompe disease regardless of ERT experience, considering trial data from ERT-naïve participants only. • For the comparison between cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa in the total population, the ML-NMR was used as it allowed adjustment for differences in participant population characteristics between RCTs, making use of both individual patient data and aggregate data. This approach enabled within- and between-study variation to be considered with populations that differ (in particular by prior treatment status in the comparisons within the total population). As requested by the EAG, Amicus has sought clinical opinion on the proportion of ERT-naïve and ERT-experienced individuals in UK clinical practice. NHS England and clinical opinion from UK consultants indicated that approximately [redacted] new individuals are diagnosed with Pompe disease in the UK each year. In comparison, the number of treated adults in England with LOPD is estimated to be [redacted] (see Section B.1.3.1 in

		the main company submission),[12] highlighting the comparatively small size of the ERT-naïve population. Despite the concerns outlined above, Amicus acknowledges that the EAG would prefer to investigate the cost-effectiveness of cipaglucosidase alfa in combination with miglustat across the ERT-naïve and ERT-experienced populations. This would test the assumption that there are minimal expected differences in cost-effectiveness between ERT-naïve and ERT-experienced adults with LOPD. The updated base case analysis therefore assesses cost-effectiveness in the total population of adults with LOPD, as well as in each subpopulation separately. The effectiveness inputs for the ERT-naïve and ERT-experienced populations are presented in Table 9 and Table 10, respectively, based on the ML-NMRs excluding single-arm trials (see response to Key Issue #4). In these analyses, cipaglucosidase alfa in combination with miglustat remains cost-effective across the total population and within each subpopulation. However, Amicus maintains that it would be inappropriate to suggest that the benefits of cipaglucosidase alfa in combination with miglustat would be of different value to individuals in either subpopulation, so assessing cost-effectiveness in the total population alone remains the most appropriate and robust approach. Considering the expected value of cipaglucosidase alfa in combination with miglustat in the total population, caution should be exercised when interpreting cost-effectiveness in each subpopulation separately.
Issue 3: Uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat	Yes	**In order to attempt to account for the lack of data on long-term effectiveness of ERTs in Pompe disease, Amicus accepts the EAG's approach of presenting analyses with different HRs for disease progression rates with alglucosidase alfa vs cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa. Expert opinion from UK consultants specialising in LOPD indicated that individuals receiving cipaglucosidase alfa in combination with miglustat will**

		likely experience disease progression in the long-term; however, the rate of this decline is expected to be [redacted] than that observed with alglucosidase alfa treatment. Expert opinion also indicated that a HR in the region of that submitted as part of the updated base case ([redacted]) is clinically plausible, whereas the HR of 0.3 explored by the EAG would not be plausible. In scenario analyses utilising different HRs ([redacted]; Scenario analyses #17–#20), cipaglucosidase alfa in combination with miglustat remains the cost-effective treatment option. However, Amicus maintains that a treatment which extends life vs standard of care should not be unduly penalised due to the cost of ongoing treatment during the period of extended life, in line with patient and clinician opinion. The assumptions utilised in the updated base case and scenario analyses related to the relative long-term effectiveness of cipaglucosidase alfa in combination with miglustat in comparison to alglucosidase alfa are detailed below. ***Assumption 1: that individuals receiving cipaglucosidase alfa in combination with miglustat and those receiving avalglucosidase alfa experience long-term disease progression*** It is well established that individuals receiving alglucosidase alfa experience long-term disease progression after 2–3 years of treatment.[5-9] Long-term data for avalglucosidase alfa (5.5 years) indicate mildly declining clinical outcomes.[13] Longer-term data are not available for either cipaglucosidase alfa in combination with miglustat or avalglucosidase alfa. However, given the similarity in the mechanisms of action of the three ERTs in question, it is accepted by clinicians that individuals receiving either cipaglucosidase alfa in combination with miglustat or avalglucosidase alfa will very likely also experience disease progression in the long term and the average age of survival is unlikely to reach that of the general population. In addition, it was assumed during the appraisal of avalglucosidase alfa that individuals receiving this treatment

		would experience long-term disease progression as with alglucosidase alfa. Therefore, the updated base case in this response continues to assume that individuals receiving cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa will experience long-term disease progression. ***Assumption 2: HRs of long-term disease progression between ERT treatments in the updated base case*** The base case analysis submitted as part of the response to the EAG's request for clarification employed a lifetime horizon, and cipaglucosidase alfa in combination with miglustat [redacted] (in the current absence of evidence). On average, in this analysis, individuals receiving cipaglucosidase alfa in combination with miglustat benefitted from [redacted] more (discounted) years of life than those receiving alglucosidase alfa in the previous base case. The EAG conducted a series of analyses varying the HR of disease progression, as detailed in the 'Scenario analyses' section within the response to this issue. Based on the lack of long-term data on disease progression with cipaglucosidase alfa in combination with miglustat, beyond stability in clinical outcomes for up to 48 months of treatment,[14] clinical and patient experts were consulted on plausible assumptions around the relative rates of long-term progression. Clinical and patient experts noted that HRs in the region of those specified below are clinically plausible, and so the following rates of long-term disease progression are assumed in the updated base case: • Disease progression with cipaglucosidase alfa in combination with miglustat [redacted] than with alglucosidase alfa (i.e. HR=[redacted] vs alglucosidase alfa)

		• Disease progression with avalglucosidase alfa [redacted] than with alglucosidase alfa (i.e. HR=[redacted] vs alglucosidase alfa or HR=[redacted] vs cipaglucosidase alfa in combination with miglustat) In the updated base case, the survival impact with cipaglucosidase alfa in combination with miglustat is as follows: • [redacted] discounted life years (i.e. longer length of life) than with alglucosidase alfa • [redacted] discounted life years (i.e. similar length of life) than with avalglucosidase alfa, indicating similar treatment effectiveness in line with the ML-NMR ***Scenario analyses*** The EAG conducted a series of analyses varying the HR of disease progression: cipaglucosidase alfa in combination with miglustat remained cost-effective with HR=0.7 but not when disease progression was slowed further to HR=0.3 (i.e. 70% slower disease progression). Clinical and patient expert feedback indicated that a HR of 0.3 applied to the next-generation ERTs was clinically implausible. Additionally, clinical feedback indicated that the HR of [redacted] presented by the EAG would also be unlikely, but could be used as the lower-bound, clinically plausible estimate for rate of decline in 6MWD (i.e. minimum HR) for a conservative scenario analysis. Table 3 presents the series of scenario analyses that were conducted varying the relative rates of disease progression, with results presented in the section 'Sensitivity analyses around revised base case'. Across these scenario analyses and in each subpopulation, cipaglucosidase alfa remains the cost-effective treatment option. **Table 3: Scenario analyses varying HRs of long-term disease progression**

Scenario	Cipa+mig vs alglu	Aval vs alglu	Rationale
Base case	[redacted]	[redacted]	Based on available OLE data for each treatment, and clinical validation
#17	[redacted]	[redacted]	To explore [redacted] progression rates between cipa+mig and aval
#18	[redacted]	[redacted]	To explore [redacted] progression rates between cipa+mig and aval, assuming the slowest plausible progression rate vs alglu (i.e. conservative scenario)
#19	[redacted]	[redacted]	To explore the slowest plausible progression rate for cipa+mig vs alglu (i.e. conservative scenario)
#20	[redacted]	[redacted]	To explore the slowest plausible progression rate for aval vs alglu

Abbreviations: alglu: alglucosidase alfa; aval: avalglucosidase alfa; cipa+mig: cipaglucosidase alfa in combination with miglustat; HR: hazard ratio; OLE: open-label extension.

Interpretation of the penalisation of life extension

From the results of the updated base case and scenarios, the improved survival with cipaglucosidase alfa in combination with miglustat continues to counter-intuitively and negatively impact cost-effectiveness estimates. Individuals receiving cipaglucosidase alfa in combination with miglustat live longer than those receiving alglucosidase alfa, which represents an important outcome for adults with LOPD and carers, addressing severe unmet needs. However, prolonged survival requires more years of active treatment and incurs more resource use over the lifetime time horizon whilst accruing relatively fewer quality-adjusted life years (QALYs) in old age. Conversely, individuals receiving alglucosidase alfa die earlier on average, and thus do not continue to incur costs. The resulting interpretation of cost-effectiveness could therefore be misleading

		in that the benefit of prolonged survival is complicated by the requirement for continued treatment. Overall, cipaglucosidase alfa in combination with miglustat is penalised for providing improved survival compared with alglucosidase alfa, which represents an unfair assessment of the value of an improved treatment to adults with LOPD and caregivers, as supported by the submissions made by patient group stakeholders to this NICE appraisal.
Issue 4: Use of single arm studies in the indirect treatment comparison	Yes	**The exclusion of single-arm trials reduces the sample size of the ML-NMR and removes all ERT-experienced participants receiving avalglucosidase alfa from the analysis, in contrast to clinical practice in the UK in which the majority of individuals are ERT-experienced. However, in recognition of the potential for bias when incorporating single-arm evidence into an ML-NMR, Amicus accepts the EAG's approach to only use RCTs in the ML-NMR, and has used these ML-NMR results in the updated base case with alglucosidase alfa and avalglucosidase alfa as comparators.** Amicus presented an ML-NMR to compare the effectiveness of cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa, measured with 6MWD and FVC % predicted, via the common comparator alglucosidase alfa, in the population of adults with LOPD (Amicus Data on File 2022 Indirect Treatment Comparison Report). Whilst PROPEL included both ERT-naïve and ERT-experienced participants, the RCT of avalglucosidase alfa (COMET) only included ERT-naïve participants by design. Therefore, an ML-NMR informed by only RCTs excludes all data from ERT-experienced participants receiving avalglucosidase alfa, resulting in a population that is not representative of the target population of interest in UK real-world practice, in which the majority of adults are ERT-experienced. Furthermore, the available RCT data in LOPD are limited by small population sizes, increasing the uncertainty associated with the ML-NMR. In excluding single-arm studies, the combined effect of the misalignment of the RCTs-only ML-NMR population and UK clinical practice, and

		the reduced sample size, was to substantially increase uncertainty in the relative effectiveness estimates (6MWD and FVC % predicted). In rare diseases, the pooling of data is often required due to the uncertainty resulting from small sample sizes and limited bodies of evidence whilst accepting the potential introduction of bias. Incorporating matched single-arm trials into the ML-NMR evidence network not only increased the sample size in the analysis, thereby reducing uncertainty, but also allowed the incorporation of clinical evidence for avalglucosidase alfa from a mix of ERT-naïve and ERT-experienced participants, better aligning with the target population of interest in UK real-world practice, than using RCT data alone. The single-arm studies were matched based on previous ERT duration in order to limit heterogeneity between the single and matched arms, using a pooled method in which the matched data are treated the same as RCT data. However, despite the increased uncertainty in the RCT-only analysis, misalignment with the target population of interest and reduced sample size, Amicus acknowledge that matching of single-arm trials can result in biased relative effect estimates when there is heterogeneity between the single and the matched arms. Hence, there is a trade-off between a potential bias in the relative effect estimates when including single-arm evidence and a large increase in uncertainty of those estimates when removing the single-arm evidence, and Amicus have adopted the conservative approach of excluding single-arm trials from the ML-NMR in order to minimise bias. Therefore, in the updated base case, results of the ML-NMR excluding single-arm trials have been used for the analyses of the total population, ERT-naïve and ERT-experienced subpopulations. Although this ML-NMR analysis excluded data on avalglucosidase alfa from ERT-experienced individuals, the ML-NMR approach allowed adjustment for differences in prior ERT duration between RCTs, making use of both individual patient data from the full PROPEL population and aggregate trial data in the regression model.

		However, Amicus would like to emphasise that including the matched single-arm studies in the evidence network provides a valuable approach to estimate the effectiveness of cipaglucosidase alfa in combination of miglustat relative to avalglucosidase alfa within a mixed ERT-naïve and ERT-experienced population. For the initial change from Baseline (i.e. to Year 1) in 6MWD and FVC % predicted, the effectiveness inputs from the ML-NMRs excluding single-arm trials used in the updated base case (with alglucosidase alfa and avalglucosidase alfa) are presented for the overall, ERT-naïve and ERT experienced populations in Table 8, Table 9 and Table 10, respectively.
Issue 5: Indirect treatment comparison including both ERT-naïve and ERT-experienced participants	Yes	**As discussed in Key Issue #2, Amicus has adopted the approach of presenting scenario analyses in the ERT-naïve and ERT-experienced subpopulations, in addition to the base case covering the total population, to demonstrate that the economic value of the treatment is consistent across subpopulations (Scenario analyses #17–#20). In line with Key Issue #4, the ML-NMR using only RCTs, rather than a Bucher indirect treatment comparison (ITC), has been used in the ERT-naïve population.** As described in Key Issue #2, there is no biologically plausible reason that the benefits observed in the ERT-experienced LOPD subpopulation would not be translatable to the ERT-naïve LOPD subpopulation. However, the revised base case analysis and scenarios have been presented separately for the ERT-naïve and ERT-experienced populations (Key Issue #2) to address the EAG's feedback and explore the consistency in the economic value of cipaglucosidase alfa in combination with miglustat between both subpopulations and the total population. Regarding the base case analysis in the ERT-naïve population, Amicus presented ML-NMR analyses alongside the original submission (Amicus Data on File 2022 Indirect Treatment Comparison Report) setting previous ERT duration to zero, which

		extrapolated results to an ERT-naïve population using data from the full PROPEL population. Conversely, the EAG undertook simple indirect comparisons in the ERT-naïve population using the Bucher method which assumes homogeneity between trials. Given that disease-modifying participant baseline characteristics differed between PROPEL and COMET, Amicus sought statistical advice from experts and concluded that an ML-NMR which can adjust for differences in population characteristics and include individual patient data from the total PROPEL population is more appropriate than a Bucher analysis. Therefore, in the fully incremental, base case economic analyses in the ERT-naïve subpopulation vs avalglucosidase alfa and alglucosidase alfa, the ML-NMR results from analyses which excluded single arm trials have been used. Amicus agree with the EAG that the ML-NMR estimates (excluding single-arm trials) are within the Bucher 95% confidence intervals (Cis) but the latter are generally more uncertain, which is expected as the Bucher analyses include data on fewer participants, whereas ML-NMR uses the total population to adjust for ERT-naïve status. In the analyses in the ERT-experienced population vs both comparators, the ML-NMRs excluding single-arm trials were also used. Previous ERT duration was set to 5 years, which equals the median previous ERT duration in PROPEL (referred to in the ITC report as the 'medium ERT duration scenario').
Issue 6: Cost-effectiveness of comparator treatments	No	**Despite not being evaluated by NICE for cost-effectiveness, alglucosidase alfa is an appropriate comparator given it is the established clinical practice for treatment of adults with Pompe disease in the UK, and was the comparator in the NICE appraisal of avalglucosidase alfa (TA821). Amicus agrees with the EAG's determination that this issue is not resolvable within the scope of the appraisal, (which covers the current treatment landscape in England), in line**

		with the approach taken by NICE as discussed during the technical engagement meeting. Therefore, no further analysis has been undertaken. The NICE process and methods guide states that comparators should only include treatments that are "established practice in the NHS".[15] Alglucosidase alfa has formed established practice in the NHS for many years, and the EAG recognise it as current standard of care: • European consensus recommendations were published in 2017, advocating the use of ERT alongside supportive care in adults and children with a confirmed diagnosis of Pompe disease[16] • Expert opinion indicates that alglucosidase alfa is currently given as a first-line treatment and nearly all people with Pompe disease have been treated with alglucosidase alfa in the UK,[9] in line with a UK study of 62 people with LOPD in which only three had not been treated with alglucosidase alfa.[17] Full details of the use of alglucosidase alfa in clinical practice in England can be found in Section B.1.3.3 of the company submission • Alglucosidase alfa has been funded by the NHS for at least 16 years and will likely continue to be funded for some years. It is reasonable to assume the opportunity cost of allocating funding for this medicine has been factored into NHS planning over this period and will be in the future Therefore, a full cost-utility analysis comparing cipaglucosidase alfa in combination with miglustat to alglucosidase alfa does demonstrate the cost-effectiveness (and hence additional value) of the intervention compared with the current use of NHS resources (i.e. compared with standard of care in LOPD). Additionally, in line with the response to Key Issue #1, a fully incremental analysis considering both alglucosidase alfa and avalglucosidase alfa is presented in this response. The positive NHB of [redacted] provided by cipaglucosidase alfa in combination with miglustat in comparison to

		alglucosidase alfa also demonstrates an overall increased improvement to population health in the NHS if the treatment is adopted. Finally, as the EAG recognised, alglucosidase alfa formed the relevant comparator in the NICE appraisal of avalglucosidase alfa. Therefore, Amicus agree with the EAG that that this issue is not resolvable within the scope of the appraisal, and that including alglucosidase alfa as a comparator in the appraisal is in line with the NICE final scope, which was based on the current treatment landscape in England.
Issue 7: Improper parameterisation of model	Yes	**Amicus acknowledges the EAG's concerns regarding the applied distributions for the sampling of likely correlated baseline characteristics as part of the first-order patient simulations. In line with the EAG's suggestion, this has therefore been amended in the economic model.** A variance-covariance matrix for the following baseline parameters has been generated from individual participant data of the entire PROPEL intention-to-treat (ITT) population (N=123): average participant age (in years), average participant weight (in kg), average participant height (in cm), average 6MWD (in m), average FVC % predicted. The variance-covariance matrix has subsequently been used to inform the joint sampling of the above parameters for each of the 30,000 patient simulations for the updated base case analysis (and scenario analyses). The variance-covariance matrix can be found in the Set-up sheet within the updated model.
Issue 8: Utilities generated using a non-reference case approach	Yes	**Amicus maintains that the utility values derived from the vignette study presented in the main company submission are robust and in line with the with the NICE hierarchy of health-related quality-of-life (HRQoL) evidence,[18] and Decision Support Unit (DSU) best practice recommendations.[19] However, Amicus accepts the value of using utility values generated from participants**

		directly for decision making, even if outputs from the PROPEL study were unable to comprehensively populate all health state utilities. EQ-5D-5L data from the PROPEL trial were not suitable for informing the utility of 'later' health states that required invasive respiratory support or a combination of mobility and respiratory support, because most of the included participants had not yet reached the later severe health states over the 52-week trial follow-up period. Given that these data were only able to inform the utility associated with three of the health states,[20] multiple utility sources would need to have been used to assign utilities to each health state in the original submission (as per Scenario analysis #6 in the original submission). Based on the NICE hierarchy of preferred HRQoL methods, if EQ-5D data from the trial or literature are not appropriate, vignettes should be used. Given the paucity of data reporting on the HRQoL of a rare disease like Pompe disease, a vignette study was conducted in line with DSU best practice recommendations.[19] The vignettes were validated by healthcare professionals and were reviewed by individuals with LOPD who had experienced that health state, to ensure they accurately represented living with LOPD. The resulting utility values used in the base case (using EQ-5D) for each health state were validated by clinical experts.[9] Amicus would like to clarify that the base case utility values in the company submission derived from EQ-5D valuation of health state vignettes rather than using the time trade-off (TTO) method, in line with the NICE hierarchy of HRQoL evidence[18] and Decision Support Unit (DSU) best practice recommendations.[19] TTO rating of vignettes informed a scenario analysis. Both sets of utility values (EQ-5D and TTO) derived from the vignette study conducted by Amicus showed a similar trend, with results from some participants yielding utilities worse than death for the most advanced clinical presentations of LOPD, highlighting the severity of the disease. TTO weights were marginally higher than EQ-5D utilities,

as has been observed in previous research.[21, 22] Therefore, the utility values derived from the vignette study are considered to have high face validity. In addition to clinical validation, the use of these values in the model is supported by their similarity to those derived from the PROPEL trial and the published values from Malottki *et al.*[23] and Kanters *et al.*[24]

Despite this support for the validity and robustness of the vignette study utility values, Amicus accepts the value of using utilities derived from participants directly, and therefore has aligned with the EAG's model which uses PROPEL utility values supplemented by values from the vignette study in the updated base case.

Table 4: Utility values used in the updated base case

Health state	Base case utility	Source
No wheelchair use or respiratory support (0–5 years alive from treatment initiation)	0.608 (0.120)	Amicus vignette study
No wheelchair use or respiratory support (6–15 years alive from treatment initiation)	0.608 (0.120)	Amicus vignette study
No wheelchair use or respiratory support (>15 years alive from treatment initiation)	[redacted]	PROPEL
Intermittent mobility support	[redacted]	PROPEL
Intermittent, non-invasive respiratory support	0.361 (0.190)	Amicus vignette study
Intermittent mobility support and intermittent, non-invasive respiratory support	0.289 (0.244)	Amicus vignette study
Wheelchair dependent	[redacted]	PROPEL
Wheelchair dependent and intermittent, non-invasive respiratory support	[redacted]	Amicus vignette study

		Wheelchair and invasive respiratory support dependent | [redacted] | Amicus vignette study [a]Utility predictions extrapolated for severe health states (i.e. mobility dependent) from PROPEL data would be outside of sample estimates and consequently should be treated with caution.
Issue 9: Resource use for invasive home mechanical ventilation	Yes	**Amicus maintains that Noyes *et al*. is the most appropriate source for invasive home mechanical ventilation given it was conducted in the UK setting, is therefore relevant to NHS England and, according to clinical expert opinion, is likely to provide an underestimate of invasive ventilation costs. Although expert opinion from UK consultants suggests that Noyes *et al*. is a conservative estimate of invasive ventilation costs, a scenario has been run using data from Gajdoš *et al*. in order to further assess the impact of ventilation costs.** In response to previous critique from the EAG that costs from Noyes *et al*. were likely to be overestimating the cost of invasive ventilation and not generalisable to an adult population, an experienced UK consultant estimates that costs associated with invasive mechanical ventilation well exceed that reported by Noyes *et al.* and would not vary substantially between adult and paediatric populations. Noyes *et al*. reports the upfront cost of invasive ventilation to be £133,277.00 and the subsequent annual cost to be £142,790.00 (accounting for inflation), lower than that reported by the clinician. Additionally, as the EAG pointed out, Noyes *et al.* was conducted in 2002, however, feedback from the clinician indicates that invasive ventilation costs are only likely to have increased since the study was conducted even after accounting for inflation. Therefore, Noyes et al. is likely to be substantially underestimating these costs, even when accounting for inflation. Noyes *et al.* was conducted in the UK setting whereas Gajdoš *et al*. was conducted in Czechia, and costs are not easily translatable across healthcare systems with different clinical pathways. Additionally, Noyes *et al.* was included and accepted during the

		appraisal of avalglucosidase alfa. Amicus therefore maintains that the invasive ventilation costs informed by Noyes *et al*. is the most appropriate. Although Noyes et al. is considered by the expert to be a conservative estimate, Amicus conducted a scenario analysis using the inputs from Gajdoš *et al*. to assess the impact of invasive ventilation costs on the cost-effectiveness of cipaglucosidase alfa in combination with miglustat in the total population (Scenario #21). In this scenario, no upfront, one-off cost was used and the annual cost of invasive ventilation was set to £57,091; cipaglucosidase alfa in combination with miglustat remained the dominant treatment. However, given Gajdoš *et al*. was conducted in Czechia and in ALS, the results have limited generalisability to the UK LOPD setting.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 5: Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: **Inpatient management costs included as per TA821**	Section 4.3.8 (Page 90)	Yes	**There is a lack of robust data to inform treatment-related differences in healthcare resource use beyond those already modelled. However, Amicus agrees that it is reasonable to include these costs in the base case for consistency with the NICE appraisal of avalglucosidase alfa (TA821) and to demonstrate their minimal impact on cost-effectiveness. The updated base case therefore includes health-state costs aligned with TA821.** Although there is a lack of robust data to inform treatment-related difference in healthcare resource use beyond those already modelled, Amicus agrees that aligning with the assumptions accepted in TA821 is a reasonable approach in the absence of more informed alternatives. Therefore, an additional annual patient management cost of £2,253.25 is included in the updated base case, in line with the NICE appraisal of avalglucosidase alfa (TA821) and the EAG's preferred assumption. This cost includes hospital inpatient visits (elective and non-elective), outpatient appointments,

			attendances at accident and emergency departments, primary care appointments and sundry pharmaceuticals.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Changes to the Company's revised base case aim to address the EAG's Key Issues #1, #2, #3, #4, #5, #7, #8 and Additional Issue #1, outlined in Table 4 below. The EAG's Key Issues #3 and #9 are subsequently explored in a series of scenario analyses (Table 6). Key Issue #6 is not resolvable in the scope of this appraisal.

Table 6: Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement
Issue 1: The inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion from the base case analysis	Avalglucosidase alfa was included as a secondary comparator and explored in scenario analyses #1 and #2 in the original company submission, and subsequently in scenario analysis #15 in the response to the EAG's points for clarification.	Avalglucosidase alfa has been included as a comparator in the fully incremental, base case analysis. The ML-NMRs (excluding single-arm trials) informed clinical effectiveness across all treatments from Baseline to Year 1 (Table 9). From Year 2 onwards, effectiveness was determined by applying HRs for long-term disease progression relative to alglucosidase alfa (see Key Issue #3 below).

Issue 2: Differences between the ERT-naïve and ERT-experienced populations	In the original submission, cost-effectiveness results were presented in the total population only.	The base case cost-effectiveness results are presented in the total, ERT-naïve and ERT-experienced populations separately. Effectiveness inputs are presented in Table 9, Table 10 and Table 11, respectively.
Issue 3: Uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat	The original company base case assumed a HR of [redacted] applied to the long-term disease progression rate with cipaglucosidase alfa in combination with miglustat vs alglucosidase alfa. Previously presented scenarios assumed: • **Scenario analysis #1**: [redacted] rate between avalglucosidase alfa and alglucosidase alfa (i.e. both with [redacted] than with cipaglucosidase alfa in combination with miglustat) • **Scenario analysis #2**: [redacted] rate with avalglucosidase alfa vs alglucosidase alfa (i.e. [redacted] with avalglucosidase alfa than with cipaglucosidase alfa in combination with miglustat) • **Scenario analysis #15**: [redacted] rate between avalglucosidase alfa and cipaglucosidase alfa in combination with miglustat (i.e. both [redacted] than with alglucosidase alfa)	In the updated base case which now includes avalglucosidase alfa, the following rates of long-term disease progression are assumed: • Disease progression with cipaglucosidase alfa in combination with miglustat [redacted] than with alglucosidase alfa (i.e. HR=[redacted] vs alglucosidase alfa) • Disease progression with avalglucosidase alfa in combination with miglustat [redacted] than with alglucosidase alfa (i.e. HR=[redacted] vs alglucosidase alfa) A set of scenario analyses explores the clinically plausible range of HRs.
Issue 4: Use of single arm studies in the indirect treatment comparison	In the scenarios corresponding to the base case in the original company submission including avalglucosidase alfa as a comparator (Scenarios #1, #2 and #15), single-arm studies were included in the ML-NMR that informed the relative treatment	The updated base case, which includes avalglucosidase alfa, utilises results from the ML-NMR excluding single-arm trials. The inputs used in

	efficacy compared to cipaglucosidase alfa in combination with miglustat.	the updated base case are summarised in Table 8, Table 9 and Table 10.
Issue 5: Indirect treatment comparison including both ERT-naïve and ERT-experienced participants	In the original submission, cost-effectiveness results of the scenarios including avalglucosidase alfa (i.e. using the ML-NMR) were presented in the total population only.	The base case cost-effectiveness results (now including avalglucosidase alfa) are presented in the total, ERT-naïve and ERT-experienced populations separately. Effectiveness inputs, including the ML-NMR values for the initial annual change, are presented in Table 8, Table 9 and Table 10, respectively.
Issue 7: Improper parameterisation of model	In the company base case, baseline characteristics were assumed to be perfectly correlated.	The base case now assumes joint distributions for relevant parameters. A variance-covariance matrix for the following baseline parameters has been generated from individual patient data of the entire PROPEL ITT population (N=123): average participant age (in years), average participant weight (in kg), average participant height (in cm), average 6MWD (in m), average %pred FVC. The variance-covariance matrix has subsequently been used to inform the joint sampling of the above parameters for each of the 30,000 participant simulations for the updated base case analysis (and scenario analyses).
Issue 8: Utilities generated using a	The company base case used EQ-5D values derived from a vignette study to inform utilities in the cost-effectiveness analysis.	Amicus have incorporated the EAG's preference to use utility values from PROPEL, supplemented by values from the vignette study for more severe

non-reference case approach		health states which were not captured in PROPEL. The utility values used in the revised base case are summarised in Table 4 (Key Issue #8).
Additional issue 1: Inpatient management costs included as per TA821	Patient management costs included regular six-monthly follow-up outpatient appointment with a consultant neurologist for all individuals, annual assessments for individuals receiving non-invasive ventilation, and annual appointments with a respiratory physiology consultant for individuals receiving invasive ventilation.	Amicus have incorporated the EAG's preference and patient management costs for hospital inpatient visits (elective and non-elective), outpatient appointments, attendances at accident and emergency departments, primary care appointments and sundry pharmaceuticals were included in line with TA821: £2,253.25 per person per year.
N/A: Participant weight	The original base case used the mean weight in the cipaglucosidase alfa in combination with miglustat arm of PROPEL, [redacted] kg.	The updated base case uses the mean weight across both treatment arms, [redacted] kg, although this update does not have substantial impact on the cost-effectiveness results as explained under 'Key issues for engagement' (see also Figure 1 showing the normal distributions of sampled participant weight when mean weight is [redacted] kg vs [redacted] kg).
N/A: Acquisition cost of avalglucosidase alfa	The original base case used an estimated cost per vial of avalglucosidase alfa of £712.12.	The updated base case uses a cost per vial of avalglucosidase alfa of £783.33, in line with the recently published list price.[4]
Company's base case following technical engagement (or revised base case)	The results of the updated fully incremental, base case analysis are presented in Table 7. Cipaglucosidase alfa in combination with miglustat remains the most cost-effective use of NHS resources.	

Table 7: Updated base case results (fully incremental analysis inclusive of patient access scheme (PAS) for cipaglucosidase alfa in combination with miglustat) HRs: Cipa+mig vs alglu: [redacted]; Aval vs alglu: [redacted]

Intervention	Costs (discounted)	QALYs (discounted)	Incremental costs (discounted)	Incremental QALYs	ICER	NHB at £20,000/QALY
Total population						
Cipa+mig	[redacted]	[redacted]	-	-	-	
Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERT-naïve population						
Cipa+mig	[redacted]	[redacted]	-	-	-	
Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERT-experienced population						
Cipa+mig	[redacted]	[redacted]	-	-	-	-
Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERT: enzyme replacement therapy; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

Effectiveness data in the updated base case

The effectiveness data utilised in the updated base case for the total, ERT-naïve and ERT-experienced populations is included below in Table 8, Table 9 and Table 10, respectively. PROPEL (ITT) data were used to inform baseline participant characteristics for each of these populations and the initial annual change for cipaglucosidase alfa in combination with miglustat. In line with Key Issue #4, data from the ML-NMR excluding single arm

trials were used for the initial annual change for alglucosidase alfa and avalglucosidase alfa. Subsequent annual change inputs are informed by Semplicini *et al*., with an assumed HR of [redacted] for cipaglucosidase alfa in combination with miglustat and HR of [redacted] for avalglucosidase alfa, both compared to alglucosidase alfa (Key Issue #3).

Table 8: Effectiveness inputs for the comparisons in the total population

Parameter	Cipaglucosidase alfa in combination with miglustat	Alglucosidase alfa	Avalglucosidase alfa	Source
Participant characteristics				
Baseline average participant age (SD), years	[redacted]			PROPEL (ITT)
Baseline average participant weight (SD), kg	[redacted]			
Baseline average participant height (SD), cm	[redacted]			
Baseline 6MWD (SD), m	[redacted]			
Baseline FVC % predicted (SD)	[redacted]			
Initial annual change				
Baseline to Year 1 6MWD (SE), m	[redacted]	[redacted]	[redacted]	• Cipaglucosidase alfa in combination with miglustat: PROPEL (ITT) • Alglucosidase alfa and avalglucosidase alfa: ML-NMR (total population, excluding single-arm trials)
Baseline to Year 1 FVC % predicted (SE)	[redacted]	[redacted]	[redacted]	
Subsequent annual change				

Parameter	Cipaglucosidase alfa in combination with miglustat	Alglucosidase alfa	Avalglucosidase alfa	Source
Relative rate of progression 6MWD (SE)	[redacted]	-2.3% (0.003)	[redacted]	• Alglucosidase alfa: Semplicini *et al*. (n=158) • Cipa+mig: assumption of [redacted] vs alglucosidase alfa • Avalglucosidase alfa: assumption of [redacted] vs alglucosidase alfa
Relative rate of progression FVC % predicted (SE)	[redacted]	-0.9 (0.001)	[redacted]	

Abbreviations: 6MWD: six-minute walk distance; ERT: enzyme replacement therapy; FVC: forced vital capacity; HR: hazard ratio; ML-NMR: multi-level network meta-regression; SD: standard deviation; SE: standard error.

Table 9: Effectiveness inputs for the comparisons in the ERT-naïve population

Parameter	Cipaglucosidase alfa in combination with miglustat	Alglucosidase alfa	Avalglucosidase alfa	Source
Participant characteristics				
Baseline average participant age (SD), years	[redacted]			PROPEL (ERT-naïve)
Baseline average participant weight (SD), kg	[redacted]			
Baseline average participant height (SD), cm	[redacted]			
Baseline 6MWD (SD), m	[redacted]			
Baseline FVC % predicted (SD)	[redacted]			
Initial annual change				

Parameter	Cipaglucosidase alfa in combination with miglustat	Alglucosidase alfa	Avalglucosidase alfa	Source
Baseline to Year 1 6MWD (SE), m	[redacted]	[redacted]	[redacted]	• Cipaglucosidase alfa in combination with miglustat: PROPEL (ERT-naïve) • Alglucosidase alfa and avalglucosidase alfa: ML-NMR (total population, excluding single-arm trials)
Baseline to Year 1 FVC % predicted (SE)	[redacted]	[redacted]	[redacted]	
Subsequent annual change				
Relative rate of progression 6MWD (SE)	[redacted]	-2.3% (0.003)	[redacted]	• Alglucosidase alfa: Semplicini *et al*. (n=158) • Cipa+mig: assumption of [redacted] vs alglucosidase alfa • Avalglucosidase alfa: assumption of [redacted] vs alglucosidase alfa
Relative rate of progression FVC % predicted (SE)	[redacted]	-0.9 (0.001)	[redacted]	

Abbreviations: 6MWD: six-minute walk distance; ERT: enzyme replacement therapy; FVC: forced vital capacity; HR: hazard ratio; ML-NMR: multi-level network meta-regression; SD: standard deviation; SE: standard error.

Table 10: Effectiveness inputs for the comparisons in the ERT-experienced population

Parameter	Cipaglucosidase alfa in combination with miglustat	Alglucosidase alfa	Avalglucosidase alfa	Source
Participant characteristics				
Baseline average participant age (SD), years	[redacted]			PROPEL (ERT-experienced)

Parameter	Cipaglucosidase alfa in combination with miglustat	Alglucosidase alfa	Avalglucosidase alfa	Source
Baseline average participant weight (SD), kg	[redacted]			
Baseline average participant height (SD), cm	[redacted]			
Baseline 6MWD (SD), m	[redacted]			
Baseline FVC % predicted (SD)	[redacted]			
Initial annual change				
Baseline to Year 1 6MWD (SE), m	[redacted]	[redacted]	[redacted]	• Cipaglucosidase alfa in combination with miglustat: PROPEL (ERT-experienced) • Alglucosidase alfa and avalglucosidase alfa: ML-NMR (total population, excluding single-arm trials)
Baseline to Year 1 FVC % predicted (SE)	[redacted]	[redacted]	[redacted]	
Subsequent annual change				
Relative rate of progression 6MWD (SE)	[redacted]	-2.3% (SE: 0.003)	[redacted]	• Alglucosidase alfa: Semplicini *et al*. (n=158) • Cipa+mig: assumption of [redacted] vs alglucosidase alfa • Avalglucosidase alfa: assumption of [redacted] vs alglucosidase alfa
Relative rate of progression FVC % predicted (SE)	[redacted]	-0.9 (0.001)	[redacted]	

Abbreviations: 6MWD: six-minute walk distance; ERT: enzyme replacement therapy; FVC: forced vital capacity; HR: hazard ratio; multi-level network meta-regression; SD:

standard deviation; SE: standard error.

Sensitivity analyses around revised base case

Scenario analyses have been conducted based on the revised company base case which explore long-term disease progression (Key Issue #3) and invasive ventilation costs (Key Issue #8).

Table 11: Revised company base case and associated scenario analyses (total population; [redacted] for cipaglucosidase alfa)

Scenario	Description	Intervention	Costs (discounted)	QALYs (discounted)	Incremental costs (discounted)	Incremental QALYs	ICER	NHB at £20,000/QALY
Base case HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]		Cipa+mig	[redacted]	[redacted]	-	-	-	
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
#17a	HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]	Cipa+mig	[redacted]	[redacted]	-	-	-	-
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
#18a	HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]	Cipa+mig	[redacted]	[redacted]	-	-	-	-
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
#19a	HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]	Cipa+mig	[redacted]	[redacted]	-	-	-	-
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

#20a	HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]	Cipa+mig	[redacted]	[redacted]	-	-	-	-
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
#21	Invasive ventilation costs informed by Gajdoš *et al*. (including removal of upfront, one-off cost)	Cipa+mig	[redacted]	[redacted]	-	-	-	-
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: alglu: alglucosidase alfa; aval: avalglucosidase alfa; cipa+mig; cipaglucosidase alfa in combination with miglustat; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 12: Revised company base case and associated scenario analyses (ERT-naïve population; [redacted] for cipaglucosidase alfa)

Scenario	Description	Intervention	Costs (discounted)	QALYs (discounted)	Incremental costs (discounted)	Incremental QALYs	ICER	NHB at £20,000/QALY
Base case HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]		Cipa+mig	[redacted]	[redacted]	-	-	-	
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
#17b	HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]	Cipa+mig	[redacted]	[redacted]	-	-	-	-
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
#18b	HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]	Cipa+mig	[redacted]	[redacted]	-	-	-	-
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

#19b	HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]	Cipa+mig	[redacted]	[redacted]	-	-	-	
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
#20b	HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]	Cipa+mig	[redacted]	[redacted]	-	-	-	-
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: alglu: alglucosidase alfa; aval: avalglucosidase alfa; cipa+mig; cipaglucosidase alfa in combination with miglustat; HR: hazard ratio; ERT: enzyme replacement therapy; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 13: Revised company base case and associated scenario analyses (ERT-experienced population; [redacted] for cipaglucosidase alfa)

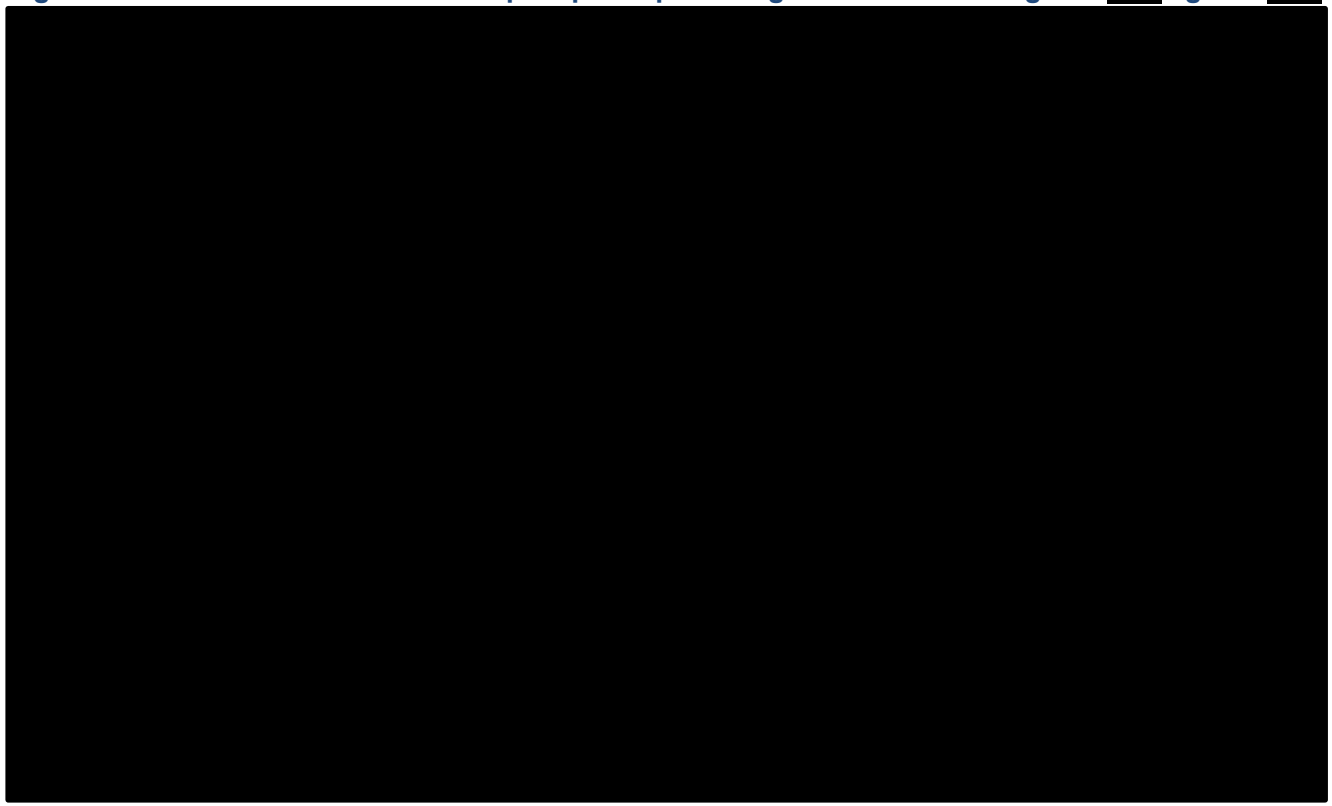
Scenario	Description	Intervention	Costs (discounted)	QALYs (discounted)	Incremental costs (discounted)	Incremental QALYs	ICER	NHB at £20,000/QALY
Base case HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]		Cipa+mig	[redacted]	[redacted]	-	-	-	-
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
#17c	HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]	Cipa+mig	[redacted]	[redacted]	-	-	-	-
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
#18c	HRs: Cipa+mig vs alglu: [redacted]	Cipa+mig	[redacted]	[redacted]	-	-	-	-
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

	Aval vs alglu: [redacted]	Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
#19c	HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]	Cipa+mig	[redacted]	[redacted]	-	-	-	-
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
#20c	HRs: Cipa+mig vs alglu: [redacted] Aval vs alglu: [redacted]	Cipa+mig	[redacted]	[redacted]	-	-	-	-
		Alglu	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
		Aval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: alglu: alglucosidase alfa; aval: avalglucosidase alfa; cipa+mig; cipaglucosidase alfa in combination with miglustat; HR: hazard ratio; ERT: enzyme replacement therapy; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year.

Appendix

Figure 1: Normal distributions of sampled participant weight when mean weight is [redacted] kg and [redacted] kg (based on 2,000 samples each)



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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease [ID3771]

Technical engagement response form – Addendum: Probabilistic Sensitivity Analysis

NICE National Institute for Health and Care Excellence

Addendum: Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was conducted in order to assess the impact of the combined uncertainty around parameter values on the results of the updated base case. The PSA was run individually for the comparisons with alglucosidase alfa and avalglucosidase alfa. As per the original submission, three hundred iterations were performed each with 10,000 patient simulations, giving a total of 3,000,000 simulations, as a pragmatic approach considering the model run-time. The PSAs were run following the same approach as that detailed in the Amicus' response to the EAG's questions for clarification: baseline parameters were probabilistically sampled (from the updated joint distributions) as part of the first-order patient simulations only, and effectiveness data varied within the PSA based on each parameter's independent normal distribution, using their respective standard errors.

Overall, cipaglucosidase alfa in combination with miglustat remained the cost-effective treatment option in the PSAs, demonstrating mean similar PSA results to those presented in the base case (Table 1):

- Cipaglucosidase alfa in combination with miglustat (with proposed PAS discount) remained dominant vs alglucosidase alfa (list price) due to its cost-savings of [redacted] and a QALY gain of [redacted] QALYs. The probability that cipaglucosidase alfa in combination with miglustat is cost-effective vs alglucosidase alfa is [redacted]% at the WTP threshold of £20,000 per QALY
- For the comparison with avalglucosidase alfa (list price), cipaglucosidase alfa in combination with miglustat remained cost-effective due to its cost-savings of [redacted] and [redacted]. The probability that cipaglucosidase alfa in combination with miglustat is cost-effective vs alglucosidase alfa is [redacted]% at the WTP threshold of £20,000 per QALY

Table 1. Updated PSA results

Comparison	Incremental costs	Incremental QALYs	ICER	NHB at £20,000/QALY	Probability cost-effective at £20,000/QALY
Cipaglucosidase alfa in combination with miglustat vs alglucosidase alfa	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Cipaglucosidase alfa in combination with miglustat vs avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

The scatter-plots and cost-effectiveness acceptability curves for cipaglucosidase alfa in combination with miglustat are presented in Figure 1 and Figure 2, respectively (vs alglucosidase alfa) and Figure 3 and Figure 4, respectively (vs avalglucosidase alfa).

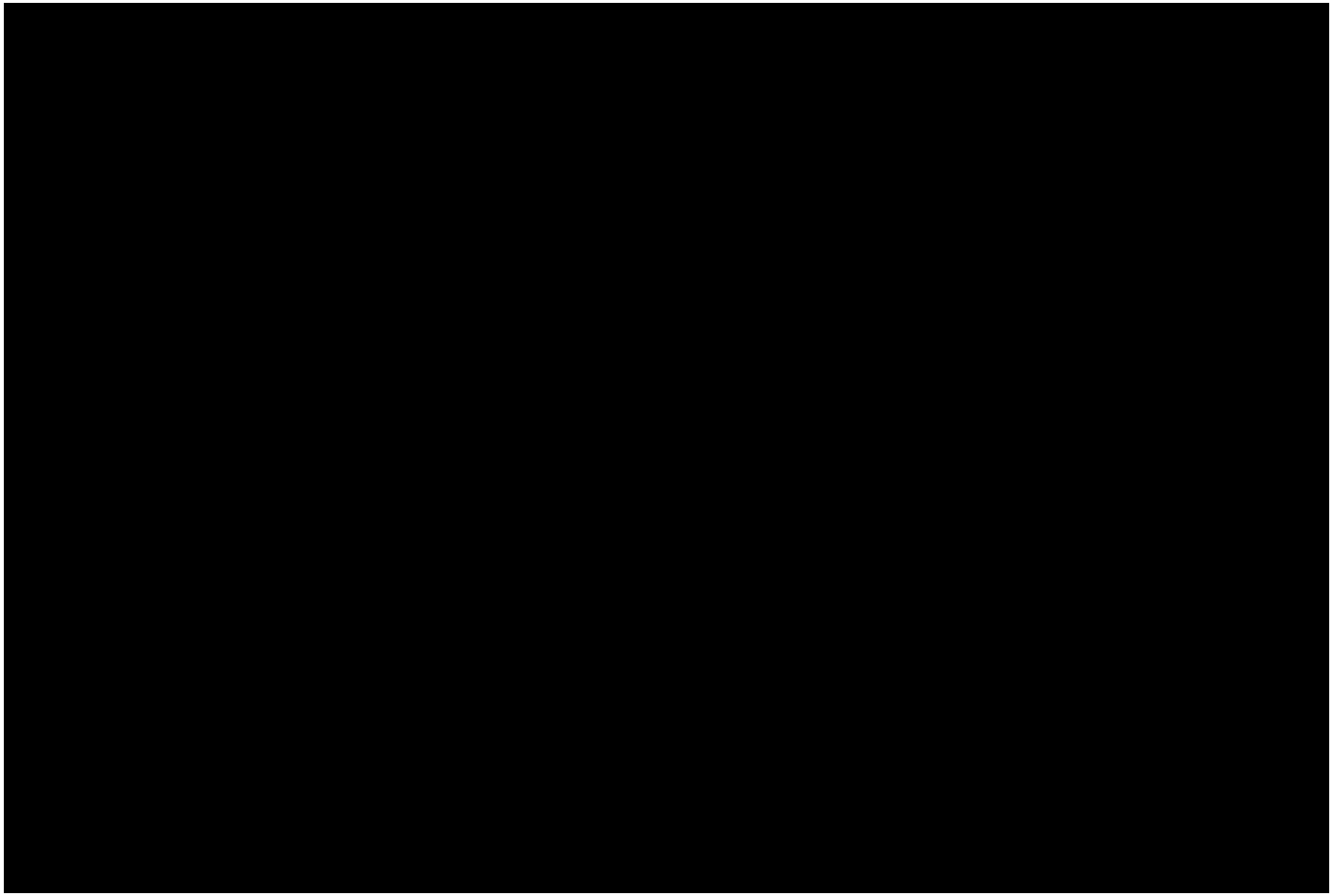
Figure 1: Cost-effectiveness scatter plot from PSA: cipaglucosidase alfa in combination with miglustat vs alglucosidase alfa (WTP threshold: £20,000 per QALY)

Abbreviations: ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay.

Figure 2: Cost-effectiveness acceptability curve from PSA: cipaglucosidase alfa in combination with miglustat vs alglucosidase alfa

Abbreviations: PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay.

Figure 3: Cost-effectiveness scatter plot from PSA: cipaglucosidase alfa in combination with miglustat vs avalglucosidase alfa (WTP threshold: £20,000 per QALY)



Abbreviations: ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay.

Figure 4: Cost-effectiveness acceptability curve from PSA: cipaglucosidase alfa in combination with miglustat vs avalglucosidase alfa

Abbreviations: PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease [ID3771]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.3). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Thursday 2nd March 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating Pompe disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	JORDI DIAZ MANERA
2. Name of organisation	NEWCASTLE UNIVERSITY
3. Job title or position	PROFESSOR OF NEUROMUSCULAR DISEASES
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Pompe disease? ☐ A specialist in the clinical evidence base for Pompe disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for Pompe disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim is to stop progression of the disease improving skeletal and respiratory muscle function in all patients (adult (LOPD) and infants) and cardiac function in the infant population (IOPD).

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	I will provide separate answers here -IOPD: increase in survival time, acquisition of motor milestones, normalization of cardiac function, long term effect: stabilization of motor function. -LOPD: 1) stabilization of the disease with no further progression of weakness and if possible 2) improvement of muscle function (desirable but not essential to consider clinically significant effect of a drug on an otherwise progressive disease)
10. In your view, is there an unmet need for patients and healthcare professionals in Pompe disease?	Yes, there are many unmet needs. 1) IOPD: improvement of muscle function to normal or almost normal values, long-term effect maintaining the improvement obtained, antibodies development in CRIM negative patients is certainly an unmet need to be solved, CNS involvement leading to cognitive and motor problems is another need. 2) LOPD: higher improvement in muscle function that the one obtained with standard for care treatment and long term effect of ERT, maintaining skeletal and respiratory muscle function for longer
11. How is Pompe disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	1) There are not approved UK guidelines. There are European guidelines produced by the European Pompe Consortium (EPOC) which is a consortium of experts in the disease. These guidelines are based on expert's opinion though and were published in 2017 (PMID: 28477382). Although are well known across experts in Pompe, my impression is that non experts are not aware of the guidelines. Moreover, the guidelines are not up to date as they were published in 2017. 2) No. It should be, but it is not. The main points of discrepancy are: a) when does the treatment need to be started in LOPD patients?, b) when does the treatment need to be stopped?, c) how often do we need to follow patients treated and non-treated (pre-symptomatic)?, d) what tests need to be done in the follow-up of patients in clinics?, e) what dose should be given to the patients IOPD and LOPD?, f) what shall we do with non-responders or patients worsening?. Clinicians apply different

	criteria (in many cases, based in self-experience) but there is not consensus on these questions. 3) The technology (cipaglucosidase + miglustat) can have an effect on improving muscle function of patients in the short and long term. Moreover, it will provide another treatment options for patients with this disease, especially for those that are worsening as there is nothing else to offer to the patients at present.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	As a general comment, I think the technology would be used more or less in the same way that the approved ERT as this is just another type of ERT with some different features. It will open the current space to other drugs and provide more options for patients, both those starting the treatment and those already on treatment. Specific answers 1) It could provide more option for treatment of patients with Pompe. I do not think that the indications of the treatment would be the same that with the approved SoC ERT. I do not think that the new technology expands the field in terms of new indications but provides healthcare providers with more options for treating patients with a drug that although having a similar profile to the Soc ERT it seems to be better in some aspects, especially improving muscle function of those experienced patients (patients already treated with ERT) switching to the new technology. I see this as an opportunity for those patients treated with the SoC but are not responding or are worsening as clinicians could try with another ERT, while at the moment there is not too much they can do with these patients. 2) I think the new technology (as all ERTs) should be used in specialist clinics only. 3) In terms of treating patients, we do not need anything new as this is just substituting one drug by another. In my opinion, companies in this field should collect post-authorization real world data on the effectivity of the new drugs for patients with Pompe disease (naïve and already treated) similarly to what is being done with the new therapies for SMA. I think that the data obtained in trials is not enough to know to what extent the new drugs are

	better than the one already in the market and probably this is what we need in this field.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	1) Yes, I expect the technology to improve muscle function more during the first months of treatment and to extent this improvement over time. This is especially true for patients switching (at least if what it has been shown in the trials published). I do think long term data is needed though to confirm these results. 2) This is doubtful, there are not enough data supporting this statement coming from the trials. My impression is that yes, the new technology could improve quality of life more than the new current treatment, especially in the long term, but this need to be demonstrated.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Based on what has been published, I would say patients switching from SoC ERT to the new technology could benefit more that naïve patients, but I think that the data available is too scarce to confirm this. Again here, I think we need much more information on the effect of the drug in patients with Pompe.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	I would be the same. No differences. Patients treated with the new technology will need to take and oral drug (miglustat) in addition to the endovenous injection, so it could be more difficult, although I think taking an oral medication the day you are treated with the enzyme is not a big deal.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Same that for the standard of care, there are no clear guidelines on when to start or stop ERT in patients with Pompe. What is agreed across all specialists is that symptomatic LOPD patients need to be treated as well as all IOPD patients. There are not specific requirements for starting the new technology.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	Not sure about this question as I am not familiar with QALY. I think that the instruments that measure quality of life in Pompe disease are not commonly used in clinical practice. The only measure I know is rPACT which is a clinical

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	scale that measure daily life activities in patients with Pompe. This scale was created by the Dutch group and is translated and validated to English.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The technology is innovative as it uses a new ERT designed for the treatment of Pompe disease and associates a chaperone (miglustat). I think the treatment could make a significant impact on the disease for the following reasons: 1) It provides a new medication to treat patients with Pompe, a disease that has just one drug. Non-responders or patients worsening could be switched. New patients can start directly this drug. This is a unmet need of the disease. 2) Long term effect could be better that with the current SoC ERT which is an unmet need of the disease. 3) Approving this drug also give the message that it is worthy investing in research in Pompe disease to companies, which is of course good for patients. (this is a personal opinion, not sure if relevant for the approval of the drug)
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are not relevant side effects of the drug
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	I think partially. So, the trials have included LOPD patients, both treatment-naïve and experienced (this means already treated with SoC ERT) that are in a moderate stage of disease progression. The trials have not included advanced patients (full time wheelchair (WC) users or ventilated patients) or mild patients, and therefore I am not sure we can extrapolate the results of the trial to this populations. I am tempted to say yes, but this is purely expeculative as there is not data and this add on the need for the company to collect real-world data.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	-Outcomes measured: the most important ones were the respiratory muscle function measured using FVC showing stabilization of the results compared with the treated with SoC-ERT who worsened and the motor function measured using 6-MWT and other motor scales. These scales are commonly used in clinical care. -The outcome measures can predict long term effect as patients stable on these measurements are probably not progressing. ON the contrary, patients who show a continuous worsening on these measures are showing disease progression on the long term. -No adverse effects
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA821]?	Yes, the company has just showed long term results of patients treated in the recently finished World Symposia in Orlando. These results show that patients treated with the new technology are stable over time
23. How do data on real-world experience compare with the trial data?	There is no real-world data of patients treated with this drug yet. All real-world data available come from patients treated with SoC ERT showing that patients progress over time despite the treatment, and al least 50% of patients show worse results of FVC and 6MWT after 10 years of treatment that at baseline. So it seems that the SoC ERT could slow disease progression but it does not stop it.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	I do not think so.

Commented [AS1]: Published Aug 22 (Avalglucosidase alfa for treating Pompe disease)

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

The inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion as a comparator from the base case analysis (avalglucosidase alfa has only been included as a comparator in scenario analyses, rather than in the base case, because currently it is not commercially available in the UK)	There is no data comparing cipaglucosidase + miglustat and avalglucosidase alfa coming from a trial. I am doubtful that the two trials can be compared, at least all patients. -Comet study (avalglucosidase alfa vs alfaglucosidase) included only naïve patients. So, the comparison between cipa and ava could be done with naïve patients only and not with experienced. -The definition of experienced in the PROPEL (cipaglucosidase) trial was at least 2 years of treatment with alfa-glucosidase. Patient who switched in the COMET from alfa to ava were treated with alfa-glucosidase for just 49 weeks which is less than 2 years. Not sure if these populations are comparable then. More data is needed here.
Differences between the ERT-naïve and ERT-experienced populations	There are many differences

(differences in baseline characteristics and expected response to treatment)	ERT-naïve: they have never been treated with the drug. It is expected that these patients are in a better condition (as most of the symptomatic are probably already on treatment). They can respond better as they still have a lot of glycogen in their muscles (which is the main target of the treatment) and they basal muscle level could be better. ERT-experienced: this population could be a bit tricky. ERT could have reduced glycogen levels considerably and therefore the effect of a new drug could be less evident here. Moreover, it is not the same being a ERT-experienced patient who has been treated for 1 year that someone who has been treated for 5 ot 10 years, as it is probable that the capacity to respond to new drugs is limited in patients treated for longer. Another aspect to put into the equation is age of patients, as there is a physiologic effect of loss of muscle mass associated with age
Uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat	I agree with this point, the data shared by the company is still limited in this regard.
Use of single arm studies in the indirect treatment comparison	Not sure if I understand what you mean by this.
Indirect treatment comparison including both ERT-naïve and ERT-experienced participants	I agree with this point as well. The main results of the PROPEL study come from a mix of patients naïve (who can probably respond more to the drug) and treated ones (who could respond less). And again it is not the same to be treated one, five or ten years.
Cost-effectiveness of comparator treatments (alglucosidase alfa has not been appraised by NICE, and therefore assessing cost effectiveness relative to alglucosidase alfa may be misleading)	I have no experience in economic assessment of a drug
Improper parameterisation of model (model uses independent distributions for each model parameter, despite the	I have no experience in economic assessment of a drug

acknowledgement that model parameters maybe correlated)	
Utilities generated using a non-reference case approach (although the company collected data on HRQoL in the PROPEL trial and identified several sources of published utility values, a different source for utility values was used in the economic model)	I have no experience in economic assessment of a drug
Resource use for invasive home mechanical ventilation (the cost of invasive mechanical ventilation may have been over costed due to the use of old data which is not generalisable to this population).	I have no experience in economic assessment of a drug
Are there any important issues that have been missed in EAR?	Not in my opinion

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Cipaglucosidase + miglustat is an effective therapy for Pompe disease based on the results of the clinical trials performed by the company.

Cipaglucosidase + miglustat is not inferior to alfaglucosidase in the short term treatment of naïve patients with LOPD

Cipaglucosidase + miglustat improves muscle function and stabilizes respiratory function of experienced LOPD patients switching from alfaglucosidase in the short term treatment

There are not enough evidences to confirm that the results observed in the short term are maintained in the long term.

The safety profile of the drug is not a problem

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease [ID3771]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.3). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Thursday 2nd March 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating Pompe disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Mark Roberts
2. Name of organisation	Salford Royal NHS Foundation Trust
3. Job title or position	Consultant Neurologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Pompe disease? ☒ A specialist in the clinical evidence base for Pompe disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NIL
8. What is the main aim of treatment for Pompe disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To prevent progression

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in walking distance by 30 m or more Improvement in vital capacity by 3% or more
10. In your view, is there an unmet need for patients and healthcare professionals in Pompe disease?	Yes, after initial improvements on current SOC, Myozyme, for up to 2 years patients deteriorate thereafter
11. How is Pompe disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Pompe is treated with IV Enzyme Replacement therapy every 2 weeks The UK centres use the EPOC guidelines ie patients are eligible for treatment if confirmed diagnosis is genetically confirmed and they are symptomatic with respiratory or skeletal muscle weakness The pathway of care is well defined, patients will be assessed in one of the UK LSD centres where initial infusions will be delivered prior to moving the patient to Homecare treatment thereafter. Technology would require patients returning to site in the LSD centres for initial infusions before then going back to homecare.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology will be used in the same way as current NHS clinical practice, the only significant difference being that patients will initially need to return to the centre for several infusions to observe any infusion associated reactions to treat these accordingly. The technology will be used within tertiary Metabolic hospital centres who remain responsible for the subsequent homecare delivery. The technology will require more time and assessment by Clinical staff, including physiotherapists who perform important, metrics, respiratory evaluation, nursing time and education brackets to address the different modality of delivery, using an oral chaperone, plus ERT. The technology will certainly require considerably more inpatient care at the centres, at least initially, as patients are initiated or switched to this new treatment.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I do expect the technology to stabilise patients who had been deteriorating on the standard of care prior to switch to the new treatment. As the technology may

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	delay the onset of respiratory insufficiency and requirement for ventilation, it seems likely that the technology will prolong life more than current care. I think the technology will improve health quality compared to current treatment as it is likely to reduce or delay ventilator requirement and wheelchair dependency.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It is likely that the treatment will have benefit across the Pompeii population, Both patient switched from current treatment and naïve patients. It would be fair to say that the current data from the phase 3 study contains few naïve patients, and particularly in this group type monitoring of benefit will be required.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Initially the technology will require all patients to be admitted for initial infusions to a specialist centre before transitioning to homecare treatment thereafter. For patients switching from current treatment, this will be the first requirement for a return to inpatient treatment often for many years this will cause an additional significant amount of increased clinical work in the centres put this will be a transient affect which is likely to retain for approximately 12 to 18 months as patients are moved to the technology assuming that the NICE appraisal supports the initiation of the new technology. An additional unique element to this treatment is the oral chaperone it will require patients to fast prior to enzyme treatment and this will need to be factored into the treatment protocols and potentially the length of inpatient stay, however, all treatments should still be possible on a single day case basis.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting treatment with the technology will be straightforward, i.e. symptomatic, naïve, patience, patience on current SOC, who have shown a deterioration on one more occasions over a period of 12 months. Stopping criteria are likely to be to 2 or consecutive measurements of deterioration over a period of 12 months, but particularly in the early phase of experience with this technology and a recently licensed competitive technology, patient may well be discussed at a national panel.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	It is likely that the technology will lead to improvement in exercise tolerance and reduced fatigue may not be captured by the QALY approach.

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The technology is innovative, combining a chaperone and enzyme replacement therapy. It is likely to stabilise patients who were previously deteriorating on standard of care. The technology can be viewed as an evolution in current enzyme replacement therapy. It is not a "step change" as the benefits of the technology are modest and the primary outcome measures did not reach statistical significance. The technology certainly office deteriorating, patience, important new treatment option, and it is also likely to be useful in patients naïve to treatment.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The trial data suggests that the new technology is well tolerated and side-effects, similar or less than current SOC. The ERT infusion time will be equivalent to SOC, but the additional fasting period may be considered by some patients to be onerous
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials on the technology do reflect current UK practice. The important trial outcome measures are the six minute walking time and vital capacity myometry and patient reported outcomes do support the use of the technology. The outcome measures used, particular the respiratory measurements to predict long-term clinical outcomes. I'm not aware of any adverse events that have come to light since the Clinical Trials.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No, there have been a number of platform and poster presentations, such as at the world muscle society 2022 and the world symposium 2023 in which long-term extension data was discussed, but this has not yet been published.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA821]?	No, there have been a number of platform and poster presentations, such as at the world muscle society 2022 and the world symposium 2023 in which long-term extension data was discussed, at both meetings indirect treatment comparisons were presented, but patient level data was not available for all subjects and this has not yet been published.
23. How do data on real-world experience compare with the trial data?	Currently, there is little real-world experience to compare to the trial data, the extension phase to the Propel Phase 3 trial suggests the treatment effect is maintained beyond the primary analysis period of one year. We have had an early access to medicine scheme in the UK but the data from this is not yet available to the best of my knowledge. This technology is not yet commercially available anywhere in the world and therefore real world evidence / experience is currently limited
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	I can foresee no equality issues.

Commented [AS1]: Published Aug 22 (Avalglucosidase alfa for treating Pompe disease)

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Table 2 Issues arising from technical engagement

The inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion as a comparator from the base case analysis (avalglucosidase alfa has only been included as a comparator in scenario analyses, rather than in the base case, because currently it is not commercially available in the UK)	Inclusion of AVAL as a second comparator, only, seems fair as AVAL is not commercially available in the UK at the time the appraisal commenced. As you will be aware, AVAL has very recently become available in the UK. Exclusion of AVAL as a comparator in the base case analysis can be justified for the same reason as above, but obviously this is a very fast moving treatment scenario, and with AVAL now being commercially available. One could consider a further round of NICE appraisal for this new Technology, though would this inevitably mean that in the interim with AVAL being commercially available many patients would be switched to that product which would be significantly detrimental to the prospects of options for the new Technology under consideration here.
Differences between the ERT-naïve and ERT-experienced populations (differences in baseline characteristics and expected response to treatment)	The limited benefit of the technology in ERT-naïve patience has vexed the Pompeii research community at an international level! The number of naïve patients in the Propel study was small, and a lack of benefit may reflect the heterogeneity of the

	disease. However, there is no clear understanding about why naive patients didn't respond better, which is rather counterintuitive given the benefits seen in the ERT experienced majority of patients who had been on treatment for an average of seven years. Most clinicians are considering using the technology in naïve, as well as ERT experienced patients, but there is clearly going to be a need for very rigourous monitoring to capture any benefits or otherwise, particularly as the comparator product, AVAL did show benefits compared to current standard of care in naive patients.
Uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat	On the available published literature, there is uncertainty about the long-term relative effectiveness of the technology, but certainly poster and platform presentations at important. International meetings suggest that the benefits of the technology are durable at least over a two-year period.
Use of single arm studies in the indirect treatment comparison	Use of single arm studies given the lack of data to compare to other comparators does seem reasonable
Indirect treatment comparison including both ERT-naïve and ERT-experienced participants	To perform an ITC, including naïve and experienced participants seems reasonable as this will address the potential benefits of the technology in both patient groups and does address the clinical questions in the real world. Obviously, it could be suggested that combining these data sets for comparison might mitigate the limited response seen in the naïve group, but in the absence of any proposed future comparative trials in naïve patients to look at the relative benefits of standard of care versus the new technology and the other comparator, this would seem a pragmatic approach.
Cost-effectiveness of comparator treatments (alglucosidase alfa has not been appraised by NICE, and therefore assessing cost effectiveness relative to alglucosidase alfa may be misleading)	As NICE did not appraise alglucosidase alfa , now the standard of care for many years, it seems relatively unlikely to occur at this later stage post commercialisation. Whilst it is clearly imperfect that the technology is being compared to a product not assessed by NICE, this seems to be a pragmatic approach as the vast majority of patients who might benefit from this technology are on the standard of care. Clearly if the new product was significantly more expensive than the standard of care, this would impact on treatment choice choices as the benefit of the new technology is relatively small. I'm

	sure you will be having extensive discussions with the company about the price point for this product.
Improper parameterisation of model (model uses independent distributions for each model parameter, despite the acknowledgement that model parameters maybe correlated)	Unable to comment
Utilities generated using a non-reference case approach (although the company collected data on HRQoL in the PROPEL trial and identified several sources of published utility values, a different source for utility values was used in the economic model)	Unable to comment
Resource use for invasive home mechanical ventilation (the cost of invasive mechanical ventilation may have been over costed due to the use of old data which is not generalisable to this population).	I agree the vast majority of patients with LOPD, who require respiratory support can be managed on non-invasive ventilation NIV, which is considerably cheaper than invasive tracheostomy based approaches. NIV costings should be used.
Are there any important issues that have been missed in EAR?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The Technology represents an evolution in ERT management of patients with Pompe disease

The technology offers is an important treatment option for patients deteriorating on standard of care
The technology may be a useful treatment option for ERT naïve patients, but real world evidence will be important
Clinical effectiveness of the new technology compared to AVAL is unclear and the use of anchored and anchored analysis and lack of clarity on all patient level data makes this a difficult comparison
Ideally, all 3 ERTs should be compared in the head-to-head study in both naïve, and ERT experienced patience, but such a study would be difficult to operationalise, would have to be international, and is relatively unlikely to occur.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease [ID3771]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with Pompe disease or caring for a patient with Pompe disease. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Patient expert statement

The deadline for your response is **5pm** on **Thursday 2nd March 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with Pompe disease

Table 1 About you, Pompe disease, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☒ A patient with Pompe disease? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Pompe disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Pompe Support Network
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with Pompe disease? **If you are a carer (for someone with Pompe disease) please share your experience of caring for them**	My experience started with a misdiagnosis of Limb-girdle Muscular Dystrophy about 35 years ago to a correct diagnosis a few years later. It didn't matter much because there was no treatment. My condition gradually deteriorated until I started to require ventilatory support at night, then started using a wheelchair and gave up walking about 25 years ago. I started requiring full time non-invasive ventilation around the same time I started treatment with Myozyme in 2006. My condition improved slightly and then mostly stabilised after treatment started. After several years my condition started to very gradually deteriorate again with my strength decreasing and breathing becoming slightly more difficult. I have used a power wheelchair since 2010 and still require full time non-invasive ventilation. I require assistance with most activities of daily living. I work part time in IT and am involved with some transport and access activism.
7a. What do you think of the current treatments and care available for Pompe disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The current treatments and care seem to be as good as they can be with regard to the drug and specialist care. The administration of the infusion treatment by Home Health companies is far from ideal. During the pandemic my partner started doing the home infusions which was a great improvement. Since switching to cipaglucosidase it has been required that we resume having a home health nurse do the infusions. I think my views are shared by others from what I have heard. I have considered switching to another home health company but have heard that the others also have problems.
8. If there are disadvantages for patients of current NHS treatments for Pompe disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	An infusion every two weeks for five or six hours is a small price to pay for relative stability of health, but it can become stressful. After hundreds of infusions, it can sometimes be difficult to cannulate. Having different nurses come with short notice of confirmation and different levels of skill with cannulation can be stressful. Fortunately I have not experienced side effects so far with either treatment.

	A relatively minor issue is the small vials that Myozyme comes in. The drug must be carefully mixed in about 20 to 50 small vials depending on dose, then is put in two different bags of saline (at least in my experience) which have to be switched during infusion. This is extra work and an opportunity for error and waste of a small amount of drug if not properly flushed.
9a. If there are advantages of cipaglucosidase alfa over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does cipaglucosidase alfa help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I am unsure if there have been advantages over the current treatment. My condition seems relatively stable but subtle changes, either positive or negative, can be hard to detect. If this treatment, over time, is even slightly better at maintaining, or even slightly improving, my condition then the effect will be significant. When one's condition is deteriorating it is very difficult to plan ahead, not knowing if the capabilities necessary for some future plan will have been maintained. Starting treatment in 2006 changed my life from constantly adjusting to new difficulties, to finding ways to adapt to my more stable situation and maximise my quality of life. The minor issue I mention in question 8 is somewhat better with cipaglucosidase alfa because the vials are larger so the preparation time and effort is about half as much, and it is given in a single bag of saline which makes the infusion just slightly less complicated.
10. If there are disadvantages of cipaglucosidase alfa over current treatments on the NHS please describe these. For example, are there any risks with cipaglucosidase alfa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The only disadvantage I can be sure of so far is that of having to fast for two hours before, and then administering the miglustat. I have difficulty swallowing. Some other Pompe patients do too. Normally to take a pill, I have to take it with food. When trying to take four capsules with liquid only, I was not sure if they were going down or getting stuck in my throat. I had trouble finding out that the contents of the capsules can be removed and mixed with water and taken that way. This will no longer be an issue for me, but the protocol for taking the capsules should mention this option for those who have difficulty swallowing to ensure the migulstat is actually in the stomach at the right time.
11. Are there any groups of patients who might benefit more from cipaglucosidase alfa or any who may benefit less? If so, please describe them and explain why	Pompe patients seem to have varied responses and tolerances to different treatments over time. Some may benefit more and some less, but I know of no way to find out which ones will benefit more. Pompe is a highly variable condition with highly variable responses to treatment.

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering Pompe disease and cipaglucosidase alfa? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	One is the measure of quality of life. I don't understand exactly how the formula is applied, but as a non-invasive ventilator dependent power wheelchair user with care needs, I hope the quality of life that I and others like me have are not undervalued. With adequate technology and equipment such as portable ventilators, lithium batteries, power wheelchair, pressure relieving bed and overhead hoist, along with good support and care, I have what I consider to be a high quality of life. I am able to travel, participate in cultural events and meet friends and family socially. I am a trustee of a charity which advocates for better transport for disabled people. I am self-employed as an IT consultant and my services are valued by my clients. If this treatment can help clear glycogen just a little bit better, and gives me an extra year or two of life at this level, it is extremely valuable to me. I also believe it is valuable to society as a whole to see that Quality of Life does not plummet when one needs a wheelchair, ventilator or some level of care. I believe in the Social Model of disability and I believe that my quality of life can be improved, even as my condition stays the same, by increased access for wheelchair users to transportation and service providers. Disabled people should have access to as many treatments as practical, even those that might be fractionally better or better tolerated by them to live fulfilling lives as long as they can. Though the choices of what I can do are limited by my impairments, many of those limits are imposed by society, and I have a high quality of life within the sphere of what is currently accessible.
13. Are there any other issues that you would like the committee to consider?	I would be concerned if this treatment is not made available, not only for those who experienced a definite and easily definable benefit from changing to it, but also because having only a single treatment available, from a single company, has been a point of stress in the past. There have been supply problems with Myozyme over the years. I am not sure where the drugs are manufactured, but as far as I know, neither alglucosidase alfa, cipaglucosidase alfa nor avalglucosidase alfa are manufactured in the UK. A single treatment can be a single point of failure, whether due to manufacturing difficulties, pandemic, natural disaster or political issues such

	as Brexit or political tensions with China. There is also the risk of a company going bankrupt or simply deciding to stop marketing a treatment for external reasons.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

The inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion as a comparator from the base case analysis (avalglucosidase alfa has only been included as a comparator in scenario analyses, rather than in the base case, because currently it is not commercially available in the UK)	
Differences between the ERT-naïve and ERT-experienced populations (differences in baseline characteristics and expected response to treatment)	

Patient expert statement

Uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat	I think all new treatments have some level of such uncertainty, especially treatments for severe rare diseases where it is not possible to do very large studies, and not desirable to do them over long periods of time while denying possibly live saving or life changing treatment. There seems to be benefit to some patients in the short to medium term which seems to me adequate justification for providing the treatment option to all who might benefit. It would be beneficial to collect data on trial participants, or perhaps the general treatment population, on an ongoing basis to monitor how the treatment performs over the long term.
Use of single arm studies in the indirect treatment comparison	
Indirect treatment comparison including both ERT-naïve and ERT-experienced participants	
Cost-effectiveness of comparator treatments (alglucosidase alfa has not been appraised by NICE, and therefore assessing cost effectiveness relative to alglucosidase alfa may be misleading)	
Improper parameterisation of model (model uses independent distributions for each model parameter, despite the acknowledgement that model parameters maybe correlated)	
Utilities generated using a non-reference case approach (although the company collected quality of life data from the PROPEL trial and identified several other published data sources, a different source for quality of	

Patient expert statement

life data was used in the economic model)	
Resource use for invasive home mechanical ventilation (the cost of invasive mechanical ventilation may have been over costed in the economic model due to the use of old data from a different patient population).	I am not sure how it would affect the analysis, but I believe many medical professionals have a bias towards invasive mechanical ventilation. More than once doctors have indicated that I should consider invasive mechanical ventilation but I do not think it would provide much useful benefit and it would increase risk. I use a mouthpiece during the day and nasal mask at night. There is sometimes difficulty with the mask at night leaking, but they can be addressed with adjustments or a different type of mask. If this treatment can maintain the ability of people to continue with non-invasive ventilation for longer, and medical professionals recognise this, it can extend the period where invasive ventilation is not required which provides a cost and quality of life benefit.
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I am not sure whether this treatment has benefitted me more than the previous treatment, but others seem to have obvious benefits, so I think it should be available.
- Even a very small benefit which allows a person to have some additional stability in their condition can have a very large effect on actual quality of life.
- Having more than one treatment available is important, not only for those who have less tolerance for one, or more benefit from one, but because of the risk of a single source being affected by unforeseen circumstances.
- Difficulty swallowing occurs in some people with Pompe and should be accounted for when writing the final protocol for the use of miglustat with cipaglucosidase alfa.
- Using a wheelchair and ventilator and having care needs definitely change quality of life, but do not necessarily lower it where the right equipment and support are provided and society does not disable people with inaccessible infrastructure and ableist attitudes.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease [ID3771]

Patient expert statement and technical engagement response form

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Information on completing this form

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A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

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Patient expert statement

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Part 1: Living with this condition or caring for a patient with Pompe disease

Table 1 About you, Pompe disease, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☒ A patient with Pompe disease? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Pompe disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	AGSD
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with Pompe disease? **If you are a carer (for someone with Pompe disease) please share your experience of caring for them**	I was finally diagnosed with Pompe in 2010 and began treatment with ERT January 2011.Prior to diagnosis life was challenging. I had numerous falls, impaired lung function, severe fatigue and chronic pain and had a serious choking episode and speech difficulties. After approximately 6 months treatment with Myozyme I began to feel healthier and saw marked improvement in pain levels, breathing and fatigue. After approximately 6 years on Myozyme the beneficial effects of the treatment were waning and in 2019 I was fortunate to be enrolled in clinical trial for Cipaglucosidase alfa with Miglustat.
7a. What do you think of the current treatments and care available for Pompe disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a) The current available treatment was successful in slowing down the progression of the condition in the first few years of starting treatment. The care from my specialist centre has been excellent. 7b) Others, like me, agree that treatment has been life changing. Some patients feel the treatment hasn't been as effective as they had hoped.
8. If there are disadvantages for patients of current NHS treatments for Pompe disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Some patients experience reactions to treatment. I reacted with hives but was able to have pre meds to deal with this. I also experienced post infusion headaches and was fatigued the following day. Some chose not to continue with treatment due to adverse reactions or not seeing any beneficial improvement in their condition
9a. If there are advantages of cipaglucosidase alfa over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	9a) The quality of my life has improved enormously, most notably my lung function has improved. I have more stamina, greatly reduced pain, improved speech, and the effects of the treatment last longer. All this means that I can do much more for myself, which in turn means my partner can continue to work and I maintain my independence and dignity. I am not so isolated now as I have the stamina and enthusiasm to mix with others in the wider community which has meant my mental health has also improved. Treatment has enabled me to travel to Australia to see my son and Grandchildren recently.

9c. Does cipaglucosidase alfa help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	9b) My improved lung function. It means I have not needed any overnight intervention such as Bi Pap plus My dignity and independence as I am not totally reliant on my partner for things like my personal care. 9c) Since starting on the trial I have not experienced any side effects, no post infusion headaches and no fatigue the following day.
10. If there are disadvantages of cipaglucosidase alfa over current treatments on the NHS please describe these. For example, are there any risks with cipaglucosidase alfa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I am not aware of any particular disadvantage and as regards potential side effects ,I haven't had any concerns but equally other patients might have a different experience.
11. Are there any groups of patients who might benefit more from cipaglucosidase alfa or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Any patient that has been on the current treatment for some time and find that it is not working as effectively might benefit. Any patient that might have had to stop treatment previously due to severe reactions. Any patient with swallowing issues might have difficulties taking the oral chaperone Miglustat.
12. Are there any potential equality issues that should be taken into account when considering Pompe disease and cipaglucosidase alfa? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	None that I am aware of. My only thought would be if suitable for very young children, given the oral chaperone which is in capsule form.

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Improved Treatments can enable the patient to live a good life, continue to work and contribute to the wider society. Patients can enjoy a better quality of life and slowing the progression of the condition means there could be less need for support from other agencies e.g. Social Care and secondary health services e.g. OT-s

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

The inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion as a comparator from the base case analysis (avalglucosidase alfa has only been included as a comparator in scenario analyses, rather than in the base case, because currently it is not commercially available in the UK)	
Differences between the ERT-naïve and ERT-experienced populations (differences in baseline characteristics and expected response to treatment)	

Patient expert statement

Uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat	
Use of single arm studies in the indirect treatment comparison	
Indirect treatment comparison including both ERT-naïve and ERT-experienced participants	
Cost-effectiveness of comparator treatments (alglucosidase alfa has not been appraised by NICE, and therefore assessing cost effectiveness relative to alglucosidase alfa may be misleading)	
Improper parameterisation of model (model uses independent distributions for each model parameter, despite the acknowledgement that model parameters maybe correlated)	
Utilities generated using a non-reference case approach (although the company collected quality of life data from the PROPEL trial and identified several other published data sources, a different source for quality of life data was used in the economic model)	We consider patient perspectives may particularly help to address this issue
Resource use for invasive home mechanical ventilation (the cost of invasive mechanical ventilation may	

Patient expert statement

have been over costed in the economic model due to the use of old data from a different patient population).	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The quality of my life has improved due to treatment
- I am maintaining my dignity and independence
- I am not so isolated and can participate in activities with family and friends.
- My pain and discomfort has been greatly reduced along with improved lung function.
- As a result of the above my mental health has also improved.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease [ID3771]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

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You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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Technical engagement response form

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AGSD-UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No tobacco industry funding**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
The inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion from the base case analysis	~~Yes~~/No	Whilst not in a position to include new data or evidence in this response, as a patient organisation representing those affected we would wish to underline the following points: Access to a choice of treatment options is crucial for people affected by Pompe given their heterogeneity of response to existing therapies. For those unable to tolerate existing treatments or who experience limited or waning response, access to range of treatment options is urgently needed to enable selection of the most appropriate and effective therapy for the individual concerned. It's vital that people have access to the best treatment option for them at the earliest opportunity to slow degeneration, maintain independence and quality of life. We note that timing of the development of avalglucosidase alfa and cipaglucosidase alfa with miglustat means that head to head comparisons are not available and that in light of the recent nature of the approval of avalglucosidase alfa, alglucosidase alfa continues to be standard therapy.

		People affected by this serious degenerative condition affecting every aspect of daily life should not experience delayed access to an alternative new treatment because of an accident of timing.
Differences between the ERT-naïve and ERT-experienced populations	~~Yes~~/No	We would underline the very small population of people diagnosed with late onset Pompe disease annually and the significant challenge of generating evidence. Given not everyone with Pompe can tolerate or is responsive to existing therapies, unavoidable limitations in the available evidence cannot be allowed to delay urgently needed access to treatment options that are most effective for them. It's crucial that the appraisal process does not prejudice access to suitable treatments based on the rarity of the condition and avoids compounding the inequalities faced by people affected.
Uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat	~~Yes~~/No	Given the progressive nature of the condition and the level of impact on quality of life there is urgent need to ensure access to new treatment options that improve current life quality and slow degeneration, pending evidence of longer term effectiveness. We would highlight that as set out in our original submission, individuals have reported unanticipated benefits from cipaglucosidase alfa with miglustat, including reduced pain and clear headedness, that are not captured in existing evidence. We would also underline that treatment decisions in Pompe are made in close partnership between specialist clinicians and those affected, with careful monitoring and review to ensure the most appropriate treatment for the individual concerned at every stage.
Use of single arm studies in the indirect treatment comparison	~~Yes~~/No	Please provide your response to this key issue, including any new evidence, data or analyses
Indirect treatment comparison including both ERT-naïve and ERT-experienced participants	~~Yes~~/No	Please provide your response to this key issue, including any new evidence, data or analyses
Cost-effectiveness of comparator treatments	~~Yes~~/No	Please provide your response to this key issue, including any new evidence, data or analyses
Improper parameterisation of model	~~Yes~~/No	Please provide your response to this key issue, including any new evidence, data or analyses

Utilities generated using a non-reference case approach	~~Yes~~/No	Please provide your response to this key issue, including any new evidence, data or analyses
Resource use for invasive home mechanical ventilation	~~Yes~~/No	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
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Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
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Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cipaglucosidase alfa with miglustat for treating Pompe disease [ID3771]

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Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Pompe Support Network
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
The inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion from the base case analysis	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Differences between the ERT-naïve and ERT-experienced populations	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Use of single arm studies in the indirect treatment comparison	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Indirect treatment comparison including both ERT-naïve and ERT-experienced participants	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Cost-effectiveness of comparator treatments	No	This issue would not have arisen if the external assessment of Cipaglucosidase alpha with Miglustat had been undertaken through the HST process. The technology, and its comparator treatments, meet every one of the HST seven eligibility requirements: 1. The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS. 2. The target patient group is distinct for clinical reasons. 3. The condition is chronic and severely disabling. 4. The technology is expected to be used exclusively in the context of a highly specialised service. 5. The technology is likely to have a very high acquisition cost. 6. The technology has the potential for life-long use. 7. The need for national commissioning of the technology is significant. The thresholds and modifiers for cost-effectiveness should be much higher than those considered in the external assessment. This also applies to alglucosidase alpha which may well be cost-effective when reviewed under the HST process.
Improper parameterisation of model	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Utilities generated using a non-reference case approach	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Resource use for invasive home mechanical ventilation	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
The inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion from the base case analysis	Yes	Avalglucosidase alfa has been commercially available since the 8th of February 2023 and patients are already being treated with the commercial enzyme replacement therapy.
Differences between the ERT-naïve and ERT-experienced populations	No	No comments
Uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat	No	No comments
Use of single arm studies in the indirect treatment comparison	No	We agree with the EAG that the inclusion of single-arm studies is inappropriate and leads to high risk of bias that cannot be quantified.
Indirect treatment comparison including both ERT-naïve and ERT-experienced participants	No	No comments

Cost-effectiveness of comparator treatments	No	No comments
Improper parameterisation of model	No	No comments
Utilities generated using a non-reference case approach	No	No comments
Resource use for invasive home mechanical ventilation	No	No comments

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

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Additional issue 1: Inaccuracy in section B.1.3.4. of CS	section B.1.3.4. of CS	Yes	We believe the statements in section B.1.3.4 of CS regarding the lack of stability of alglucosidase alfa in circulation to be misleading. Whilst it is true that, like many lysosomal enzymes, alglucosidase alfa is more stable at lower pH, this is not something that has been demonstrated to impact its effectiveness. Both alglucosidase alfa and avalglucosidase alfa are known to be stable for at least eight hours at neutral pH without the need for a small molecule stabiliser or chaperone (1). Further, activity assays performed in house by Sanofi have shown that alglucosidase alfa retains near full activity under physiological conditions for 24 hours. The pharmacokinetic and pharmacodynamic data (2,3) on these well characterised enzymes show that they retain activity during their short time in the circulation.

			References 1. Anding, A., Baranowski, K., Brezzani, A., et al., (2001) Mol Genet Metab, 132, S15 2. European Medicines Agency, Myozyme, Summary of Product Characteristics, Available: https://www.ema.europa.eu/en/documents/product-information/myozyme-epar-product-information_en.pdf 3. European Medicines Agency, Nexviadyme, Summary of Product Characteristics, Available: https://www.ema.europa.eu/en/documents/product-information/nexviadyme-epar-product-information_en.pdf

Single Technology Appraisal (STA)

Cipaglucosidase alfa with miglustat for treating Pompe disease [ID3771]

EAG addendum: review of company's response to technical engagement

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Correspondence to	Professor Alison Eastwood, CRD, University of York, York, YO10 5DD
Date completed	15/03/2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR135712.

Declared competing interests of the authors

Description of any pecuniary relationship with sponsors, both personal and of the TAR Centre. If there are none, please state 'none'.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

Table of Contents

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1 OVERVIEW

This addendum to the External Assessment Report (EAR) report presents the External Assessment Group's (EAG) critique of the additional evidence provided by the company in their response to a number of key issues that were raised by the EAG in its report, which were discussed at technical engagement.

The technical engagement covered 9 key issues for consideration summarised in Table 1. The company's response to technical engagement indicates that they accepted several alterations and assumptions preferred by the EAG. This includes the inclusion of avalglucosidase alfa as a comparator (issue 1), the separate modelling of ERT-naïve and ERT-experienced populations (issue 2), the removal of single arm studies from the ML-NMRs (issue 4), and the use of PROPEL trial utilities (issue 8). The company have updated the model responding to issue 7 regarding corrections to the parameterisation of the model.

The results of the company's updated base case along with additional scenarios presented in the company response are replicated inclusive of all cPAS discounts in a confidential appendix to this document.

Table 1: Summary of the key issues

Issue		**Resolved?**
1	The inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion from the base case analysis	Yes
2	Differences between the ERT-naïve and ERT-experienced populations	Partially but remains uncertain
3	Uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat	No, uncertainty remains
4	Use of single arm studies in the indirect treatment comparison	Yes
5.	Indirect treatment comparison including both ERT-naïve and ERT-experienced participants	Partially but remains uncertain
6.	Cost-effectiveness of comparator treatments	No, uncertainty remains
7.	Improper parameterisation of the model	Yes
8.	Utilities generated using a non-reference case approach	Yes but remains uncertain
9.	Resource use for invasive home mechanical ventilation	No, uncertainty remains

2 DESCRIPTION AND CRITIQUE OF ADDITIONAL EVIDENCE

2.1 Issue 1: The inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion from the base case analysis

The company acknowledges that avalglucosidase alfa was made available on the NHS in February 2023 and have included it as a comparator in their updated base case. However, the company maintains that alglucosidase alfa remains established care at present given avalglucosidase alfa was only recently made commercially available.

The EAG's response

In the company's original submission, avalglucosidase alfa was not included in the company's base case and only included in scenario analyses in the economic model. The company argued that at the time of submission, avalglucosidase alfa was not yet commercially available in the UK for the treatment of adults with late onset Pompe disease (LOPD). This is inconsistent with the NICE scope and current NICE guidance. In addition, clinical advice to the EAG suggests that it is widely accepted that avalglucosidase alfa will replace alglucosidase alfa as the preferred first-line treatment option in patients with LOPD. Where ERT experienced patients are considering switching, avalglucosidase alfa represents the only alternative. The EAG considers that assessment of the clinical and cost-effectiveness of cipaglucosidase alfa with miglustat should consider avalglucosidase alfa as a relevant comparator.

The company have now included avalglucosidase alfa as a comparator in their updated base case, therefore the EAG considers this issue resolved.

2.2 Issue 2: Differences between the ERT-naïve and ERT-experienced populations

The company have accepted the EAG's approach to explore the results for the ERT-naïve and ERT-experienced population separately, although they state that there is no biological plausibility for a difference in expected benefit between ERT-naïve and ERT-experienced adults with Pompe disease.

The company present the updated base case cost-effectiveness results by total, ERT-naïve and ERT-experienced populations separately. In these analyses, cipaglucosidase alfa in combination with miglustat remains cost-effective across the total population and within each subpopulation. However, the company maintains that the value of cipaglucosidase alfa in combination with miglustat should be assessed in the overall population of adults with LOPD.

The EAG's response

As discussed in the EAG report, there are several important differences in the baseline characteristics of ERT-naïve and ERT-experienced patients recruited to the PROPEL trial. Clinical advice provided

to the EAG indicates that a larger, but delayed, treatment effect is expected for the ERT-naïve population compared to the ERT-experienced population who would already have an improved clinical status from previous treatment.

There is also uncertainty in any indirect comparison between avalglucosidase alfa and cipaglucosidase alfa as relative effectiveness estimates are drawn from distinctly different populations; the PROPEL trial population primarily consists of ERT-experienced patients, while the COMET trial exclusively recruited ERT-naïve patients. The EAG considers it important to appropriately reflect this uncertainty by considering the ERT-naïve and ERT-experienced populations separately. Resolving uncertainty regarding how treatment effects differ across ERT-naïve and ERT-experienced patients would require additional comparative trial evidence in these populations. The ML-NMR implemented by the company helps mitigate the need for this evidence but is limited by the lack of data (see Issue 5).

In the original submission, cost-effectiveness results were presented in the total population only; the company have now also presented the base case cost-effectiveness results by ERT-naïve and ERT-experienced populations separately. The EAG considers this issue has been partially resolved but uncertainty remains.

2.3 Issue 3: Uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat

The company recognises there is uncertainty in the long-term effectiveness of alternative ERTs and broadly accepts the EAG approach to exploring the uncertainty in long-term treatment effects. The company, however, questions the plausibility of 0.3 HR explored in the EAG's scenario analysis and highlights expert opinion that patients receiving cipaglucosidase alfa in combination with miglustat are unlikely to experience such a dramatic slowing in their disease progression over the long-term. The company argue that the rate of disease progression for patients on cipaglucosidase alfa in combination with miglustat is expected to be [redacted] compared to treatment with alglucosidase alfa, and consider the HR of 0.3 explored by the EAG to be clinically implausible.

The company has updated their base case model with the assumption that the rate of long-term disease progression is [redacted] (HR=[redacted]) with cipaglucosidase alfa in combination with miglustat, and [redacted] (HR=[redacted]) with avalglucosidase alfa, compared to alglucosidase alfa. The model therefore assumes a long-term treatment effect for cipaglucosidase alfa in combination with miglustat relative to both alglucosidase alfa and avalglucosidase alfa. Uncertainty in the long-term effectiveness is explored in scenario analyses using HRs ranging from [redacted].

The EAG's response

As discussed in Section 4.3.6 of the EAG report, the long-term effectiveness of cipaglucosidase alfa in combination with miglustat is a significant area of uncertainty, with limited data to substantiate the base case assumptions which are not informed by any data and as such represent arbitrary values. The EAG notes that the company have updated their base case to assume that avalglucosidase alfa slows disease progression relative to alglucosidase alfa. The modelled treatment effect of [redacted] however, [redacted] The EAG does not consider this assumption appropriate given the limited evidence available and considers there to be no *priori* reason to believe this is the case. The EAG also notes that [redacted] the claimed benefits of cipaglucosidase alfa in combination with miglustat.

The EAG also maintains that a wide range of HRs are plausible given the lack of long-term evidence for both cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa. Limited longer-term evidence on the effectiveness of cipaglucosidase alfa in combination with miglustat is available from the ATB200-02 study which showed improvements in 6MWD and FVC % predicted were matinined thoughout the follow up period with minimal evidence of decline.[1] This suggests that the that more optimistic HR explored by the EAG could be plausible, though it is important to recognise the limitations of the ATB200-02 study which was a small single arm study. The EAG considers there to be substantial uncertainty in the long-term effectiveness of cipaglucosidase alfa in combination with miglustat. The limited evidence available, however, does appear to be inconsistent with the rate of decline assumed in the base case model. Further clinical expert opinion and evidence on longer-term efficacy would be helpful in resolving this uncertainty.

2.4 Issue 4: Use of single arm studies in the indirect treatment comparison

The company have accepted the EAG's approach to only include RCTs in the multi-level network meta-regression (ML-NMR). The company's updated base case, which includes avalglucosidase alfa, utilises results from the ML-NMR excluding single-arm trials.

The EAG's response

In the original company submission, single arm studies were included in the ML-NMR to inform the relative treatment effect of cipaglucosidase alfa in combnation with miglustat including avalglucosidase alfa as a comparator. This approach may be appropriate when single arm studies are needed to connect a network, but in this case RCT data are available although the numbers are very small. The EAG considers that the inclusion of single arm studies may increase precision but with a

high risk of bias which cannot be quantified. The company acknowledged the potential for bias and have now excluded the single arm studies. The EAG considers this issue resolved.

2.5 Issue 5: Indirect treatment comparison including both ERT-naïve and ERT-experienced participants

The company accepted the EAG's approach to explore ERT-naïve and ERT-experienced populations separately. The company's updated base case cost-effectiveness analyses (which include avalglucosidease alfa as a comparator) present results in the total, ERT-naïve and ERT-experienced populations; these revised analyses use estimates from ML-NMRs including RCTs only, excluding single arm studies.

The EAG's response

As discussed in Section 3.4 of the EAG Report, in the original submission, the company undertook an indirect treatment comparison to inform the scenario analysis which compared cipaglucosidase alfa in combination with miglustat and avalglucosidase alfa, however the results were presented in the total population only.

The company used ML-NMR to adjust for differences in the populations of studies included in the analysis. While ML-NMR may correct for population differences and estimate effects in each specific population, small sample sizes limit the reliability of the results (e.g. only 27 ERT-naïve participants were included in the PROPEL trial and used to inform the meta-regression).

The clinical advisor to the EAG suggested that combining ERT-naïve and ERT-experienced patients as a mixed population is not meaningful. The EAG considers that these subgroups should be considered separately (see Issue 2).

The ML-NMR in the company submission included single arm trials; the EAG consider this may increase precision but with a high risk of bias (see Issue 4).

The company have updated the analyses to address the EAG's concerns, presenting the results separately and only including RCTs. However, uncertainty in the estimates remains given the limited trial evidence available.

2.6 Issue 6: Cost-effectiveness of comparator treatments

The company agrees with the EAG that this issue is not resolvable within the scope of this appraisal and highlights that their submission is consistent with both the NICE scope and NICE methods. The company's response notes alglucosidase alfa represents current UK clinical practice for the treatment of adults with Pompe disease in the UK and is therefore the most appropriate comparator.

Alglucosidase alfa is routinely commissioned by the NHS and it is reasonable to assume the opportunity cost associated with this funding decision has been appropriately accounted for in NHS planning.

The EAG's response

As discussed in the EAG report, the EAG acknowledges that alglucosidase alfa is currently used in the NHS for treating Pompe disease and the company submission is consistent with both the NICE scope and NICE methods. However, the EAG maintains that the presented economic analysis is flawed and is likely to significantly overestimate the value of cipaglucosidase alfa to the NHS because of the cost-ineffectiveness of alglucosidase alfa. The EAG believes that this issue could only be resolved by assessing the cost-effectiveness of all ERTs relative to each other and also to BSC. The EAG notes that the company raised concerns in their response to Issue 3 about the counterintuitive results generated by the model. These suggest that improved survival negatively impacts cost-effectiveness estimates. These counter-intuitive results are a direct consequence of the cost-ineffectiveness of comparator treatments and, as highlighted by the EAGs scenario analysis, lead to perverse results whereby more effective treatments are not cost-effective because they positively impact survival. This can also lead to situations where, to maintain cost-effectiveness, a more effective treatment must have lower per-cycle acquisition costs than a less effective comparator treatment. The EAG consider this issue cannot be resolved in the scope of this appraisal.

2.7 Issue 7: Improper parameterisation of the model

The company acknowledged the EAG's concerns regarding the specification of the model and has updated the economic analysis so that baseline characteristics are correlated.

The EAG's response

The EAG has verified the company's update to the economic model and can confirm that the changes made have been appropriately implemented so that baseline characteristics are now correlated. The updates made by the company address concerns raised by the EAG. This issue is resolved.

2.8 Issue 8: Utilities generated using a non-reference case approach

The company acknowledged the EAG's concerns regarding using utility values from the vignette study especially when these utility values are available from PROPEL study or published literature. The company noted the value of using utility values generated from participants directly for decision-making.

The EAG's response

The updated company base case uses the utility value set derived from the PROPEL trial with additional values for more severe health states (not reached by participants in the PROPEL trial)

provided by the vignette study. These updated assumptions align with the EAG preferred base case and as such the EAG considers this issue resolved. Uncertainty, however, remains around the appropriateness of supplementary values provided by the vignette study. As noted in the EAG report, the utility values generated by the vignette study are substantially lower than those obtained from either the PROPEL trial or the published literature. The partial use of the vignette study may therefore overestimate the impact of Pompe disease in the more severe health states. In this regard, the EAG highlights a consultation submission from a patient who is both wheelchair and non-invasive ventilation dependent.[2] They raised concerns that their quality of life may be undervalued and noted that with adequate technology and equipment, they consider themselves to have a high quality of life. The vignette study suggests that a corresponding utility value for this patient would be just 0.08, and does not appear to be consistent with the patient's submission.

2.9 Issue 9: Resource use for invasive home mechanical ventilation

In their response to a critique by the EAG, the company preferred to use Noyes et al.[3] as their source for invasive home mechanical ventilation, given it was conducted in the UK setting. The company conducted a scenario analysis using data for invasive home mechanical ventilation from Gajdoš et al, an alternative study conducted in the Czech Republic and identified by the EAG.

The EAG's response

The EAG considers there to be substantive uncertainty in the costs of invasive home mechanical ventilation applied in the model. While the Noyes et al. study was conducted in the UK, the study sample was derived from a paediatric populations, published in 2006.[3] The EAG acknowledges the limitations in two alternative studies identified by the EAG, neither of which are from UK setting. However, both these studies are much more recent than the Noyes study and suggest that the Noyes et al study may be significantly overestimating the costs of invasive home mechanical ventilation. Given the impact of this parameter, the EAG feels a more conservative approach may be appropriate, particularly as in the alglucosidase alfa comparison the model predicts substantial costs savings due to avoidance of the use of invasive home mechanical ventilation. The EAG considers this issue unresolved and unresolvable given the data available. Insights from clinicians and commissioners may provide some insight into the cost of home mechanical ventilation to the NHS.

3 UPDATED MODELLING ASSUMPTIONS

In response to the issues noted in the EAR, and following the additional analyses undertaken by the company, an updated base-case cost-effectiveness model was presented.

The following EAG-preferred assumptions are incorporated within the company's revised model:

- Issue 1: The inclusion of avalglucosidase alfa as a secondary comparator only and its exclusion from the base case analysis
- Issue 2: Differences between the ERT-naïve and ERT-experienced populations
- Issue 4: Use of single arm studies in the indirect treatment comparison
- Issue 5: Indirect treatment comparison including both ERT-naïve and ERT-experienced participants
- Issue 7: Improper parameterisation of model
- Issue 8: Utilities generated using a non-reference case approach

In addition, the following issues have been partially accommodated in the company's revised model:

- Issue 3: Uncertainty over the long-term relative effectiveness of cipaglucosidase alfa in combination with miglustat

The company maintain their original position on the following assumptions:

- Issue 9: Resource use for invasive home mechanical ventilation

The company also updated the base case to include inpatient management costs as per the NICE appraisal of avalglucosidase alfa (TA821)[4] and in line with the EAG's preferred assumption.

3.1 Results

The results of the company's updated base case are summarised in Table 2. These results are inclusive of the approved PAS discounts for cipaglucosidase alfa but are exclusive of confidential PAS discounts for comparator treatments. Results with PAS discounts for all comparators are provided in a confidential appendix separate to this document.

In the company's revised base-case, cipaglucosidase alfa in combination with miglustat generated [redacted] and [redacted] incremental QALYs versus alglucosidase alfa and avalglucosidase alfa respectively.

Table 2 Updated company base case results: HRs compared to alglucosidase alfa of [redacted] for cipaglucosidase alfa w. miglustat and [redacted] for avalglucosidase alfa.

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/QALY)
Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	-	-	-	-
Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; NHB, net health benefit.

3.2 Updated EAG base-case analysis

The EAG does not have a single base case analysis due to uncertainties in relative effectiveness estimates. Results from the revised company base-case along with the EAG exploratory analyses, which retain the majority of the assumptions in the original EAG scenario analyses, are presented in Table 3,

Table 4 and

Table 5. The EAG scenario results for the whole population have been calculated by averaging the results from the ERT-Naïve and ERT-Experienced populations.

Table 3 EAG exploratory scenario analyses on the revised company base case (ERT-Naïve)

Assumptions	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/QALY)
1. Revised company base case: HR of [redacted] applied to cipaglucosidase alfa w. miglustat HR of [redacted] applied to avalglucosidase alfa	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. HR applied to cipaglucosidase alfa w. miglustat a) HR of 0.3	Alglucosidase alfa	[redacted]	[redacted]				
	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
3. HR applied to avalglucosidase alfa a) HR of 0.3	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c) HR of 0.85	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4. Higher mortality in State 7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Alternative invasive mechanical ventilation cost **a) Annual cost of £37,838 from Nonoyama et al.**	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) Annual cost of £57,091 from Gajdoš et al.	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4 EAG exploratory scenario analyses on the revised company base case (ERT-Experienced)

Assumptions	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/QALY)
1. Revised company base case: HR of [redacted] applied to cipaglucosidase alfa w. miglustat HR of [redacted] applied to avalglucosidase alfa	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. HR applied to cipaglucosidase alfa w. miglustat a) HR of 0.3	Alglucosidase alfa	[redacted]	[redacted]				
	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
3. HR applied to avalglucosidase alfa a) HR of 0.3	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c) HR of 0.85	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Higher mortality in State 7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Alternative invasive mechanical ventilation cost	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
a) Annual cost of £37,838 from Nonoyama et al.	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) Annual cost of £57,091 from Gajdoš et al.	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5 EAG exploratory scenario analyses on the revised company base case (whole population; scenarios generated using model averaging approach)

Assumptions	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	NHB (£20,000/QALY)
1. Revised company base case: HR of [redacted] applied to cipaglucosidase alfa w. miglustat HR of [redacted] applied to avalglucosidase alfa	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. HR applied to cipaglucosidase alfa w. miglustat a) HR of 0.3	Alglucosidase alfa	[redacted]	[redacted]				
	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
3. HR applied to avalglucosidase alfa a) HR of 0.3	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) HR of 0.7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c) HR of 0.85	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Higher mortality in State 7	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Alternative invasive mechanical ventilation cost	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
a) Annual cost of £37,838 from Nonoyama et al.	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) Annual cost of £57,091 from Gajdoš et al.	Cipaglucosidase alfa w. miglustat	[redacted]	[redacted]				
	Alglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Avalglucosidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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