# CONFIDENTIAL UNTIL PUBLISHED
# External Assessment Group Report
# Cipaglucosidase alfa with miglustat for treating Pompe disease


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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.

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**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.

**Copyright statement**

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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).<br>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]<br>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.<br>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).<br>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.<br>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.<br>The EAG has undertaken the simple indirect comparison in ERT-naïve participants and this is presented in section 3.5.1.<br>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].<br>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.<br>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.<br>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.<br>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.<br>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.<br>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] | | | | | |
| **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] |
| **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]<br>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.<br>However, in the company's response to the EAG's points for clarification, they stated that [redacted] |
| Comparator(s) | • Alglucosidase alfa<br>• Avalglucosidase alfa | • Primary comparator: Alglucosidase alfa<br>• 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.<br>In view of the lack of direct comparative data on avalglucosidase alfa versus cipaglucosidase alfa in combination with |

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|---|---|---|---|---|
| | | | 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:<br>• change in respiratory function<br>• change in motor function<br>• change in muscular function<br>• mortality<br>• immunogenicity response<br>• adverse effects of treatment<br>• health-related quality of life (HRQoL) | The outcome measures to be considered include:<br>• change in motor function (assessed using the six-minute walk test [6MWT])<br>• change in respiratory function (assessed using sitting forced vital capacity [FVC] % predicted)<br>• change in muscular function (assessed using manual muscle testing and the Gait, Stairs, Gowers' manoeuvre, and Chair [GSGC] assessments)<br>• HRQoL<br>• immunogenicity response<br>• 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.<br>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.<br>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.<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>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.<br>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:<br>• people who have received prior treatment with alglucosidase alfa<br>• 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.<br>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.<br>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 |

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|---|---|---|---|---|
| | | | 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.<br>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.<br>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.<br>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.<br>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.<br>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.<br>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.<br>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.<br>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.<br>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.<br>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**<br>Cipaglucosidase alfa + miglustat (n=85)<br>Alglucosidase alfa + placebo (n=37) | 20.79 (42.77)<br>7.24 (40.28) | [redacted] | [redacted] | [redacted] |
| **ERT-experienced**<br>Cipaglucosidase alfa + miglustat (n=61)<br>Alglucosidase alfa + placebo (n=29) | 16.89 (40.39)<br>-0.02 (39.34) | [redacted] | [redacted] | [redacted] |
| **ERT-naïve**<br>Cipaglucosidase alfa + miglustat (n=20)<br>Alglucosidase alfa + placebo (n=7) | 33.44 (48.70)<br>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**<br>Cipaglucosidase alfa + miglustat (n=85)<br>Alglucosidase alfa + placebo (n=37) | -0.93 (6.23)<br>-3.95 (4.89) | 2.66 [redacted] | 0.37 to 4.95 | 0.02 |
| **ERT-experienced**<br>Cipaglucosidase alfa + miglustat (n=65)<br>Alglucosidase alfa + placebo (n=30) | 0.05 (5.84)<br>-4.02 (5.01) | 3.51 [redacted] | 1.03 to 5.99 | 0.01 |
| **ERT-naïve**<br>Cipaglucosidase alfa + miglustat (n=20)<br>Alglucosidase alfa + placebo (n=7) | -4.10 (6.53)<br>-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**<br>Cipaglucosidase alfa + miglustat (n=85)<br>Alglucosidase alfa + placebo (n=37) | 1.56 (3.78)<br>0.88 (2.58) | 0.96 [redacted] | -0.48 to 2.40 | [redacted] |
| **ERT-experienced**<br>Cipaglucosidase alfa + miglustat (n=65)<br>Alglucosidase alfa + placebo (n=30) | 1.63 (4.13)<br>0.85 (2.81) | 0.70 [redacted] | -1.08 to 2.49 | [redacted] |
| **ERT-naïve**<br>Cipaglucosidase alfa + miglustat (n=20)<br>Alglucosidase alfa + placebo (n=7) | 1.36 (2.55)<br>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**<br>Cipaglucosidase alfa + miglustat (n=85)<br>Alglucosidase alfa + placebo (n=37) | -0.53 (2.54)<br>0.77 (1.81) | -1.414 [redacted] | -2.46 to -0.36 | [redacted] |
| **ERT-experienced**<br>Cipaglucosidase alfa + miglustat (n=55)<br>Alglucosidase alfa + placebo (n=25) | -0.53 (2.53)<br>0.61 (1.83) | -1.19 [redacted] | -2.38 to 0.00 | [redacted] |
| **ERT-naïve**<br>Cipaglucosidase alfa + miglustat (n=19)<br>Alglucosidase alfa + placebo (n=7) | -0.56 (2.64)<br>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**<br>Cipaglucosidase alfa + miglustat (n=85)<br>Alglucosidase alfa + placebo (n=37) | 1.94 (7.50)<br>0.19 (10.82) | 1.87 [redacted] | -1.51 to 5.25 | [redacted] |
| **ERT-experienced**<br>Cipaglucosidase alfa + miglustat (n=65)<br>Alglucosidase alfa + placebo (n=30) | 1.76 (7.18)<br>-0.97 (11.20) | 3.14 [redacted] | -0.73 to 7.02 | [redacted] |
| **ERT-naïve**<br>Cipaglucosidase alfa + miglustat (n=20)<br>Alglucosidase alfa + placebo (n=7) | 2.50 (8.62)<br>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**<br>Cipaglucosidase alfa + miglustat (n=85)<br>Alglucosidase alfa + placebo (n=37) | -2.02 (5.76)<br>-1.67 (6.62) | 0.04 [redacted] | -2.12, 2.20 | [redacted] |
| **ERT-experienced**<br>Cipaglucosidase alfa + miglustat (n=65)<br>Alglucosidase alfa + placebo (n=30) | -1.87 (5.84)<br>-0.27 (5.26) | -0.84 [redacted] | -3.16 to 1.49 | [redacted] |
| **ERT-naïve**<br>Cipaglucosidase alfa + miglustat (n=20)<br>Alglucosidase alfa + placebo (n=7) | -2.50 (5.63)<br>-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**<br>Cipaglucosidase alfa + miglustat [redacted]<br>Alglucosidase alfa + placebo [redacted] | [redacted]<br>[redacted] | [redacted]<br>[redacted] | [redacted]<br>[redacted] |
| **ERT-experienced**<br>Cipaglucosidase alfa + miglustat [redacted]<br>Alglucosidase alfa + placebo [redacted] | [redacted]<br>[redacted] | [redacted]<br>[redacted] | [redacted]<br>[redacted] |
| **ERT-naïve**<br>Cipaglucosidase alfa + miglustat [redacted]<br>Alglucosidase alfa + placebo [redacted] | [redacted]<br>[redacted] | [redacted]<br>[redacted] | [redacted]<br>[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**<br>Cipaglucosidase alfa + miglustat [redacted]<br>Alglucosidase alfa + placebo [redacted] | [redacted] | [redacted] | [redacted] |
| **ERT-experienced**<br>Cipaglucosidase alfa + miglustat [redacted]<br>Alglucosidase alfa + placebo [redacted] | [redacted] | [redacted] | [redacted] |
| **ERT-naïve**<br>Cipaglucosidase alfa + miglustat [redacted]<br>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<br>• Confirmed diagnosis of Pompe disease (GAA deficiency and/or 2 confirmed GAA mutations)<br>• Treatment naïve<br>• Upright FVC 30-85% predicted<br>• Walk ≥ 40 metres without stopping and without assistive devices | • Pompe-specific cardiac hypertrophy<br>• Requiring invasive ventilation<br>• Wheelchair dependent<br>• Clinically significant organic disease<br>• Previous/current immune tolerance induction therapy<br>• Positive pregnancy test or unwilling/ unable to test if of childbearing potential<br>• Breastfeeding |
| LOTS[15] | • Age ≥ 8 years old<br>• Confirmed diagnosis of Pompe disease (GAA deficiency and 2 GAA gene mutations)<br>• Lower limbs muscle weakness <80% of predicted value<br>• Able to undergo and produce reproducible muscle and pulmonary function tests<br>• Upright FVC 30-79% predicted<br>• Walk ≥ 40 metres in 6 minutes on 2 consecutive days (assistive devices allowed)<br>• Postural drop in FVC ≥10% from upright to supine position.<br>• Testable muscle in bilateral knee flexors and knee extensors. | • Requiring invasive ventilation<br>• Requiring non-invasive ventilation whilst awake and upright<br>• Positive pregnancy test or female of childbearing potential not protected by highly effective contraception or unwilling or unable to test for pregnancy<br>• Enzyme replacement therapy with GAA received<br>• Investigational product used within 30 days prior to enrolment or enrolled in another study with clinical evaluations.<br>• Medical condition or major congenital anomaly which may interfere with compliance. |
| NEO[21] | • Age ≥ 18 years old<br>• Confirmed diagnosis of Pompe disease (GAA enzyme deficiency and/or confirmed GAA gene mutation)<br>• Walk ≥ 50 metres without stopping and without assistive devices (assistive device for walking outdoors is allowed)<br>• Upright FVC ≥ 50% predicted<br>• Negative pregnancy test if woman is of childbearing potential<br><br>GROUP 2 (ERT-experienced) only:<br>• Previously treated with alglucosidase alfa for ≥ 9 months. | • Cardiac hypertrophy<br>• Wheelchair dependent<br>• Requiring invasive ventilation<br>• Unable to adhere to study protocol<br>• Significant organic disease<br>• MRI exam not possible<br><br>GROUP 1 (ERT-naive) only:<br>• Previous treatment with ERT for Pompe disease<br><br>GROUP 2 (ERT-experienced) only:<br>• 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<br>Mean difference (95% credible interval) | ML-NMR relative effect<br>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: $-3.7 \pm 0.6$, $P < .001$). 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).

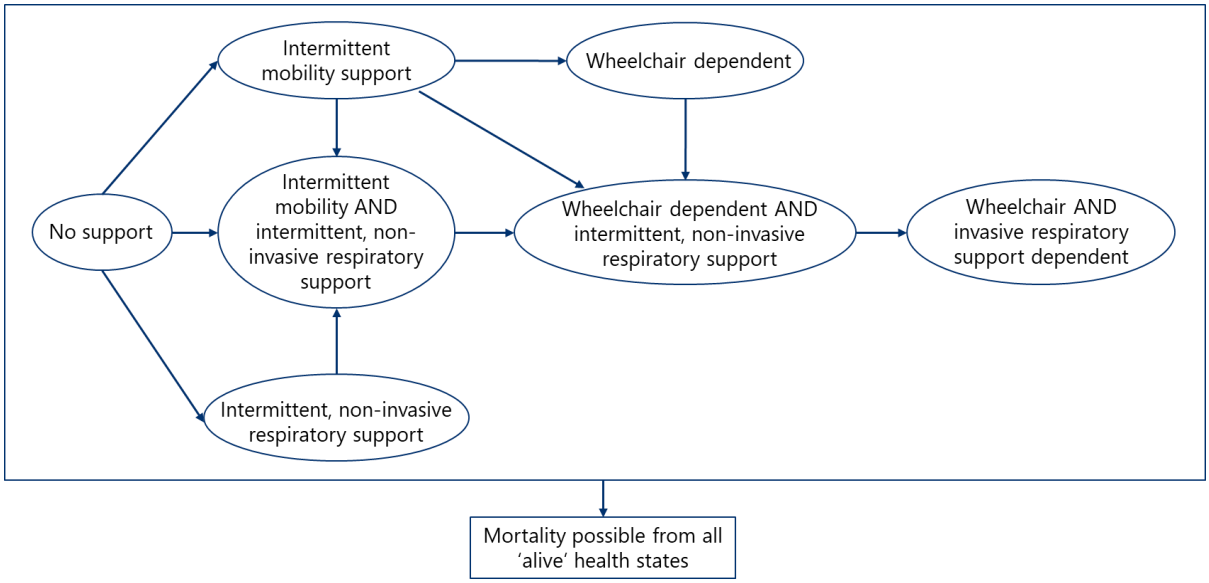
This model structure is depicted graphically in Figure 1 and comprises seven ‘alive’ health states which defined requirements for respiratory and/or mobility support. Support was classified into three levels: no support, intermittent support and wheelchair-dependent/invasive respiratory support dependant. 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 2$^{nd}$ 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]<br>Avalglucosidase alfa: [redacted] | Alglucosidase alfa: [redacted]<br>Avalglucosidase alfa: [redacted] | Alglucosidase alfa: [redacted]<br>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.<br>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.<br>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.<br>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

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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. | | | | | | | | |